ABROGATING PROINFLAMMATORY CYTOKINE PRODUCTION DURING ONCOLYTIC REOVIRUS THERAPY

BACKGROUND

Reovirus is a dsRNA virus with tropism to cancer cells having an activated Ras pathway. It has been demonstrated that administration of reovirus into tumor bearing animals results in generation of a robust anti-viral response mediated by both the humoral and cellular arms of the immune system. This anti-viral response can antagonize the oncolytic effectiveness of the therapeutic virus. As such, combinational use of immune suppressing agents to overcome this immune antagonism of reovirus oncolysis has been explored. It has been demonstrated that co-administration of agents that ablate the generation of neutralizing anti-reovirus antibodies (NARA) can result in morbidity in the test animals. The response in the test animals has been characterized by reovirus replication outside of the target tumor tissues, suggesting that humoral immunity serves a protective role in preventing reovirus infection of the host (Qiao et al., *Clin. Cancer Res.* 14(1):259-69 (2008)).

SUMMARY

Provided herein are methods for treating a proliferative disorder in a subject comprising administering to the subject one or more reoviruses and one or more agents that modulate expression or activity of pro-inflammatory cytokines. For example, the agents may inhibit expression or activity of pro-inflammatory cytokines.

In one aspect, there is provided the use of one or more reoviruses and

one or more platinum compounds that inhibit expression or activity of a pro-inflammatory cytokine but do not inhibit production of neutralizing anti-reovirus antibodies (NARA) in the manufacture of a medicament for treating a proliferative disorder in a subject.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A, 1B, 1C and 1D show reduced tumor growth and increased survival following reovirus/cisplatin combination therapy. C57Bl/6 (Figures 1A and 1C) and C3H (Figures 1B and 1D) mice bearing subcutaneous B16.F10 and K1735 tumors, respectively, were treated on days 1 and 4 with either reovirus alone via intratumoral (i.t.) injection (squares), cisplatin alone via intraperitoneal (i.p.) administration (triangles), or reovirus and cisplatin in combination (circles). Control treated mice (diamonds) received PBS. Tumors were measured on the days indicated and tumor volume expressed as tumor volume relative to volume at commencement of treatment (Figures 1A and 1B). Mice

were euthanized when tumors exceeded 15mm in any one dimension. Survival is expressed as Kaplan-Myer plots (Figures 1C and 1D).

Figure 2 is a graph showing the neutralizing anti-reovirus antibody (NARA) response after no treatment (control) or treatment with reovirus, cisplatin or the combination of reovirus and cisplatin.

Figures 3A, 3B, 3C, 3D, 3E, 3F, and 3G are graphs showing pro-inflammatory cytokine response is abrogated by cisplatin. The response of IL-1I (Figure 3A), IL-3 (Figure 3B), IL-6 (Figure 3C), IL-12 (Figure 3D), IL-17 (Figure 3E), MIP-1I (Figure 3F) and RANTES (Figure 3G) were measured after no treatment (control) or treatment with reovirus, cisplatin or the combination of reovirus and cisplatin.

DETAILED DESCRIPTION

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 replication in the cell. Based upon these discoveries, methods have been developed for using reoviruses to treat proliferative disorders. It has been demonstrated that reovirus therapy results in release of pro-inflammatory cytokines. The pro-inflammatory cytokines antagonize reovirus infection and reovirus spread into the tumor tissue. The protective function of the humoral arm of the immune system in preventing reovirus toxicity has been further suggested by the observation that while, athymic mice manifest no morbidity to reovirus infection, SCID mice and B-cell knock-out animals invariably die from reovirus infection.

Reovirus oncolysis can be enhanced *in vitro* by the use of cytotoxic agents. Surprisingly, as described herein, the combinational use of platinum compounds does not impact the production of NARA but has a profound effect on the production of pro-inflammatory cytokines including: IL-lI, IL-3, IL-6, IL-12 p70, IL-17, MIP-lI, and RANTES. Inhibition of pro-inflammatory cytokines by cisplatin prevents T-cell recognition of reovirus infected cells and allows virus replication to ensue without cellular immunity antagonism. However, cisplatin allows production of protective neutralizing anti-reovirus antibodies (NARA) NARA and its concomitant benefits (e.g., preventing reovirus toxicities in patients). The use of platinum compounds to selectively block both innate and adaptive T-cell responses, while having no effect on B-cell activity, has not previously been described.

Provided herein is a method of treating a proliferative disorder in a subject comprising administering a reovirus to the subject and administering to the subject an agent that modulates pro-inflammatory cytokines.

For example, the agent inhibits the expression or activity of the pro-inflammatory cytokines. As used herein, the term modulate refers to a change (positive or negative) of 10, 20, 30, 40, 50, 60, 70, 80, 90 percent or greater as compared to a control level. As used herein, control refers to a reference standard from an untreated sample or subject. By way of example, a control level is the level of expression or activity in a control sample in the absence of a stimulus. The control can be prior to, after recovery, or without the stimulus.

Optionally, the cytokine modulating agent blocks T-cell responses while having little to no effect on B-cell activity. Thus, the agent inhibits pro-inflammatory cytokines but does not inhibit or minimally inhibits production of NARA. Optionally, the agent is a platinum compound. Suitable platinum compounds include, but are not limited to, cisplatin, carboplatin, metaplatin and oxaliplatin.

Other agents that inhibit pro-inflammatory cytokines include, but are not limited to, TNF-I antibodies such as infliximab, CDP571, CDP870, and adalimumab; recombinant, human soluble p55 TNF receptors such as onercept; soluble TNF receptor and Fc fragment fusion proteins such as etanercept; pegylated Fab fragments of humanized antibody to TNF such as certolizumab pegol; chimeric antibodies to anti-I chain of IL-2 receptor such as basiliximab or daclizumab; IL-12p40 antibodies such as ABT-874; IL-6 receptor antibodies such as MRA or tocilizumab; IFN-K antibodies such as fontolizumab; antibodies that inhibit IL-1 binding to the IL-1 receptor such as AMG108; caspase-1 inhibitors that inhibit cytokine-release such as diarylsulphonylurene; IL-15 antibodies such as mepolizumab; IL-8 antibodies such as ABX-IL-8; IL-9 antibodies including IL-9 monoclonal antibodies; recombinant human IL-21 also referred to as 494C10; inhibitors of TNF-I, IL-19, IL-6 and granulocyte monocyte-colony stimulating factor expression such as biophylum sensitivum; NF-PB signaling blockers that inhibit pro-inflammatory cytokine expression such as simvastatin; and inhibitors of IL-6 expression and NF-PB activation such as (-)-epigallocatechin-3-gallate (EGCG).

Other agents include human recombinant lactoferrin, which inhibits cellular release of proinflammatory cytokines and prometastatic cytokines (including IL-6, IL-8, granulocyte macrophage colony-stimulating factor and TNF-α). Inhibitors of dendritic cell derived IL-12 and IL-18 such as rapamycin and sanglifehrin are also suitable for use

in the provided methods. Rapamycin is an immunosuppressant that inhibits T cell mTOR kinase activation, and Sanglifehrin A is a cyclophilin-binding immunosuppressant that also inhibits IL-2 dependent T cell proliferation. Also suitable for use in the provided methods is dietary rutin colitis, which suppresses the induction of pro-inflammatory cytokines such as IL-1β, IL-6, and GM-CS.

Optionally, the method further includes selecting a subject with a proliferative disorder, wherein the subject is in need of inhibition of a pro-inflammatory cytokine response. For example, such a subject may include a subject with little response to reovirus alone or with a progressive resistance to reovirus therapy.

As used herein, the term proliferative disorder refers to any cellular disorder in which the cells proliferate more rapidly than normal tissue growth. A proliferative disorder includes, but is not limited to, neoplasms, which are also referred to as tumors. A neoplasm can include, 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 1, and leukemia. A neoplasm can be 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 proliferating disorders for which reovirus is used as a treatment, at least some of the proliferating cells associated with the disorder may 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 and 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, mutation within B-Raf. See, for example, Brose et al., 2002, *Cancer Res.* 62:6997-7000. A proliferative disorder that results, at least in part, by the activation of ras, an upstream element of ras, or an element in the ras signaling pathway is referred to herein as a ras-mediated proliferative disorder. In addition, the reovirus is useful for treating proliferative disorders caused by mutations or dysregulation of PKR. See, for example, Strong et al., 1998, *EMBO J.* 17:3351-62.

Optionally, the provided methods further comprise the step of selecting a subject with a ras-mediated proliferative disorder. Optionally, the provided methods comprise the

step of determining whether the proliferative disorder is a ras-mediated proliferative disorder. Such methods for determining whether a proliferative disorder has a certain phenotype are known. See, for example, U.S. Patent No. 7,306,902, which is incorporated herein by reference in its entirety.

As used herein, reovirus refers to any virus classified in the reovirus genus, whether naturally occurring, modified, or recombinant. Reoviruses are viruses with 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 genome consists of double-stranded RNA in 10-12 discrete segments with a total genome size of 16-27 kbp. The individual RNA segments vary in size. Three distinct but related types of reoviruses have been recovered from many species. All three types share a common complement-fixing antigen.

The human reovirus includes three serotypes: type 1 (strain Lang or T1L), type 2 (strain Jones, T2J), and type 3 (strain Dearing or strain Abney, T3D). The three serotypes are easily identifiable on the basis of neutralization and hemagglutinin-inhibition assays. A reovirus according to this disclosure can be a type 3 mammalian orthoreovirus. Type 3 mammalian orthoreoviruses include, without limitation, Dearing and Abney strains (T3D or T3A, respectively). See, for example, ATCC Accession Nos. VR-232 and VR-824.

The reovirus may be naturally occurring or modified. The reovirus is naturally-occurring when it can be isolated from a source in nature and has not been intentionally modified by humans in the laboratory. For example, the reovirus can be from a field source, that is, from a human who has been infected with the reovirus. The reovirus may also be selected or mutagenized for enhanced oncolytic activity.

The reovirus may be modified but still capable of lytically infecting a mammalian cell having an active ras pathway. The reovirus may be chemically or biochemically pretreated (e.g., by treatment with a protease, such as chymotrypsin or trypsin) prior to administration to the proliferating cells. Pretreatment with a protease removes the outer coat or capsid of the virus and may increase the infectivity of the virus. The reovirus may be coated in a liposome or micelle (Chandran and Nibert, J. of Virology 72(1):467-75 1998). For example, the virion may be treated with chymotrypsin in the presence of micelle-forming concentrations of alkyl sulfate detergents to generate a new infectious subviral particle (ISVP).

The reovirus may be a recombinant reovirus. For example, the recombinant reovirus can be a reassortant reovirus, which includes genomic segments from two or more genetically distinct reoviruses. Reassortment of reovirus genomic segments may

occur following infection of a host organism with at least two genetically distinct reoviruses. Reassortment of viruses can be generated in cell culture, for example, by co-infection of permissive host cells with genetically distinct reoviruses. Accordingly, the provided methods include the use of a recombinant reovirus resulting from reassortment of genome segments from two or more genetically distinct reoviruses, including but not limited to, human reovirus, such as type 1 (e.g., strain Lang), type 2 (e.g., strain Jones), and type 3 (e.g., strain Dearing or strain Abney); non-human mammalian reoviruses; or avian reovirus. Recombinant reovirus can also be made by genetic engineering, chemically synthesized, or treatment with chemical or physical mutagens. Optionally, the provided methods include the use of recombinant reoviruses resulting from reassortment of genome segments from two or more genetically distinct reoviruses wherein at least one parental virus is genetically engineered, comprises one or more chemically synthesized genomic segment, has been treated with chemical or physical mutagens, or is itself the result of a recombination event. Optionally, the provided methods include the use of the recombinant reovirus that has undergone recombination in the presence of chemical mutagens, including but not limited to, dimethyl sulfate and ethidium bromide, or physical mutagens, including but not limited to, ultraviolet light and other forms of radiation.

Optionally, the provided methods include the use of reoviruses with mutations (including insertions, substitutions, deletions or duplications) in one or more genome segments. Such mutations can comprise additional genetic information as a result of recombination with a host cell genome or can comprise synthetic genes. For example, mutant reoviruses as described herein can contain a mutation that reduces or essentially eliminates expression of a sigma3 polypeptide or that results in the absence of a functional sigma3 polypeptide as described in U.S. Serial No. 12/124,522, which is incorporated by reference herein in its entirety. A mutation that eliminates expression of a sigma3 polypeptide or that results in the absence of a functional sigma3 polypeptide can be in the nucleic acid encoding the sigma3 polypeptide (i.e., the S4 gene) or in a nucleic acid that encodes a polypeptide that regulates the expression or function of the sigma3 polypeptide.

As used herein, a mutation that reduces the expression of a sigma3 polypeptide refers to a mutation that results in a decrease in the amount of sigma3 polypeptides, compared to a reovirus expressing wild type levels of sigma3 polypeptide, of at least 30% (e.g., at least 40%, 50%, 60%, 70%, 80%, 90%, or 95%). As used herein, a mutation that essentially eliminates expression of a sigma3 polypeptide refers to a mutation that results

in a decrease in the amount of sigma3 polypeptides, relative to the amount of sigma3 polypeptides produced by a wild type reovirus, of at least 95% (e.g., 96%, 97%, 98%, 99%, or 100%). As used herein, a mutation that results in a decrease in or absence of a functional sigma3 polypeptide refers to a mutation that allows expression of the sigma3 polypeptide but that results in a sigma3 polypeptide that is not able to assemble or incorporate into the viral capsid. It would be understood that it may be desirable or necessary for sigma3 polypeptides to retain other functionalities (e.g., the ability to bind RNA) in order that the mutant reovirus retain the ability to propagate.

A mutation in a sigma3 polypeptide as described herein can result in a sigma3 polypeptide that is incorporated into the capsid at levels that are reduced relative to a sigma3 polypeptide that does not contain the mutation (e.g., a wild type sigma3 polypeptide). A mutation in a sigma3 polypeptide as described herein also can result in a sigma3 polypeptide that cannot be incorporated into a viral capsid. Without being bound by any particular mechanism, a sigma3 polypeptide may have reduced function or lack function due, for example, to an inability of the sigma3 polypeptide and the mu1 polypeptide to bind appropriately, or due to a conformational change that reduces or prohibits incorporation of the sigma3 polypeptide into the capsid.

In addition to a mutation that abolishes or reduces expression of the sigma3 polypeptide or that results in a non-functional or reduced-function sigma3 polypeptide, a mutant reovirus as described herein also can contain one or more further mutations (e.g., a second, third, or fourth mutation) in one of the other reovirus capsid polypeptides (e.g., mu1, lambda2, and/or sigma1). Reoviruses containing a mutation affecting the sigma3 polypeptide and, optionally, a further mutation in any or all of the other outer capsid proteins can be screened for the ability of such mutant reoviruses to infect and cause lysis of cells. For example, neoplastic cells that are resistant to lysis by wild type reovirus can be used to screen for effective mutant reoviruses described herein.

For example, a further mutation can reduce or essentially eliminate expression of a mu1 polypeptide or result in the absence of a functional mu1 polypeptide. The mu1 polypeptide, which is encoded by the M2 gene, is likely involved in cell penetration and may play a role in transcriptase activation. Each virion contains about 600 copies of mu1 polypeptides, which are present in the form of 1:1 complexes with sigma3 polypeptides. The mu1 polypeptide is myristolated on its N-terminus, and then the myristolated N-terminal 42 residues are cleaved off, resulting in a C-terminal fragment (mu1C). Additionally or alternatively, a further mutation can reduce or essentially eliminate expression of a lambda2 polypeptide or result in the absence of a functional lambda2

polypeptide, and/or a further mutation can reduce or essentially eliminate expression of a sigma1 polypeptide or result in the absence of a functional sigma1 polypeptide. The lambda2 polypeptide is encoded by the L2 gene and is involved in particle assembly, and exhibits guanylyltransferase and methyltransferase activity. The sigma1 polypeptide is encoded by the S1 gene and is involved in cell-attachment and serves as the viral hemagglutinin.

For example, the reovirus 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, as described in U.S. Serial No. 12/046,095, which is incorporated by reference herein in its entirety. By way of example, the one or more amino acid modifications in the lambda-3 polypeptide are 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 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. Optionally, the lambda-3 polypeptide includes the sequence shown in SEQ ID NO:18. Further by way of example, the one or more amino acid modifications in the sigma-3 polypeptide are 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. Optionally, the sigma-3 polypeptide includes the sequence shown in SEQ ID NO:14. Further by way of example, the one or more amino acid modifications in the mu-1 polypeptide is an Asp at residue 73 numbered relative to GenBank Accession No. M20161.1. Optionally, the mu-1 polypeptide includes the sequence shown in SEQ ID NO:16. Also by way of example, the amino acid modification mu-2 polypeptide is a Ser at residue 528 numbered relative to GenBank Accession No. AF461684.1. Optionally, the mu-1 polypeptide includes the sequence shown in SEQ ID NO:15. A reovirus as described herein having one or more modifications can further include a reovirus sigma-2 polypeptide. Such a sigma-2 polypeptide has 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. Optionally, the sigma-2 polypeptide includes the sequence shown in SEQ ID NO:12.

Optionally, the reovirus 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, as described in U.S. Serial No. 12/046,095, which is incorporated by reference herein in its entirety. By way of example, the one or more nucleic acid modifications in the L1 genome segment are 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. Optionally, the L1 genome segment includes the sequence shown in SEQ ID NO:8. Further by way of example, the one or more nucleic acid modifications in the S4 genome segment is an A at position 74 and an A at position 624, numbered relative to GenBank Accession No. K02739. Optionally, the S4 genome segment includes the sequence shown in SEQ ID NO:4. 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 is a T at position 1595, numbered relative to GenBank Accession No. AF461684.1. Optionally, the M1 genome segment includes the sequence shown in SEQ ID NO:5. A reovirus as described herein can include any modification or combination of modifications disclosed herein. Optionally, 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. Optionally, a reovirus as disclosed herein is identified as IDAC Accession No. 190907-01.

A mutation or modification as referred to herein can be a substitution, insertion or deletion of one or more nucleotides. Point mutations include, for example, single 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 mutation in a nucleic acid can result in one or more conservative or non-conservative amino acid substitutions in the encoded polypeptide, which may result in conformational changes or loss or partial loss of function, a shift in the reading frame of translation (frame-shift) resulting in an entirely different polypeptide encoded from that point on, a premature stop codon resulting in a truncated polypeptide (truncation), or a mutation in a reovirus nucleic acid may not change the encoded polypeptide at all (silent

or nonsense). See, for example, Johnson and Overington, 1993, *J. Mol. Biol.* 233:716-38; Henikoff and 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.

Mutations can be generated in the nucleic acid of a reovirus using any number of methods 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 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 and Thompson, 1990, *Nucl. Acids Res.* 18:3439; Bohnsack, 1996, *Meth. Mol. Biol.* 57:1; Deng and Nickoloff, 1992, *Anal. Biochem.* 200:81; and Shimada, 1996, *Meth. Mol. Biol.* 57:157. Other methods are used routinely in the art to modify the sequence of a protein or polypeptide. For example, nucleic acids containing a mutation can be generated using PCR or chemical synthesis, or polypeptides having the desired change in amino acid sequence can be chemically synthesized. See, for example, Bang and Kent, 2005, *Proc. Natl. Acad. Sci. USA* 102:5014-9 and references therein.

Nucleic acids from reovirus particles can be isolated using standard commercially available nucleic acid methodology. See also, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe and Howley, eds., 2006, Lippincott Williams and Wilkins. As used herein, isolated nucleic acids refer to nucleic acids that are separated from other nucleic acids with which they are usually associated. Thus, 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 can include an engineered nucleic acid such as a recombinant or synthetic nucleic acid.

A mutant reovirus as described herein can be generated by reconstituting genome segments containing at least a mutation or modification using methods known in the art. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe and Howley, eds., 2006, Lippincott Williams and 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. A mutant reovirus also can be generated by expressing the reovirus genome segments using a plasmid-based reverse genetic system to produce an ISVP. See, for example, Kobayashi et al., 2007, *Cell Host and Microbe* 1:147-57. As used herein, a genetically-engineered or mutant ISVP is a mutant reovirus and refers to an ISVP generated from a reovirus carrying a genetically-engineered or a spontaneously generated mutation affecting at least the sigma3 polypeptide. The ISVPs described herein are stable and can be propagated as ISVPs for multiple (e.g., more than one, e.g., 2, 3, 4, 5, 10, 20, 50, or more) passages.

The mutant reoviruses described herein, produced via a genetically-engineered ISVP or via a plasmid-based reverse genetic system, can be cultured in, for example, human neoplastic cells or L929 mouse fibroblast cells. Mutant reoviruses disclosed herein can be cultured in cells that are only permissive to reovirus strains lacking the sigma3 polypeptide. Using such cell lines to passage the mutant reoviruses described herein can allow for selection of the mutants and also can be used to reduce or prevent reversions of the mutation(s).

The mutant reoviruses described herein, optionally, exhibit increased infectivity and/or decreased immunogenicity as compared to a non-mutant reovirus (e.g., a control reovirus) and can be selected on the basis of such traits. Increased infectivity can be evidenced by an increase in the range of neoplastic cells and/or the number of cells that are infected by a mutant reovirus compared to a reovirus that expresses a functional sigma3 polypeptide (e.g., an intact virion; e.g., a wild type reovirus). Decreased immunogenicity of mutant reoviruses can be evidenced by the inability of such mutant reoviruses to induce a significant immune response in the subject. The mutant reoviruses described herein also can be screened and selected for other desirable traits including, but not limited to, a faster rate of replication; a faster rate of packaging; the ability to induce apoptosis; the ability to affect lysis in and effectively kill human neoplastic cells lines; the ability to release effective tumor epitopes; interaction with standard chemotherapies; and an increased number of viral progeny. Additionally, mutant reoviruses can be selected for the ability to lytically infect a neoplastic cell (e.g., a mammalian cell having an active Ras pathway). See, for example, U.S. Patent No. 7,052,832.

The reovirus is optionally a reovirus modified to reduce or eliminate an immune reaction to the reovirus. Such a modified reovirus is referred to herein as an immunoprotected reovirus. Such modifications include, but are not limited to, packaging of the reovirus in a liposome, a micelle, or other vehicle to mask the reovirus from the immune system. Alternatively, the outer capsid of the reovirus virion particle may be

removed since the proteins present in the outer capsid are the major determinant of the host humoral and cellular responses.

Reoviruses can be purified using standard methodology. See, for example, Schiff et al., "Orthoreoviruses and Their Replication," Ch 52, in *Fields Virology*, Knipe and Howley, eds., 2006, Lippincott Williams and 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 mutant reoviruses refer to reoviruses that have been separated from cellular components that naturally accompany them. Typically, reoviruses 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 they are naturally associated.

The herein provided reoviruses and agents can be administered *in vitro* or *in vivo* in a pharmaceutically acceptable carrier. Thus, pharmaceutical compositions that include a reovirus and/or agent that inhibits pro-inflammatory cytokines as described herein are provided. See, for example, U.S. Patent No. 6,576,234 regarding reoviruses. In addition to one or more reoviruses and/or agents that inhibit pro-inflammatory cytokines, a pharmaceutical composition typically includes a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier can be a solid, semi-solid, or liquid material that can act as a vehicle, carrier or medium for the reovirus. Thus, compositions containing a reovirus and/or the provided agents can be in the form of tablets, pills, powders, lozenges, sachets, 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.

Optionally, the compositions containing a reovirus are suitable for infusion. For intravenous infusions, there are two types of fluids that are commonly used, crystalloids and colloids. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. Colloids contain larger insoluble molecules, such as gelatin; blood itself is a colloid. The most commonly used crystalloid fluid is normal saline, a solution of sodium chloride at 0.9% concentration, which is close to the concentration in the blood (isotonic). Ringer's lactate or Ringer's acetate is another isotonic solution often used for large-volume fluid replacement. A solution of 5% dextrose in water, sometimes called D5W, is often used instead if the patient is at risk for having low blood sugar or high sodium.

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 can be formulated to provide quick, sustained or delayed release of a mutant reovirus 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 can be found in Remington: The Science and Practice of Pharmacy (21th ed.) ed. David B. Troy, Lippincott Williams & Wilkins, 2005. For preparing solid compositions such as tablets, a mutant reovirus can be mixed with a pharmaceutical carrier to form a solid composition. Optionally, tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, a tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be 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 can be 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 and/or other agents 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 may contain suitable pharmaceutically acceptable excipients as described herein. Such compositions can be administered by the oral or nasal respiratory route for local or systemic effect. Compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent or intermittent positive pressure breathing machine.

Solution, suspension, or powder compositions may be administered, orally or nasally, from devices which deliver the formulation in an appropriate manner.

Another formulation that is optionally employed in the methods of the present disclosure includes transdermal delivery devices (e.g., patches). Such transdermal patches may be used to provide continuous or discontinuous infusion of a mutant reovirus as described herein. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, for example, U.S. Patent No. 5,023,252. Such patches can be constructed for continuous, pulsatile, or on-demand delivery of mutant reoviruses.

As described above, reoviruses and/or other agents are, if necessary, coated in a liposome or micelle to reduce or prevent an immune response in a mammal that has developed immunity toward a reovirus. Such compositions are referred to as immunoprotected reoviruses and/or agents. See, for example, U.S. Patent Nos. 6,565,831 and 7,014,847. In addition, a mutant reovirus as disclosed herein (e.g., one that lacks or is deficient in sigma3 polypeptide or function) can be proteolytically treated with an enzyme to remove or partially remove any of the other outer capsid proteins present.

In the provided methods, the reovirus is administered in a manner so that it can ultimately contact the target tumor or tumor cells, for example, systemically. The route by which the reovirus is administered, as well as the formulation, carrier or vehicle, depends on the location as well as the type of the target cells. A wide variety of administration routes can be employed. For example, for a solid tumor that is accessible, the reovirus can be administered by injection directly to the tumor. For a hematopoietic tumor, for example, the reovirus can be administered intravenously or intravascularly. For tumors that are not easily accessible within the body, such as metastases, the reovirus is administered in a manner such that it can be transported systemically through the body of the mammal and thereby reach the tumor (e.g., intravenously or intramuscularly). Alternatively, the reovirus can be administered directly to a single solid tumor, where it then is carried systemically through the body to metastases. The reovirus can also be administered subcutaneously, intraperitoneally, intrathecally (e.g., for brain tumor), topically (e.g., for melanoma), orally (e.g., for oral or esophageal cancer), rectally (e.g., for colorectal cancer), vaginally (e.g., for cervical or vaginal cancer), nasally, by inhalation spray or by aerosol formulation (e.g., for lung cancer).

Optionally, the virus is administered continuously to a subject at least once per day or up to throughout the day on consecutive days, for a period of time. Thus, the virus is administered, for example, to subjects by means of intravenous administration in any

pharmacologically acceptable solution, or as an infusion over a period of time. For example, the substance may be administered systemically by injection (e.g., IM or subcutaneously) or taken orally daily at least once per day, or administered by infusion in a manner that results in the daily delivery into the tissue or blood stream of the subject. When the virus is administered by infusion over a period of time, the period of time is, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, or 24 hours, or any time between 1 and 24 hours, inclusive, or more. Optionally, the period of time is 5, 15, 30, 60, 90, 120, 150 or 180 minutes, or any time between 5 and 180 minutes, inclusive, or more. Thus, for example, the virus is administered by infusion for 60 minutes or about 60 minutes. Administrations can be repeated daily for 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 21, 28 days or any number of days between 2 and 28 days, inclusive, or longer.

Therapeutic agents, such as the agents that inhibit production of pro-inflammatory cytokines, of the provided methods are also administered via a wide variety of administration routes. Thus, the agents are administered via any of several routes of administration, including, topically, orally, parenterally, intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally, intrahepatically, intracranially, nebulization/inhalation, or by instillation via bronchoscopy. Optionally, the therapeutic agents are administered continuously in the manner set forth in the description above with respect to oncolytic viruses. Thus, for example, the agent is administered, for example, to subjects by means of intravenous administration in any pharmacologically acceptable solution, or as an infusion over a period of time. Optionally, the agents are administered locally at or near the site of the tumor. Alternatively, the agents are administered systemically. The agents that inhibit pro-inflammatory cytokines are administered in an amount sufficient (i.e., an effective amount) to inhibit one or more pro-inflammatory cytokines. By way of example, effective amounts of platinum compounds include from about 5 to 1000 mg/m^2 of tumor volume, or any amount in between 5 and 1000 mg/m^2, inclusive, or more. Thus, for example effective amounts of cisplatin include from about 175-200 mg/m^2 and effective mounts for carboplatin include from about 100-600 mg/m^2. Effective amounts of other agents range from 0.001-10,000 mg/kg body weight or any amount in between 0.001 and 10,000 mg/kg body weight, inclusive. Optionally, effective amounts of platinum compounds include approximately 2 to 7 mg/mL minute (AUC) as calculated by the Calvert formula. Optionally, effective amounts of platinum compounds include approximately 5 or 6 mg/mL minute (AUC) as calculated by the Calvert formula. Optionally, the platinum compounds are administered as an intravenous infusion over a period of 30 minutes.

The reovirus 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 to proliferating cells affects lysis (e.g., oncolysis) of the affected cells, resulting in a reduction in the number of abnormally proliferating cells, a reduction in the size of a neoplasm, and/or a reduction in or elimination of symptoms (e.g., pain) associated with the proliferating disorder. As used herein, the term oncolysis means at least 10% of the proliferating cells are lysed (e.g., at least about 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 of lysis of cells *in vitro* (e.g., from a biopsy of the proliferating cells). An effective amount of a virus will be determined on an individual basis and may be based, at least in part, on the particular virus used; the individual's size, age, gender; and the size and other characteristics of the abnormally, proliferating cells. For example, for treatment of a human, approximately 10^3 to 10^{12} plaque forming units (PFU) of a virus are used, depending on the type, size and number of proliferating cells or neoplasms present. The effective amount can be, for example, 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). Optionally, the effective amount is about $1x10^8$ to about $1x10^{12}$ $TCID_{50}$. Optionally, the effective amount is about $1x10^{10}$ $TCID_{50}$.

By way of example, 5-6 mg/ml minute (AUC as calculated by the Calvert formula) of an agent that inhibits pro-inflammatory cytokines, such as carboplatin, is administered to the subject and $1x10^{10}$ $TCID_{50}$ to $3x10^{10}$ $TCID_{50}$ of a reovirus is administered to the subject. Optionally, the agent that inhibits pro-inflammatory cytokines is administered as a thirty minute to one hour intravenous infusion. Optionally, the reovirus is administered as a one hour intravenous infusion.

Optimal dosages of viruses and therapeutic agents and compositions comprising viruses and agents depend on a variety of factors. The exact amount required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the severity of the disease being treated, the particular virus or vector used and its mode of administration. Thus, it is not possible to specify an exact amount for every composition. However, an appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the guidance provided herein.

Effective dosages and schedules for administering the compositions may be determined empirically. For example, animal models for a variety of proliferative disorders can be obtained from The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609 USA. Both direct (e.g., histology of tumors) and functional measurements (e.g., survival of a subject or size of a tumor) can be used to monitor response to therapies. These methods involve the sacrifice of representative animals to evaluate the population, increasing the animal numbers necessary for the experiments. Measurement of luciferase activity in the tumor provides an alternative method to evaluate tumor volume without animal sacrifice and allowing longitudinal population-based analysis of therapy.

The dosage ranges for the administration of compositions are those large enough to produce the desired effect in which the symptoms of the disease are affected. The dosage should not be so large as to cause adverse side effects, such as unwanted cross-reactions and anaphylactic reactions. The dosage can be adjusted by the individual physician in the event of any counterindications.

Dosages vary and are administered in one or more dose administrations daily, for one or several days. The provided viruses and therapeutic agents are administered in a single dose or in multiple doses (e.g., two, three, four, six, or more doses). For example, where the administration is by infusion, the infusion can be a single sustained dose or can be delivered by multiple infusions. Treatment may last from several days to several months or until diminution of the disease is achieved.

Combinations of the provided viruses and therapeutic agents are administered either concomitantly (e.g., as an admixture), separately but simultaneously (e.g., via separate intravenous lines into the same subject), or sequentially (e.g., one of the compounds or agents is given first followed by the second). Thus, the term combination is used to refer to concomitant, simultaneous, or sequential administration of two or more agents. By way of example, the agent that inhibits proinflammatory cytokines is administered prior to or at the same time as the oncolytic virus. When one compound is administered prior to another compound, the first compound is administered minutes, hours, days, or weeks prior to administration of the second compound. For example, the first compound can be administered at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, or 72 hours, or any time between 1 and 72 hours, inclusive, prior to administration of a second compound. Optionally, the first compound is administered more than 72 hours prior to the second compound. By way of another example, the first compound can be administered at 1, 5, 15, 30, 60, 90, or 120 minutes, or any time between 1 and 120

minutes, inclusive, prior to administration of a second compound. Optionally, the first compound is administered at 1, 2, 3, 4, 5, 6, 7, 14, 21, or 28 days, or any amount in between 1 and 28, inclusive, days prior to administration of the second compound. Optionally, the first compound is administered more than 28 days prior to the second compound. For example, the agent that inhibits proinflammatory cytokines is administered from about 1 to 8 hours prior to administration of the oncolytic virus. By way of another example, the agent that inhibits pro-inflammatory cytokines is administered at a time of about one hour prior to administration of the oncolytic virus.

By way of example, one cycle of treatment includes administering the agent that inhibits proinflammatory cytokines and the oncolytic virus includes on day 1. On days 2, 3, 4 and 5, only the oncolytic virus is administered to the subject. Optionally, the subject receives multiple cycles of treatment, for example, two, three, four, five or more cycles of treatment.

Reoviruses or a pharmaceutical composition comprising such reoviruses are optionally packaged into a kit. The kit also includes one or more agents or pharmaceutical compositions comprising such agents that inhibit pro-inflammatory cytokines. It is contemplated that a kit, optionally, also includes one or more chemotherapeutic agents, one or more immunosuppressive agents, and/or one or more anti-antireovirus antibodies. A pharmaceutical composition can be 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 mutant reovirus calculated to produce the desired therapeutic effect in association with a suitable pharmaceutically acceptable carrier.

It is contemplated that the provided methods may be combined with other tumor therapies such as chemotherapy, radiotherapy, surgery, hormone therapy and/or immunotherapy. Thus, the oncolytic virus may be administered in conjunction with surgery or removal of the neoplasm. Therefore, provided herewith are methods for the treatment of a solid neoplasm comprising surgical removal of the neoplasm and administration of an oncolytic virus at or near to the site of the neoplasm.

It is further contemplated that the compositions in the provided methods are, optionally, administered in conjunction with or in addition to known anticancer compounds or chemotherapeutic agents. Chemotherapeutic agents are compounds which may inhibit the growth of tumors. Such agents, include, but are not limited to. 5-fluorouracil, mitomycin C, methotrexate, hydroxyurea, cyclophosphamide, dacarbazine, mitoxantrone, anthracyclins (Epirubicin and Doxurubicin), antibodies to receptors, such

as herceptin, etopside, pregnasome, hormone therapies such as tamoxifen and anti-estrogens, interferons, aromatase inhibitors, progestational agents and LHRH analogs.

As used herein the terms treatment, treat, treating or ameliorating refers to a method of reducing the effects of a disease or condition or symptom of the disease or condition. Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% reduction or amelioration in the severity of an established disease or condition or symptom of the disease or condition. For example, the method for treating cancer is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to control. Thus the reduction can be a 10, 20, 30, 40, 50, 60, 70, 80, 90, 100% or any percent reduction in between 10 and 100 as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition or symptoms of the disease or condition.

As used herein, references to decreasing, reducing, or inhibiting include a change of 10, 20, 30, 40, 50 ,60, 70 ,80, 90 percent or greater as compared to a control level. Such terms can include but do not necessarily include complete elimination.

As used herein, the term subject can be a vertebrate, more specifically a mammal (e.g., a human, horse, pig, rabbit, dog, sheep, goat, non-human primate, cow, cat, guinea pig or rodent), a fish, a bird or a reptile or an amphibian. The term does not denote a particular age or sex. Thus, adult and newborn subjects, whether male or female, are intended to be covered. As used herein, patient or subject may be used interchangeably and can refer to a subject with a disease or disorder. The term patient or subject includes human and veterinary subjects.

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 methods 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 an inhibitor is disclosed and discussed and a number of modifications that can be made to a number of molecules including the inhibitor are discussed, each and every combination and permutation of the inhibitor, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept

applies to all aspects of this disclosure including, but not limited to, steps in methods of using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application.

A number of aspects have been described. Nevertheless, it will be understood that various modifications may be made. Furthermore, when one characteristic or step is described it can be combined with any other characteristic or step herein even if the combination is not explicitly stated. Accordingly, other aspects are within the scope of the claims.

Examples

Example 1. Anti-tumor Activity of Reovirus and Cisplatin in Mouse Melanoma Model.

Reovirus type 3 Dearing (RV) has demonstrated oncolytic activity in numerous *in vitro* systems, *in vivo* murine models and early clinical trials. To further these studies, the *in vitro* and *in vivo* oncolytic activity of RV in combination with cisplatin (CP), a pseudoalkylating chemotherapeutic which causes DNA cross-linking and is active in a wide range of cancers, was examined. The effect of RV and CP was assessed *in vitro* for synergistic tumor kill and mechanism of tumor death. A synergistic interaction (combination index value (CIV) of less than one) was observed between RV and CP (CIV: ED50, 0.42±0.03; ED75, 0.30±0.02; ED90, 0.24±0.01) on B16.F10 cells. Flow cytometric analysis showed a marked increase in apoptotic cells following combined exposure, compared to single agent exposure.

For *in vivo* evaluation, subcutaneous B16.F10 tumors in C57Bl/6 mice or K1735 tumors in C3H mice were treated with intratumoral (i.t.) RV and intraperitoneal (i.p.) CP either alone or in combination. Tumor volume was estimated thrice weekly. Tumors and organs were harvested post-treatment for viral retrieval and histology; serum samples were tested for cytokine production and induction of neutralising anti-reovirus antibody (NARA). Figures 1A, 1B, 1C and 1D show reduced tumor growth and increased survival following reovirus/cisplatin combination therapy. C57Bl/6 (Figures 1A and 1C) and C3H (Figures 1B and 1D) mice bearing subcutaneous B16.F10 and K1735 tumors respectively

were treated on days 1 and 4 with either reovirus alone i.t. (squares), cisplatin alone i.p. (triangles), or reovirus and cisplatin in combination (circles). Control treated mice (diamonds) received PBS. Tumors were measured on the days indicated and tumor volume expressed as tumor volume relative to volume at commencement of treatment (Figures 1A and 1B). Mice were euthanized when tumors exceeded 15mm in any one dimension. Survival is expressed as Kaplan-Myer plots (Figures 1C and 1D). These data show reduced tumor growth and extended median survival time was observed in mice treated with RV/CP combination therapy compare to single agent treatments (Figures 1A, 1B, 1C and 1D). Mean relative tumor volumes ±SD at day 12 were, control: all reached endpoint, RV alone: 8.92±6.94, CP alone: 9.87±2.80, RV plus CP: 3.86±2.24. Median survival (days) were, control: 6, RV: 12, CP: 8, combination of RV and CP: 17. Live virus was recovered from the tumors of all RV only treated animals and from the liver and heart of 1/6 mice. In contrast live virus was detected in only 50% of tumors from combination treated mice but in the liver of 4/6 mice. CP did not affect the neutralizing anti-reovirus antibody (NARA) response to RV (Figure 2), but caused a marked attenuation of production of proinflammatory cytokines to RV when used in combination (Figures 3A, 3B, 3C, 3D, 3E, 3F, and 3G).

Taken together, these results show that the addition of chemotherapeutic agents can significantly enhance the anti-tumor efficacy of RV therapy. Furthermore, a reduction in viral inflammatory responses in vital organs by concomitant chemotherapy may allow more intensive dosing schedules to increase overall efficacy of the reovirus.

Example 2. Reovirus and Carboplatin Protocols for Humans.

This is a study design of reovirus given intravenously with carboplatin every 3 weeks.

Carboplatin is administered as a 30 minute intravenous infusion at a dose calculated by the Calvert formula (AUC 5 mg/mL minute or 6 mg/mL minute with GFR measured by 51Cr EDTA). Reovirus is then administered as a 1 hour intravenous infusion at a dose of $1x10^{10}$ or $3x10^{10}$ $TCID_{50}$.

On days 2 through 5, only reovirus will be administered, using the same dose and method as used on Day 1.

Table 2 - Dosing Methods

	Carboplatin Dose AUC mg/mL min Day 1 only	Reovirus dose ($TCID_{50}$) Days 1 - 5
Method 1	5	$1x10^{10}$
Method 2	5	$3x10^{10}$
Method 3	6	$1x10^{10}$
Method 4	6	$3x10^{10}$

WHAT IS CLAIMED IS:

1. Use of one or more reoviruses and

one or more platinum compounds that inhibit expression or activity of a pro-inflammatory cytokine but do not inhibit production of neutralizing anti-reovirus antibodies (NARA) in the manufacture of a medicament for treating a proliferative disorder in a subject.

2. The use of claim 1, wherein approximately 10^3 to 10^{12} plaque forming units (PFU) of the oncolytic virus is to be administered to the subject.

3. The use of claim 2, wherein approximately 10^8 to 10^{12} plaque forming units (PFU) of the oncolytic virus is to be administered to the subject.

4. The use of claim 1, wherein approximately 10^8 to 10^{12} $TCID_{50}$ of the oncolytic virus is to be administered to the subject.

5. The use of claim 1, wherein approximately 5 to 1000 mg/m^2 of the agent that inhibits proinflammatory cytokines is to be administered to the subject.

6. The use of claim 1, wherein approximately 0.001-10,000 mg/kg body weight of the agent that inhibits proinflammatory cytokines is to be administered to the subject.

7. The use of claim 1, wherein 2 to 7 mg/mL minute (AUC) of the agent that inhibits proinflammatory cytokines is to be administered to the subject.

8. The use of claim 1, wherein the platinum compound is selected from the group consisting of cisplatin, carboplatin and oxaliplatin.

9. The use of claim 8, wherein approximately 175-200 mg/m^2 of the cisplatin is to be administered to the subject.

10. The use of claim 8, wherein approximately 200-600 mg/m^2 of the carboplatin is to be administered to the subject.

11. The use of claim 8, wherein 5 or 6 mg/mL minute (AUC) of the carboplatin is to be administered to the subject.

12. The use of any one of claims 1-11, wherein the reovirus is a mammalian reovirus or a human reovirus.

13. The use of claim 12, wherein the human reovirus is selected from the group consisting of serotype 1 reovirus, serotype 2 reovirus and serotype 3 reovirus.

14. The use of claim 12, wherein the human reovirus is serotype 3 reovirus.

15. The use of claim 12, wherein the human reovirus has IDAC Accession No. 190907-01.

16. The use of any one of claims 1-11, wherein the agent that inhibits pro-inflammatory cytokines is to be administered at the same time, before or after the reovirus.

17. The use of claim 16, wherein the agent that inhibits pro-inflammatory cytokines is to be administered at the same time as the reovirus.

18. The use of claim 16, wherein the agent that inhibits pro-inflammatory cytokines is to be administered before the reovirus.

19. The use of claim 18, wherein the agent is to be administered from 1 to 12 hours before the oncolytic virus.

20. The use of claim 18, wherein the agent is to be administered from 1 to 60 minutes before the oncolytic virus.

21. The use of claim 1, wherein the reovirus is to be administered in multiple doses.

22. The use of claim 21, wherein the agent that inhibits pro-inflammatory cytokines is to be administered once.

23. The use of claim 21, wherein the agent that inhibits pro-inflammatory cytokines is to be administered in multiple doses.

SEQUENCE LISTING

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<120> ABROGATING PROINFLAMMATORY CYTOKINE PRODUCTION DURING ONCOLYTIC REOVIRUS THERAPY

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

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<210> SEQ ID NO:5
<211> 2304
<212> DNA
<213> Reovirus

<400> SEQ ID NO:5
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<211> 2204
<212> DNA
<213> Reovirus

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<210> SEQ ID NO:7
<211> 2241
<212> DNA
<213> Reovirus

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<210> SEQ ID NO:8
<211> 3854
<212> DNA
<213> Reovirus

<400> SEQ ID NO:8
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<211> 3916
<212> DNA
<213> Reovirus

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<210> SEQ ID NO:10
<211> 3901
<212> DNA
<213> Reovirus

<400> SEQ ID NO:10
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c 3901

<210> SEQ ID NO:11
<211> 455
<212> PRT
<213> Reovirus

<400> SEQ ID NO:11

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

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


<210> SEQ ID NO:12
<211> 418
<212> PRT
<213> Reovirus

<400> SEQ ID NO:12
Met Ala Arg Ala Ala Phe Leu Phe Lys Thr Val Gly Phe Gly Gly Leu
 1               5                  10                  15
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                 250                 255
Leu Asn His Ser Ala Gln Ile Arg Pro Gly Asn Arg Ser Leu Phe Val
            260                 265                 270
Met Pro Thr Ser Pro Asp Trp Asn Met Asp Val Asn Leu Ile Leu Ser
        275                 280                 285
Ser Thr Leu Thr Gly Cys Leu Cys Ser Gly Ser Gln Leu Pro Leu Ile
    290                 295                 300
Asp Asn Asn Ser Val Pro Ala Val Ser Arg Asn Ile His Gly Trp Thr
305                 310                 315                 320
Gly Arg Ala Gly Asn Gln Leu His Gly Phe Gln Val Arg Arg Met Val
                325                 330                 335
Thr Glu Phe Cys Asp Arg Leu Arg Arg Asp Gly Val Met Thr Gln Ala
            340                 345                 350
Gln Gln Asn Gln Val Glu Ala Leu Ala Asp Gln Thr Gln Gln Phe Lys
        355                 360                 365
Arg Asp Lys Leu Glu Thr Trp Ala Arg Glu Asp Asp Gln Tyr Asn Gln
    370                 375                 380
Ala His Pro Asn Ser Thr Met Phe Arg Thr Lys Pro Phe Thr Asn Ala
385                 390                 395                 400
Gln Trp Gly Arg Gly Asn Thr Gly Ala Thr Ser Ala Ala Ile Ala Ala
                405                 410                 415
Leu Ile
```

<210> SEQ ID NO:13
<211> 254
<212> PRT
<213> Reovirus

<400> SEQ ID NO:13

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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
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> SEQ ID NO:14
<211> 366
<212> PRT
<213> Reovirus

<400> SEQ ID NO:14

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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 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


<210> SEQ ID NO:15
<211> 365
<212> PRT
<213> Reovirus

<400> SEQ ID NO:15
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


<210> SEQ ID NO:16
```

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

<400> SEQ ID NO:16

```
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
    450                 455                 460
Lys Gly Ile Ala Gly Val Asp Ser Leu Asp Asp Leu Ile Lys Trp Val
465                 470                 475                 480
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                 560
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                 640
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                 720
Arg Gly Ala Ala Tyr Ser Ala Arg Leu Ala Phe Arg Ser Asp Leu Ala
                725                 730                 735
```

<210> SEQ ID NO:17
<211> 708
<212> PRT
<213> Reovirus

<400> SEQ ID NO: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
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
        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> SEQ ID NO:18
<211> 721
<212> PRT
<213> Reovirus

<400> SEQ ID NO: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
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> SEQ ID NO:19
<211> 1267
<212> PRT
<213> Reovirus

<400> SEQ ID NO:19

```
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 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
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
900 905 910
Trp Met Val Ala Asn Gly Tyr Val Thr Asp Arg Cys Ser Pro Val Phe
915 920 925
Gly Asn Ala Asp Tyr Arg Arg Cys Phe Asn Glu Leu Lys Leu Tyr Gln
930 935 940
Gly Tyr Tyr Met Ala Gln Leu Pro Arg Asn Pro Lys Lys Ser Gly Arg
945 950 955 960
Ala Ala Pro Arg Glu Val Arg Glu Gln Phe Thr Gln Ala Leu Ser Asp
965 970 975
Tyr Leu Leu Gln Asn Pro Glu Leu Lys Ser Arg Val Leu Arg Gly Arg
980 985 990
Ser Glu Trp Glu Lys Tyr Gly Ala Gly Ile Ile His Asn Pro Pro Ser
995 1000 1005
Leu Phe Asp Val Pro His Lys Trp Tyr Gln Gly Ala Gln Glu Ala Ala
1010 1015 1020
Ile Ala Thr Arg Glu Glu Leu Ala Glu Met Asp Glu Thr Leu Met Arg
1025 1030 1035 1040
Ala Arg Arg His Arg Tyr Ser Ser Phe Ser Lys Leu Leu Glu Ala Tyr
1045 1050 1055
Leu Leu Val Lys Trp Arg Met Cys Glu Ala Arg Glu Pro Ser Val Asp
1060 1065 1070
Leu Arg Leu Pro Leu Cys Ala Gly Ile Asp Pro Leu Asn Ser Asp Pro
1075 1080 1085
Phe Leu Lys Met Val Ser Val Gly Pro Met Leu Gln Ser Thr Arg Lys
1090 1095 1100
Tyr Phe Ala Gln Thr Leu Phe Met Ala Lys Thr Val Ser Gly Leu Asp
1105 1110 1115 1120
Val Asn Ala Ile Asp Ser Ala Leu Leu Arg Leu Arg Thr Leu Gly Ala
1125 1130 1135
Asp Lys Lys Ala Leu Thr Ala Gln Leu Leu Met Val Gly Leu Gln Glu
1140 1145 1150
Ser Glu Ala Asp Ala Leu Ala Gly Lys Ile Met Leu Gln Asp Val Asn
1155 1160 1165
Thr Val Gln Leu Ala Arg Val Val Asn Leu Ala Val Pro Asp Thr Trp
1170 1175 1180
Met Ser Leu Asp Phe Asp Ser Met Phe Lys His His Val Lys Leu Leu
1185 1190 1195 1200
Pro Lys Asp Gly Arg His Leu Asn Thr Asp Ile Pro Pro Arg Met Gly
1205 1210 1215
Trp Leu Arg Ala Ile Leu Arg Phe Leu Gly Ala Gly Met Val Met Thr
1220 1225 1230
Ala Thr Gly Val Ala Val Asp Ile Tyr Leu Glu Asp Ile His Gly Gly
1235 1240 1245
Gly Arg Ser Leu Gly Gln Arg Phe Met Thr Trp Met Arg Gln Glu Gly
1250 1255 1260
Arg Ser Ala
1265

<210> SEQ ID NO:20
<211> 1289
<212> PRT
<213> Reovirus

<400> SEQ ID NO: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
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 Phe 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
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
660 665 670
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
820 825 830
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
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
1250 1255 1260
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
1285

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<213> Reovirus

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20 25 30
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

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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
                85                  90                  95
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
        115                 120                 125
Asn Ala Asn Glu Leu Ser Arg Ser Gly Asn Val Asp Asn Glu Gly Gly
    130                 135                 140
Ser Asn Gln Lys Pro Met Ser Thr Arg Ile Ala Glu Ala Thr Ser Ala
145                 150                 155                 160
Ile Val Ser Lys His Pro Ala Arg Val Gly Leu Pro Pro Thr Ala Ser
                165                 170                 175
Ser Gly His Gly Tyr Gln Cys His Val Cys Ser Ala Val Leu Phe Ser
            180                 185                 190
Pro Leu Asp Leu Asp Ala His Val Ala Ser His Gly Leu His Gly Asn
        195                 200                 205
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
                245                 250                 255
Thr Trp Asp Ala Gly Leu Cys Thr Ser Phe Lys Ile Val Pro Ile Val
            260                 265                 270
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                 470                 475                 480
Trp Ala Leu Thr Glu Cys Ala Gln Gly Tyr Val Thr Val Thr Ser Pro
                485                 490                 495
Tyr Ala Pro Ser Val Asn Arg Leu Met Pro Tyr Arg Ile Ser Asn Ala
            500                 505                 510
Glu Arg Gln Ile Ser Gln Ile Ile Arg Ile Met Asn Ile Gly Asn Asn
        515                 520                 525
Ala Thr Val Ile Gln Pro Val Leu Gln Asp Ile Ser Val Leu Leu Gln
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    530                 535                 540
Arg Ile Ser Pro Leu Gln Ile Asp Pro Thr Ile Ile Ser Asn Thr Met
545                 550                 555                 560
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
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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
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
Pro Pro Ile Thr Ala Val Val Met Gly Val Pro
1265                1270                1275
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