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(54) Title: NOVEL MYXOMA GENES FOR IMMUNE MODULATION

(57) Abstract: The present invention provides novel genes of the viral genus leporipox that encode novel immunomodulatory proteins. The present invention also provides therapeutic compositions containing these novel polypeptides and methods for use for treating a variety of inflammatory and autoimmune disorders. In one preferred embodiment, the present invention provides methods for producing the novel immunomodulatory polypeptides in a substantially pure form. In another preferred embodiment, the invention provides methods for treating individuals diagnosed with autoimmune or inflammatory disorders by gene therapy. In yet another preferred embodiment, the methods and compositions of the present invention may be used to treat cancer. Finally, the invention provides methods to identify and isolate additional leporipox virus immunomodulatory polypeptides.



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NOVEL MYXOMA GENES FOR IMMUNE MODULATION

FIELD OF THE INVENTION

This invention relates generally to the field of immunology and specifically to novel viral genes and proteins and methods for use of the same as immune modulators.

BACKGROUND OF THE INVENTION

5 Viruses propagate by living within cells of higher-order vertebrates. Accordingly, they have evolved to specifically avoid the host immune system. In fact, virus survival is dependent upon strategies which can evade, suppress, counteract, or otherwise circumvent the myriad of host responses to a foreign invader. The selective
10 pressure conferred by the effector elements of the immune system of the host can clearly be a powerful element of evolutionary pressure; in fact all eukaryotic viruses existing today contain imprints or remnants of their battles with the immune system as evidenced by the presence of encoded proteins that suppress the immune system or as evidenced by survival strategies that allow the virus to evade immune system
15 detection.

The specific strategy or strategies used by a virus varies dramatically according to its genome capacity. Viruses with small genomes ensure their survival by exploiting weaknesses or gaps in the host immune repertoire to evade detection. Alternatively, the smaller genome replicates very rapidly, effectively outpacing the
20 immune response. The larger DNA viruses (*i.e.* the adenoviruses, herpesviruses, iridoviruses and poxviruses) specifically encode proteins that function to protect the virus from immune recognition and/or clearance by the infected host. Such “subversive” viral proteins are useful therapeutics for the treatment of inflammatory and auto-immune disorders.

Recent studies on the myxoma virus, a virus of the genus *leporipox*, which also includes Shope Fibroma virus, have shown that these viruses are among those that disrupt the immune system by a variety of strategies. Myxoma virus is the infectious agent of a virulent systemic disease of domestic rabbits called myxomatosis.

5 Originally described in the last century, myxoma was the first viral pathogen discovered for a laboratory animal and was the first viral agent ever deliberately introduced into the environment for the explicit purpose of pest eradication. Since its release into the Australian and European feral rabbit populations more than 40 years ago, the field strains of both the rabbit and virus have been subjected to mutual
10 evolutionary and selective pressures that have resulted in a steady-state enzootic in the inoculated areas (Fenner, F. and Ratcliffe, F.N., "Myxomatosis," *Cambridge University Press*, London, 1965).

Myxoma shares many of the biological features associated with poxviruses, namely cytoplasmic location of replication and a large double stranded 160 kilobase
15 DNA genome. Multiple lines of evidence indicate that myxoma, like poxviruses, encodes multiple gene products whose function is to permit the spread and propagation of the virus in a variety of host tissues. Some of these viral proteins interact with known components of the host's immune system or interfere with intracellular signal transduction to specifically counteract or subvert the development
20 of the host inflammatory response and acquired cellular immunity. Poxviruses in general have been a rich source of such immunomodulatory proteins.

Examples of such immunomodulatory gene products include myxoma growth factor (MGF), which stimulates neighboring cells in a paracrine-like fashion via the cellular epidermal growth factor receptor; Serp 1, a secreted glycoprotein with serine
25 protease inhibitor activity that prevents development of the early inflammatory response; T1, a soluble scavenger of CC chemokines that plays a central role in the host defense against virus infection; T7, a secreted viral homologue of the cellular interferon- γ receptor, that binds and inhibits rabbit interferon- γ ; and M11L, a surface

receptor-like protein that interferes within the inflammatory response by an unknown mechanism. The SERP-1 protein has been used successfully as an anti-inflammatory agent.

Host and viral immunomodulatory proteins include chemotactic cytokines, called "chemokines." Chemokines are small molecular weight immune ligands that are chemoattractants for leukocytes, such as neutrophils, basophils, monocytes, and T cells. There are two major classes of chemokines, both of which contain four conserved cysteine residues that form disulfide bonds in the tertiary structure of the proteins. The α class is designated C-X-C (where X is any amino acid), and includes Il-8, CTAP-III, gro/MGSA and ENA-78; and the β class, designated C-C, includes MCP-1, MIP-1 α and β , and Regulated on Activation, Normal T Expressed and Secreted protein (RANTES). The designations of the classes are according to whether an intervening residue spaces the first two cysteines in the motif. In general, most C-X-C chemokines are chemoattractants for neutrophils, but not monocytes, whereas C-C chemokines appear to attract monocytes, but not neutrophils. Recently, a third group of chemokines, the "C" group, was designated by the discovery of a new protein called lymphotactin. The chemokine family is believed to be critically important in the infiltration of lymphocytes and monocytes into sites of inflammation.

Both the host and virus may also encode a class of proteins that regulate apoptosis (or cell death). The relationship between viruses and apoptosis is complex, in part because all viruses are faced with the need to first productively replicate within a receptive intracellular environment, then to spread to other cells or tissues, and finally to seek out new hosts in order to continue the chain of propagation. Thus, there are times when the premature induction of apoptosis can be detrimental to the virus, for example, by disrupting the viral replicative life cycle, while at other times apoptosis can become advantageous, for example, by facilitating virus dissemination and secondary infection of phagocytes or other immune cells. As viruses have

acquired mechanisms to evade the host's immune system, viruses have collectively evolved strategies to either inhibit or stimulate apoptosis, depending on the particular virus/host interaction.

There exists a need for new drugs that are useful for the treatment of human inflammatory and autoimmune disorders. Identification of novel immunomodulatory agents may reveal new pharmaceuticals that can be used to suppress inflammation and dysregulation of the immune system. In addition, novel agents provide new probes and targets that can be used to identify novel elements of the cellular immune repertoire and new classes of drugs. Such tools may promote understanding of the molecular mechanisms by which viral immunomodulators function and may reveal targets for pharmacological intervention that could be of substantial benefit in treating these diseases.

SUMMARY OF THE INVENTION

In general the present invention provides novel nucleic acids encoding novel immunomodulatory proteins that may be used as therapeutic immunomodulatory proteins for the treatment of a variety of immunomodulatory disorders.

In one aspect, the invention provides a substantially pure *leporipox* virus immunomodulatory polypeptide, that may be derived from, for example, myxoma virus or Shope fibroma virus. In preferred embodiments, the polypeptide can encode a chemokine, a cytokine (*e.g.* SEQ ID NO:32), an immunomodulator, an anti-inflammatory polypeptide, an immunoreceptor, or multi-transmembrane receptor protein, or have an identifiable signal sequence. In other preferred embodiments, the polypeptide can include an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40.

In another aspect, the invention provides a substantially pure *leporipox* virus nucleic acid molecule (for example, genomic DNA, cDNA, or synthetic DNA, or mRNA) comprising a sequence encoding a *leporipox* virus polypeptide, *e.g.*, a myxoma virus polypeptide or a Shope fibroma virus polypeptide. In a preferred embodiment, the nucleic acid molecule encodes a polypeptide including an amino acid sequence that is substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40. In other preferred embodiments, the nucleic acid molecule can be genomic DNA, cDNA, and mRNA. In other preferred embodiments, the nucleic acid molecule can encode a polypeptide with an identifiable signal sequence, a chemokine, a cytokine (*e.g.*, (SEQ ID NO: 32), an immunomodulator, an anti-inflammatory polypeptide, an immunoreceptor, or a multi-transmembrane receptor protein.

The invention also provides a vector (*e.g.*, a gene therapy vector) including the *leporipox* virus nucleic acid molecule; a cell (*e.g.*, a bacterial, yeast, nematode, or mammalian cell, such as a human cell or a rodent cell), that may include the vector; a non-human transgenic animal including the *leporipox* virus nucleic acid molecule; a non-human transgenic animal having a knockout mutation in one or both alleles encoding a polypeptide substantially identical to a *leporipox* virus polypeptide; and a cell from the non-human transgenic animals. In a preferred embodiment, the nucleic acid molecule of the vector is operably linked to regulatory sequences, including a promoter, for expression of a *leporipox* virus polypeptide. The promoter can be the promoter native to the *leporipox* gene. In addition, transcriptional and translational regulatory regions are preferably native to a *leporipox* gene. A constitutive promoter

or an inducible promoter is also included in the invention. In related aspects, the invention features substantially pure nucleic acid encoding truncated and augmented leporipox polypeptides substantially identical to those described in Figures 21-40.

In related aspects, the invention features a transgenic animal containing a transgene which encodes a leporipox virus polypeptide and methods of using the leporipox virus nucleotide sequence to engineer a transgenic animal having a knockout mutation in the leporipox gene. For example, the invention provides transgenic animals having a loss of function mutation in a gene substantially identical to a leporipox virus polypeptide. In a preferred embodiment of the present invention, the loss of function mutation is in any of the genes of Figures 1-20 that encode the proteins of Figures 21-40. The invention also features a cell that expresses a leporipox virus gene (*i.e.*, a transgenic cell). In various embodiments, the cell is a transformed animal cell.

In other related aspects, the cell that expresses a leporipox virus gene is present in a patient needing treatment in the form of immunomodulation (*e.g.*, immunosuppression or immunostimulation). Alternatively, the patient is experiencing any of a wide variety of inflammatory or autoimmune disorders (*e.g.*, an allergic reaction, acute inflammation, rheumatoid arthritis transplant rejection, restenosis, asthma, uveitis or inflammatory bowel disease).

In another aspect, the invention provides a nucleic acid molecule having at least 50% nucleotide sequence identity to a sequence encoding a *leporipox* virus polypeptide or fragment thereof, where the fragment includes at least six amino acids, and the nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule. In a preferred embodiment, the nucleic acid molecule has 100% complementarity to a nucleotide sequence encoding a *leporipox* virus polypeptide or fragment thereof, where the fragment includes at least six amino acids, and the nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.

In another aspect, the invention provides a nucleic acid molecule that includes a sequence that is antisense to the coding strand of a *leporipox* virus nucleic acid molecule or a fragment thereof.

5 In another aspect, the invention provides an antibody that specifically binds to a *leporipox* virus polypeptide. In a preferred embodiment of this aspect, the polypeptide comprises an amino acid sequence that is substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40. In another aspect, the invention features a purified antibody that binds specifically to a murine or human *leporipox* protein. Such an antibody may be used in any standard immunodetection method for the identification of a *leporipox* polypeptide. Such an antibody may also be used to inhibit *leporipox* protein function and to predict prognosis following tumor diagnosis. In various embodiments, the antibody may be an intact monoclonal or polyclonal antibody, but may also be an immunologically-active antibody fragment, such as an Fab' or (Fab')₂ fragment, or a genetically engineered Fv fragment (see USPN 4,946,788, hereby incorporated by reference). In another aspect, the invention provides a method of detecting a *leporipox* virus polypeptide in a sample, by contacting the sample with the antibody of the invention, and assaying for the binding of the antibody to the polypeptide.

25 In another aspect, the invention provides a probe for analyzing a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof, the probe having at least 50% nucleotide sequence identity to a sequence encoding a *leporipox* virus polypeptide or fragment thereof, where the fragment includes at least six amino acids, and the probe hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule. In a preferred embodiment of this aspect, the probe has 100% complementarity to a nucleic acid molecule encoding a *leporipox*

virus polypeptide or fragment thereof, where the fragment includes at least six amino acids, and the probe hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.

In another aspect, the invention provides a method of detecting a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof in a cell, by contacting a *leporipox* virus nucleic acid molecule or a fragment thereof, where the fragment is greater than about 18 nucleotides in length, with a preparation of genomic DNA from said cell, under hybridization conditions providing detection of DNA sequences having about 50% or greater nucleotide sequence identity to a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20.

In another aspect, the invention provides a method of identifying a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof by providing a mammalian cell sample; introducing by transformation into the cell sample a candidate gene; expressing the candidate gene within the cell sample; and determining whether the sample elicits an altered level of immune function, where an alteration in the level of immune function identifies a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof.

In another aspect, the invention provides a method of identifying a test compound that modulates the expression or activity of a *leporipox* virus polypeptide, by contacting said *leporipox* virus polypeptide with the test compound, and determining the effect of the test compound on the *leporipox* virus polypeptide.

In another aspect, the invention provides a method of targeting proteins for secretion from a cell, by attaching an identifiable signal sequence selected from a *leporipox* virus polypeptide to a protein of interest, such that protein of interest is secreted from said cell.

In another aspect, the invention provides a method of immunomodulation in a mammal, by administering to the mammal a therapeutically effective amount of a *leporipox* virus polypeptide or fragment thereof, where the polypeptide has an immunomodulatory effect in the mammal. In another aspect, the invention features a method of immunomodulation wherein the method involves: (a) providing the *leporipox* virus gene under the control of a promoter providing controllable expression of the *leporipox* virus gene in a cell wherein the *leporipox* virus gene is expressed in a construct capable of delivering a *leporipox* protein in an amount effective to decrease inflammation or inhibit autoimmune reaction. The polypeptide may also be provided directly, for example, in cell culture, for therapeutic uses. In preferred embodiments, *leporipox* virus polypeptide is delivered by expression of the *leporipox* virus gene using a tissue-specific or cell type-specific promoter, or by a promoter that is activated by the introduction of an external signal or agent, such as a chemical signal or agent. In preferred embodiments, the method is used for improving prognosis in patients with tumors. The method includes providing a *leporipox* virus protein that acts as an inducer of apoptosis in the region of the tumor either by providing an effective amount of the polypeptide or by providing an effective amount of a transgene expressing the polypeptide. In one such embodiment the tumor is a solid tumor, *e.g.* lymphoma (*e.g.*, Hodgkin's), plasmacytoma, carcinoma (*e.g.*, gastric, colonic, and lung carcinomas), melanoma, and sarcoma.

In another aspect, the invention features a recombinant polypeptide capable of mediating immunomodulatory events wherein the polypeptide includes a domain having a sequence which has at least 80% identity to at least one of the sequences of Figures 21-40. More preferably, the region of identity is 90% or greater; most preferably the region of identity is 95% or greater.

In another aspect, the invention provides a method of immunomodulation in a mammal, by administering to said mammal a therapeutically effective amount of a compound that modulates the activity of a *leporipox* virus polypeptide, where the compound has an immunomodulatory effect in said mammal.

In another aspect, the invention provides a method of treating a mammal having an immunomodulatory disorder, by administering to the mammal a therapeutically effective amount of a compound that modulates the activity of a *leporipox* virus polypeptide, where the compound has an immunomodulatory effect in said mammal. In other aspects, the invention provides a method for modulating cell (e.g., a mammalian cell) proliferation or apoptosis by administering to the cell a *leporipox* virus polypeptide or a compound that modulates the activity of a *leporipox* virus polypeptide (e.g., a chemical, a drug, or an antibody that specifically binds the *leporipox* virus polypeptide and neutralizes the polypeptide's activity). In related aspects, the present invention provides a method for treating AIDS, cirrhosis of the liver, neurodegeneration, myelodysplastic syndrome or ischemic injury by administration of a *leporipox* virus polypeptide with apoptotic activity.

In another aspect, the invention provides a pharmaceutical composition including at least one dose of a therapeutically effective amount of a *leporipox* virus polypeptide or fragment thereof, in a pharmaceutically acceptable carrier, the composition being formulated for the treatment of an immunomodulatory disorder.

In preferred embodiments of some of the above aspects, the *leporipox* virus polypeptide includes an amino acid sequence substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40, and fragments and analogs thereof.

In other preferred embodiments of some of the above aspects, the immunomodulation includes immunosuppression, immunostimulation, cell proliferation, apoptosis, decreasing T cell stimulation, or decreasing inflammation in a mammal (e.g., a human). The mammal may be diagnosed with a tumor (e.g., a carcinoma, a plasmacytoma, a lymphoma, or a sarcoma).

In other preferred embodiments of some of the above aspects, the *leporipox* virus polypeptide is a multi-transmembrane receptor related protein or includes an amino acid sequence substantially identical to the sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40 and fragments and
5 analogs thereof.

In other preferred embodiments of some of the above aspects, the mammal has a condition selected from the group consisting of acute inflammation, rheumatoid arthritis, transplant rejection, restenosis, asthma, allergies, inflammatory bowel disease, uveitis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis, systemic
10 lupus erythematosus, nephrotic syndrome lupus, multiple sclerosis, myasthenia gravis, type I and type II diabetes mellitus, glomerulonephritis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, microbial infection, malignancy and metastasis, autoimmune disease, cirrhosis, endotoxemia, atherosclerosis, reperfusion injury and inflammatory responses, AIDS, cirrhosis of the
15 liver, neurodegeneration, myelodysplastic syndrome, and ischemic injury. It is particularly preferred that the mammal be diagnosed with an inflammatory or autoimmune disease (as those listed herein above). Alternatively, in other preferred embodiments, the mammal has a tumor (*e.g.*, a carcinoma, a plasmacytoma, a lymphoma or a sarcoma).

20 In another aspect, the invention features a method of reducing inflammation. For example, damage occurring during asthmatic reactions, inflammatory bowel diseases (*i.e.*, Crohn's Disease and ulcerative colitis), eosinophilic colitis, or allergic rhinitis. The method includes inhibiting inflammation normally caused by an immunostimulatory leporipox virus polypeptide. Preferably, leporipox virus
25 polypeptide activity is reduced using an agonist such as an anti-leporipox virus polypeptide antibody or leporipox virus polypeptide fragment. In some embodiments, the antagonist is a leporipox polypeptide having a deletion of amino acids or having

an addition of amino acids on the carboxy or alternatively the amino terminus. Where amino acids are added they may be random or they may be selected to have particular biological properties such as stability or hydrophilicity.

In another aspect, the invention features a method of isolating a leporipox virus gene or fragment thereof from a cell, involving: (a) providing a sample of cellular DNA; (b) providing a pair of oligonucleotides having sequence homology to a conserved region of a leporipox virus gene (for example, oligonucleotides which include fragments of the sequences shown in Figures 1-20); (c) combining the pair of oligonucleotides with the cellular DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and (d) isolating the amplified leporipox virus gene or fragment thereof. Where a fragment is obtained by PCR, standard library screening techniques may be used to obtain the complete coding sequence. In preferred embodiments, amplification is carried out using a reverse-transcription polymerase chain reaction, for example, the RACE method.

In another aspect, the invention features a method of identifying a leporipox virus gene in a cell, involving: (a) providing a preparation of cellular DNA (for example, from the human genome); (b) providing a detectably-labeled DNA sequence (for example, prepared by the methods of the invention) having homology to a conserved region of a leporipox virus gene; (c) contacting the preparation of cellular DNA with the detectably-labeled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (d) identifying a leporipox virus gene by its association with the detectable label.

In another aspect, the invention features a method of isolating a leporipox virus gene from a recombinant DNA library, involving: (a) providing a recombinant DNA library; (b) contacting the recombinant DNA library with a detectably-labeled gene fragment produced according to the PCR method of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a leporipox virus gene by its association with the detectable label.

In another aspect, the invention features a method of isolating a leporipox virus gene from a recombinant DNA library, involving: (a) providing a recombinant DNA library; (b) contacting the recombinant DNA library with a detectably-labeled leporipox virus oligonucleotide of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a leporipox virus gene by its association with the detectable label.

In another aspect, the invention features a leporipox virus gene isolated according to the method involving: (a) providing a sample of cellular DNA; (b) providing a pair of oligonucleotides having sequence homology to a conserved region of a leporipox virus gene; (c) combining the pair of oligonucleotides with the cellular DNA sample under conditions suitable for polymerase chain reaction-mediated DNA amplification; and (d) isolating the amplified leporipox virus gene or fragment thereof.

In another aspect, the invention features a leporipox virus gene isolated according to the method involving: (a) providing a preparation of cellular DNA; (b) providing a detectably-labeled DNA sequence having homology to a conserved region of a leporipox virus gene; (c) contacting the preparation of DNA with the detectably-labeled DNA sequence under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (d) identifying a leporipox virus gene by its association with the detectable label.

In another aspect, the invention features a leporipox virus gene isolated according to the method involving: (a) providing a recombinant DNA library; (b) contacting the recombinant DNA library with a detectably-labeled leporipox virus gene fragment produced according to the method of the invention under hybridization conditions providing detection of genes having 50% or greater sequence identity; and (c) isolating a leporipox virus gene by its association with the detectable label.

In another aspect, the invention features a method of identifying a leporipox virus gene involving: (a) providing a mammalian cell sample; (b) introducing by transformation (*e.g.* viral, chemical, or mechanical transformation) into the cell

sample a candidate leporipox virus gene (*e.g.*, obtained from a cDNA expression library); (c) expressing the candidate leporipox virus gene within the cell sample or isolating the leporipox virus polypeptide from the tissue sample or protein isolated therefrom; and (d) determining whether the cell sample elicits immunomodulatory activity (*e.g.*, an alteration in neutrophil chemotaxis, where a decrease in neutrophil specific chemotaxis identifies a leporipox virus gene).

In another aspect, the invention features a leporipox virus gene isolated according to the method involving: (a) providing a cell sample; (b) introducing by transformation into the cell sample a candidate leporipox virus gene; (c) expressing the candidate leporipox virus gene within the tissue sample; and (d) determining whether the tissue sample elicits a leporipox virus protein mediated response or decrease thereof, where a response identifies a leporipox virus gene.

In another aspect, the invention features a method of detecting a leporipox virus gene in a cell involving: (a) contacting the leporipox virus gene or a portion thereof greater than 9 nucleic acids, preferably greater than 18 nucleic acids in length with a preparation of genomic DNA from the cell under hybridization conditions providing detection of DNA sequences having about 50% or greater sequence identity to the conserved DNA sequences of Figures 1-20, or the sequences which are conserved among leporipox virus polypeptides relative to other proteins, as deduced from the polypeptide sequences provided in Figures 21-40. Preferably, the region of sequence identity used for hybridization is the region of 9 nucleic acids or more encoding the region of highest conservation between the sequences shown in any of Figures 1-20 or among homologs thereof.

In another aspect, the invention features a method of producing a leporipox polypeptide (viral, rodent or human) which involves: (a) providing a cell transformed with DNA encoding a leporipox virus polypeptide positioned for expression in the cell (for example, present on a plasmid or inserted in the genome of the cell); (b) culturing the transformed cell under conditions for expressing the DNA; and (c) isolating the leporipox polypeptide.

Definitions

“Polypeptide” or “polypeptide fragment” means a chain of two or more amino acids, regardless of any post-translational modification (*e.g.*, glycosylation or phosphorylation), constituting all or part of a naturally or non-naturally occurring polypeptide. By “post-translational modification” is meant any change to a polypeptide or polypeptide fragment during or after synthesis. Post-translational modifications can be produced naturally (such as during synthesis within a cell) or generated artificially (such as by recombinant or chemical means). A “protein” can be made up of one or more polypeptides.

“*Leporipox* virus immunomodulatory polypeptide” or “*leporipox* virus polypeptide” means a *leporipox* virus polypeptide having immunomodulatory activity that is substantially identical to any of the myxoma virus polypeptide sequences described in Figures 21-40, or a fragment thereof. Specifically excluded from this definition are myxoma virus CBPI and CBPII, and Shope Fibroma virus CBPI and CBPII (U.S. Patent No. 5, 834,419, PCT publication WO 96/33730, and PCT publication WO 97/44054). A *leporipox* virus polypeptide may also be defined as encoding a polypeptide with at least 50%, preferably at least 75%, more preferably at least 90%, and most preferably at least 95% of the biological activity, *e.g.*, immunomodulatory or anti-inflammatory activity, compared to a reference *leporipox* virus polypeptide having an amino acid sequence substantially identical to those described in Figures 21-40. The term *leporipox* virus polypeptide includes homologs, *e.g.* human or murine homologs, of the sequences described herein.

By “biologically active fragment” is meant a polypeptide fragment of a *leporipox* virus polypeptide that exhibits immunomodulatory properties that are at least 30%, preferably at least 50%, more preferably at least 75%, and most preferably at least 100%, compared with the immunomodulatory properties of a full length *leporipox* virus polypeptide. By “analog” is meant any substitution, addition, or deletion in the amino acid sequence of a *leporipox* virus polypeptide that exhibits

properties that are at least 30%, preferably at least 50%, more preferably at least 75%, and most preferably at least 100%, compared with the immunomodulatory properties of a *leporipox* virus polypeptide from which it is derived. Fragments and analogs can be generated using standard techniques, for example, solid phase peptide synthesis or
5 polymerase chain reaction.

“*Leporipox* virus immunomodulatory nucleic acid molecule” or “*leporipox* virus nucleic acid molecule” means a nucleic acid molecule a nucleic acid molecule, such as a genomic DNA, cDNA, or RNA (*e.g.*, mRNA) molecule, that encodes a polypeptide having the characteristics or biological activities of any *leporipox* virus
10 polypeptide described herein, or a fragment thereof. A *leporipox* virus nucleic acid molecule has at least 30% nucleic acid sequence identity, preferably at least 50% nucleic acid sequence identity, more preferably at least 75% nucleic acid sequence identity, and most preferably at least 95% nucleic acid sequence identity to a reference *leporipox* virus nucleic acid molecule as described herein.

15 The term “identity” is used herein to describe the relationship of the sequence of a particular nucleic acid molecule or polypeptide to the sequence of a reference molecule of the same type. For example, if a polypeptide or nucleic acid molecule has the same amino acid or nucleotide residue at a given position, compared to a reference molecule to which it is aligned, there is said to be “identity” at that position.

20 The level of sequence identity of a nucleic acid molecule or a polypeptide to a reference molecule is typically measured using sequence analysis software with the default parameters specified therein, such as the introduction of gaps to achieve an optimal alignment (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University
25 Avenue, Madison, WI 53705, BLAST, or PILEUP/PRETTYBOX programs). These software programs match identical or similar sequences by assigning degrees of identity to various substitutions, deletions, or other modifications. Conservative

substitutions typically include substitutions within the following groups: glycine, alanine, valine, isoleucine, and leucine; aspartic acid, glutamic acid, asparagine, and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine.

A nucleic acid molecule or polypeptide is said to be “substantially identical” to a reference molecule if it exhibits, over its entire length, at least 50%, preferably at least 55%, 60%, or 65%, and most preferably 75%, 85%, 90%, 95%, or 99% identity to the sequence of the reference molecule. For polypeptides, the length of comparison sequences is at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides.

Alternatively, or additionally, two nucleic acid sequences are “substantially identical” if they hybridize under high stringency conditions. By “high stringency conditions” is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO₄, pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V), at a temperature of 65°C, or a buffer containing 48% formamide, 4.8X SSC, 0.2 M Tris-Cl, pH 7.6, 1X Denhardt’s solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42°C. (These are typical conditions for high stringency northern or Southern hybridizations.) High stringency hybridization is also relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to northern and Southern hybridizations, these techniques are usually performed with relatively short probes (*e.g.*, usually 16 nucleotides or longer for PCR or sequencing and 40 nucleotides or longer for *in situ* hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and examples of them can be found, for example, in Ausubel *et*

al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998, which is hereby incorporated by reference.

By “probe” or “primer” is meant a single-stranded DNA or RNA molecule of defined sequence that can base pair to a second DNA or RNA molecule that contains a complementary sequence (“target”). The stability of the resulting hybrid depends upon the extent of the base pairing that occurs. This stability is affected by parameters such as the degree of complementarity between the probe and target molecule, and the degree of stringency of the hybridization conditions. The degree of hybridization stringency is affected by parameters such as the temperature, salt concentration, and concentration of organic molecules, such as formamide, and is determined by methods that are well known to those skilled in the art. Probes or primers specific for *leporipox* virus nucleic acid molecules, preferably, have greater than 45% sequence identity, more preferably at least 55-75% sequence identity, still more preferably at least 75-85% sequence identity, yet more preferably at least 85-99% sequence identity, and most preferably 100% sequence identity to the nucleic acid sequences encoding the amino acid sequences described herein. Probes can be detectably-labeled, either radioactively or non-radioactively, by methods that are well-known to those skilled in the art. Probes can be used for methods involving nucleic acid hybridization, such as nucleic acid sequencing, nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA), and other methods that are well known to those skilled in the art. A molecule, *e.g.*, an oligonucleotide probe or primer, a gene or fragment thereof, a cDNA molecule, a polypeptide, or an antibody, can be said to be “detectably-labeled” if it is marked in such a way that its presence can be directly identified in a sample. Methods for detectably-labeling molecules are well known in the art and include, without limitation, radioactive labeling (*e.g.*, with an isotope, such as ³²P or ³⁵S) and nonradioactive labeling (*e.g.*, with a fluorescent label, such as fluorescein).

By a “substantially pure polypeptide” is meant a polypeptide (or a fragment thereof) that has been separated from proteins and organic molecules that naturally accompany it. Typically, a polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the polypeptide is a *leporipox* virus polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure *leporipox* virus polypeptide can be obtained, for example, by extraction from a natural source (*e.g.*, a mammalian cell), by expression of a recombinant nucleic acid molecule encoding a *leporipox* virus polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A polypeptide is substantially free of naturally associated components when it is separated from those proteins and organic molecules that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the cell in which it is naturally produced is substantially free from its naturally associated components. Accordingly, substantially pure polypeptides not only include those derived from eukaryotic organisms, but also those synthesized in *E. coli* or other prokaryotes.

An antibody is said to “specifically bind” to a polypeptide if it recognizes and binds to the polypeptide (*e.g.*, a *leporipox* virus polypeptide), but does not substantially recognize and bind to other molecules (*e.g.*, non-*leporipox* virus related polypeptides) in a sample, *e.g.*, a biological sample, that naturally includes the polypeptide. A preferred antibody binds to any *leporipox* virus polypeptide sequence that is substantially identical to the polypeptide sequences shown in Figures 21-40, or portions thereof.

“Substantially pure nucleic acid molecule” means a nucleic acid molecule that is free of the components that naturally accompany it. For example, a substantially pure DNA is free of the genes that, in the naturally-occurring genome of the organism

from which the DNA of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (*e.g.*, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By a “promoter” is meant a minimal nucleic acid sequence element sufficient to direct transcription. If desired, constructs of the invention can include promoter elements that are sufficient to render promoter-dependent gene expression controllable in a cell type-specific, tissue-specific, or temporal-specific manner, or inducible by external signals or agents. Such elements can be located in the 5', 3', or intron regions of a gene.

By “operably linked” is meant that a gene and one or more regulatory sequences are connected in such a way as to permit gene expression when the appropriate molecules (*e.g.*, transcriptional activator proteins) are bound to the regulatory sequences.

By an “antisense molecule,” as used herein in reference to nucleic acid molecules, is meant a nucleic acid molecule having a sequence that is complementary to at least 75 nucleotides, and preferably at least 100, 150, or 200 nucleotides, of the coding strand of a gene, such as a *leporipox* virus gene. An antisense nucleic acid molecule can be, for example, capable of preferentially lowering the production of a *leporipox* virus polypeptide encoded by a *leporipox* virus gene.

By a “transgene” is meant a DNA molecule that is inserted by artifice into a cell (*e.g.*, the nuclear genome of a cell), and is incorporated into the genome of an organism that develops from the cell. Such a transgene can be partly or entirely heterologous (*i.e.*, foreign) to the transgenic organism, or can be a gene that is

homologous to an endogenous gene of the organism. An organism or animal (*e.g.*, a mammal, such as a mouse, rat, or goat) can be said to be “transgenic” if it developed from a cell that had a transgene inserted into it by artifice.

By a “knockout mutation” is meant an artificially-induced alteration in a nucleic acid molecule (created by recombinant DNA technology or deliberate exposure to a mutagen) that reduces the biological activity of the polypeptide normally encoded therefrom by at least 80% relative to the unmutated gene. The mutation can be, without limitation, an insertion, deletion, frameshift mutation, or a missense mutation. A “knockout animal” is preferably a mammal, and more preferably a mouse, containing a knockout mutation, as defined above.

By “vector” is meant a genetically engineered plasmid or virus, derived from, for example, a bacteriophage, adenovirus, retrovirus, poxvirus, herpesvirus, or artificial chromosome, that is used to transfer a polypeptide (*e.g.*, a *leporipox* virus polypeptide) coding sequence, operably linked to a promoter, into a host cell, such that the encoded peptide or polypeptide is expressed within the host cell.

“Conserved region” means any stretch of six or more contiguous amino acids exhibiting at least 80%, preferably 90%, and most preferably 95% amino acid sequence identity between two or more of the *leporipox* virus family members.

By “transformation” is meant any method for introducing foreign molecules (*e.g.*, nucleic acid molecules) into a cell. Lipofection, DEAE-dextran-mediated transfection, microinjection, protoplast fusion, calcium phosphate precipitation, retroviral delivery, electroporation, and biolistic transformation are just a few of the many transformation methods that are well known to those skilled in the art that can be used in the invention. For example, biolistic transformation is a method for introducing foreign molecules into a cell using velocity-driven microprojectiles such as tungsten or gold particles. Such methods can include helium-driven, air-driven, and gunpowder-driven techniques. Biolistic transformation can be applied to the transformation or transfection of a wide variety of cell types, intracellular organelles, and intact tissues including, without limitation, mitochondria, chloroplasts, bacteria,

yeast, fungi, algae, animal tissue, and cultured cells. A “transformed cell,” “transfected cell,” or “transduced cell,” is a cell (or a descendent of a cell) into which a DNA molecule encoding a polypeptide has been introduced, by means of recombinant DNA techniques.

5 By “sample” is meant a tissue biopsy, amniotic fluid, cell, blood, serum, urine, stool, or other specimen obtained from a patient or test subject. The sample can be analyzed to detect a mutation in a *leporipox* virus gene, expression levels of a *leporipox* virus gene or polypeptide, or the biological function of a *leporipox* virus polypeptide, by methods that are known in the art. For example, methods such as
10 sequencing, single-strand conformational polymorphism (SSCP) analysis, or restriction fragment length polymorphism (RFLP) analysis of PCR products derived from a patient sample can be used to detect a mutation in a *leporipox* virus gene; ELISA can be used to measure levels of *leporipox* virus polypeptide; and PCR can be used to measure the level of a *leporipox* virus nucleic acid molecule.

15 By “neutralizing antibody” is meant an antibody that interferes with any of the biological activities of a *leporipox* virus polypeptide, (*e.g.*, the ability of the *leporipox* virus polypeptide M141 (mVOX2) to inhibit T cell costimulatory signals). A neutralizing antibody may reduce the ability of a *leporipox* virus polypeptide to carry out its specific biological activity by about 50%, more preferably by about 70%,
20 and most preferably by about 90% or more. Any standard assay for the biological activity of any *leporipox* virus polypeptide, including those described herein, may be used to assess potentially neutralizing antibodies that are specific for *leporipox* virus polypeptides

By “pharmaceutically acceptable carrier” is meant a carrier that is
25 physiologically acceptable to the treated mammal while retaining the therapeutic properties of the compound with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline solution. Other physiologically acceptable carriers and their formulations are known to one skilled in

the art and described, for example, in *Remington: The Science and Practice of Pharmacy*, (19th edition), ed. A. Gennaro, 1995, Mack Publishing Company, Easton, PA.

By “test compound” is meant a chemical, be it naturally-occurring or artificially-derived, that is assayed for its ability to act as an immunomodulator, an anti-inflammatory, or an anti-tumor agent by employing one of the assay methods described herein. Test compounds may include, for example, peptides, polypeptides, synthesized organic molecules, naturally occurring organic molecules, nucleic acid molecules, and components thereof.

“Therapeutically effective amount” as used herein in reference to dosage of a medication, refers to the administration of a specific amount of a pharmacologically active agent (*e.g.*, a *leporipox* virus polypeptide) tailored to each individual patient manifesting symptoms characteristic of a specific disorder. For example, a patient receiving the treatment of the present invention might be experiencing an autoimmune or inflammatory disease. A person skilled in the art will recognize that the optimal dose of a pharmaceutical agent to be administered will vary from one individual to another. Dosage in individual patients should take into account the patients height, weight, rate of absorption and metabolism of the medication in question, the stage of the disorder to be treated, and what other pharmacological agents are administered concurrently.

By “treating “ or “treatment” is meant the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement or associated with the cure of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed

to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. The phrase “treatment” also includes symptomatic treatment, that is, treatment directed toward constitutional symptoms of the associated disease, pathological condition, or disorder.

By “modulate” or “modulating” is meant changing, either by decrease or increase, the biological activity.

“Immune function” or “immunoreactivity” refers to the ability of the immune system to respond to foreign antigen as measured by standard assays well known in the art.

“Immunomodulation” or “immunomodulatory” refers to an alteration in the overall immunoreactivity of the immune system in a mammal upon treatment with an agent, such as a polypeptide of the present invention, or fragments and analogs thereof. “Immunomodulator” refers to an agent that induces an alteration (*i.e.*, immunosuppression or immunostimulation) as measured by an alteration of virulence in mutated viruses or a variety of immunoassays well known in the art (for example chemotaxis assays as described herein). For example, in the present invention, an immunomodulator may elicit an altered level of immune function whereby the alteration in the level of immune function identifies a *leporipox* virus polypeptide. Preferably, the alteration is by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80% relative to an untreated control of similar type. By “immunomodulatory disorder” is meant any pathophysiological condition that is characterized by an alteration in immune function. The alteration may include, for example, a decrease in immune cell number or size, an increase in cell apoptosis or death, or a decrease in immune cell growth, survival or differentiation. By “immunomodulatory disorder” is also meant any disease which involves the immune response or immunity in general. More specifically, such a disorder is a malfunction

of the immune system that reduces the ability of an organism to resist foreign substances in the body (*e.g.*, viruses, bacteria, bacterial toxins, plant pollen, fungal spores, animal danders, medications, foods, allogeneic or xenogeneic transplanted organs) or causes the body to produce antibodies against its own tissues (*e.g.*, autoimmune disorders), resulting in tissue injury. Immunological disorders can also occur when a malfunctioning immune system (caused by, for example, genetic defect, illness, injury, malnutrition, medications such as those used for chemotherapy) results in an increase in frequency or severity of infections. Immunological disorders are often accompanied by inflammation, which is the body's reaction to tissue injury, and results in the accumulation of white blood cells, macrophages, and lymphocytes at the site of injury.

By "pathophysiological condition" is meant a disturbance of function and/or structure of a living organism, resulting from an external source, a genetic predisposition, a physical or chemical trauma, or a combination of the above, including, but not limited to, any mammalian disease..

"Immunosuppression" refers to a decrease in the overall immunoreactivity of the immune system upon administration of an immunomodulator in comparison to the immunoreactivity of an immune system that has not been contacted with the particular immunomodulator. Preferably, the decrease is by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80% relative to an untreated control of similar type.

"Immunostimulation" refers to an increase in the overall immunoreactivity of the immune system upon administration of an immunomodulator in comparison to the immunoreactivity of an immune system that has not been contacted with the particular immunomodulator. Preferably, the increase is by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80%.

“Decreasing T cell stimulation” means lowering the level of T cell stimulation as measured by, for example, chromium release assay, by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80% relative to an untreated control of similar type.

5 “Decreasing inflammation” means decreasing the number of inflammatory cells (leukocytes, for example eosinophils) in the target tissue by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80% relative to an untreated control tissue of similar type. Preferably the decrease in the number of leukocyte cells is at least two-fold.

10 By “cell proliferation” is meant the growth or reproduction of similar cells. By “inhibiting proliferation” is meant the decrease in the number of similar cells by at least 10%, more preferably by at least 20%, and most preferably by at least 50%. By “stimulating proliferation” is meant an increase in the number of similar cells by at least 10%, more preferably by at least 20%, and most preferably by at least 50%.

15 By “apoptosis” is meant the process of cell death where a dying cell displays a set of well-characterized biochemical hallmarks which include cytolemmal blebbing, cell soma shrinkage, chromatin condensation, and DNA laddering.

An “anti-inflammatory” agent is an immunomodulatory agent capable of decreasing the overall inflammation or immune function upon administration to an individual. Preferably, the decrease is by at least 20-40%, more preferably by at least 50-75%, and most preferably by more than 80% relative to an untreated control of similar type.

20 By “cytokine” is meant a small molecular weight polypeptide that plays an important role in regulating the immune response, by for example, signaling adjacent cells.

25 By “chemokine” is meant a small molecular weight ligand which is a chemoattractant for leukocytes (*e.g.*, neutrophils, basophils, monocytes, and T cells), and is important for infiltration of lymphocytes and monocytes into sites of inflammation.

“Identifiable signal sequence” means a sequence of amino acids that may be identified by homology or biological activity to a peptide sequence with the known function of targeting a polypeptide to a particular region of the cell. Preferably the signal sequence directs the polypeptide to the cellular membrane wherefrom the polypeptide may be secreted. Alternatively, the signal sequence may direct the polypeptide to an intracellular compartment or organelle, such as the Golgi apparatus. One of ordinary skill in the art can identify a signal sequence by, for example, using readily available software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705, BLAST, or PILEUP/PRETTYBOX programs).

A “multi-transmembrane receptor protein” is an amphipathic protein having multiple hydrophobic regions that span the lipid bilayer of the cell membrane from the cytoplasm to the cell surface interspersed between hydrophilic regions that are exposed to water on both sides of the membrane. The number of hydrophobic regions in an amphipathic protein is often proportional to the number of times that proteins spans the lipid bilayer. Many multi-transmembrane receptor-related proteins act as receptors for various ligands (*e.g.*, cytokines) that act to initiate transduction of a signal from the cell surface where the ligand is binding to the interior of the cell. The initiation is often in the form of a conformational change in the multi-transmembrane receptor upon ligand binding. One of ordinary skill in the art can such protein by, for example, using readily available software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705, BLAST, or PILEUP/PRETTYBOX programs).

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the cDNA sequence of M035 (SEQ ID NO:1).

Figure 2 shows the cDNA sequence of M037 (SEQ ID NO:2).

Figure 3 shows the cDNA sequence of M046 (SEQ ID NO:3).

5 **Figure 4** shows the cDNA sequence of M102 (SEQ ID NO:4).

Figure 5 shows the cDNA sequence of M103 (SEQ ID NO:5).

Figure 6 shows the cDNA sequence of M110 (SEQ ID NO:6).

Figure 7 shows the cDNA sequence of M116 (SEQ ID NO:7).

Figure 8 shows the cDNA sequence of M125 (SEQ ID NO:8).

10 **Figure 9** shows the cDNA sequence of M134 (SEQ ID NO:9).

Figure 10 shows the cDNA sequence of M153 (SEQ ID NO:10).

Figure 11 shows the cDNA sequence of M141 (mVOX-2) (SEQ ID NO:11).

Figure 12 shows the cDNA sequence of M118 (SEQ ID NO:12).

Figure 13 shows the cDNA sequence of M135 (SEQ ID NO:13).

15 **Figure 14** shows the cDNA sequence of M144 (SEQ ID NO:14).

Figure 15 shows the cDNA sequence of M121 (SEQ ID NO:15).

Figure 16 shows the cDNA sequence of M122 (SEQ ID NO:16).

Figure 17 shows the cDNA sequence of M154 (SEQ ID NO:17).

Figure 18 shows the cDNA sequence of M104 (SEQ ID NO:18).

20 **Figure 19** shows the cDNA sequence of M107 (SEQ ID NO:19).

Figure 20 shows the cDNA sequence of M128 (SEQ ID NO:20).

Figure 21 shows the amino acid sequence of M035 (SEQ ID NO:21).

Figure 22 shows the amino acid sequence of M037 (SEQ ID NO:22).

Figure 23 shows the amino acid sequence of M046 (SEQ ID NO:23).

25 **Figure 24** shows the amino acid sequence of M102 (SEQ ID NO:24).

Figure 25 shows the amino acid sequence of M103 (SEQ ID NO:25).

Figure 26 shows the amino acid sequence of M110 (SEQ ID NO:26).

Figure 27 shows the amino acid sequence of M116 (SEQ ID NO:27).

Figure 28 shows the amino acid sequence of M125 (SEQ ID NO:28).

Figure 29 shows the amino acid sequence of M134 (SEQ ID NO:29).

Figure 30 shows the amino acid sequence of M153 (SEQ ID NO:30).

Figure 31 shows the amino acid sequence of M141 (mVOX-2) (SEQ ID NO:31).

Figure 32 shows the amino acid sequence of M118 (SEQ ID NO:32).

Figure 33 shows the amino acid sequence of M135 (SEQ ID NO:33).

Figure 34 shows the amino acid sequence of M144 (SEQ ID NO:34).

Figure 35 shows the amino acid sequence of M121 (SEQ ID NO:35).

Figure 36 shows the amino acid sequence of M122 (SEQ ID NO:36).

Figure 37 shows the amino acid sequence of M154 (SEQ ID NO:37).

Figure 38 shows the amino acid sequence of M104 (SEQ ID NO:38).

Figure 39 shows the amino acid sequence of M107 (SEQ ID NO:39).

Figure 40 shows the amino acid sequence of M128 (SEQ ID NO:40).

DETAILED DESCRIPTION OF THE INVENTION

Typical naturally-occurring viral proteins act primarily as immunosuppressors. Conceivably, these molecules have been obtained by the virus through an ancient act of molecular piracy and subsequently are structurally optimized for a particular pharmacological phenotype of benefit to the virus. Against the extensive array of immune modalities, viruses have successfully co-evolved distinct strategies to thwart the host immune response. The myxoma virus propagates in tissues (*e.g.*, skin, respiratory tract and lymph nodes) that are readily accessible to a variety of the effector elements of the immune system. Like all poxviruses, myxoma has adapted to this inhospitable immune environment by expressing a wide range of proteins to systematically block each threatening aspect of the immune system.

The present invention provides novel genes that have the potential to treat a wide range of immunopathological conditions. Using standard molecular biological techniques well known in the art, a total of 1,925 DNA segments were isolated and

sequenced using a shotgun sequencing approach with Bluescript primers (Stratagene, La Jolla, CA) to assemble a final contiguous myxoma viral gene sequence.

We have identified 20 novel genes within the myxoma genome that are herein disclosed as MO35, MO37, MO46, M102, M103, M110, M116, M125, M134, M153, 5 M141, M118, M135, M144, M121, M122, M154, M104, M107, and M128 (SEQ ID NOs:1-20; Figures 1-20). The identification of start and stop codons within the cDNA sequences has permitted the prediction of the corresponding amino acid sequences (SEQ ID NOs: 21-40; Figures 21-40).

Many cDNA sequences of the present invention are novel, yet have significant 10 homologies to other known genes or possess identifiable structural or functional domains. Predominantly, each of these genes encode polypeptides that are either homologous to an immunoregulatory protein or have recognizable domains that are known to have an immunoregulatory function. For example, cDNA sequence M141 (or mVOX) (SEQ ID NO:11; Figure 11), has significant homology to the mammalian 15 OX-2 gene. Some of the novel genes can be separated into three general categories: 1) anti-inflammatory proteins M118, M 135, and M144 (SEQ ID NOs:12-14; Figures 12-14, respectively); 2) immunoreceptor-regulated genes M121, M122, and M154 (SEQ ID NOs:15-17; Figures 15-17, respectively); and 3) multi-transmembrane receptor-related genes M104, M107, and M128 (SEQ ID NOs: 18-20; Figures 18-20, 20 respectively).

The remaining novel genes encode proteins that are secreted from the myxoma-infected cells and have identifiable signal sequences. However, nucleic acid and protein sequence analysis algorithms have yielded no significant homology of these genes to known sequences. Furthermore, no structural or functional domains 25 can be detected within the amino acid motif sequences disclosed herein. The functions of the proteins encoded by these novel genes may range among a wide variety of possibilities. Some of these genes may encode proteins that are important in modulating inflammation. Other genes may encode proteins that control viral replication and assembly. Alternatively, analysis of these genes and the polypeptides

that they encode may elucidate the mechanism utilized by myxoma and possibly other *leporipox* viruses during infection and persistence within mammals. Still other proteins might be key regulators of cell proliferation or apoptosis. As mentioned previously, poxviruses express a variety of proteins that are able to modulate the innate cellular apoptotic response triggered by virus infection.

One of ordinary skill in the art will readily appreciate that any such proteins might be useful as therapeutic agents to treat a variety of human diseases. For example, the present invention may yield novel anti-inflammatories (*e.g.*, for treatment of ischemic injury). Alternatively or additionally, the present invention may yield anti-viral compounds (*e.g.*, for treatment of AIDS). Yet other proteins may be used as drugs for treatment of proliferative diseases (*e.g.*, cancer or myelodysplastic syndrome) or cell death (*e.g.*, neurodegeneration, muscular dystrophy, cirrhosis of the liver).

We believe that, upon expression in myxoma infected cells, for example, all of the genes disclosed herein, or modified variants thereof shall yield polypeptides that are secreted by the infected cell. This expectation is based upon two observations: 1) the absence of a retention sequence (such as the RDEL motif in T4) that would persistently localize these polypeptides to an organelle within the cell; and 2) the presence of a signal sequence that would mediate targeting of these proteins, either for insertion into the cell membrane or for secretion into the extracellular milieu. Some of the proteins of the present invention, *i.e.*, those with significant homology to other known immunomodulatory proteins or functional domain are described in greater detail below.

Virokines

As mentioned above, one strategy of immune evasion by viruses is the capture and expression of host cytokines and growth factors (virokines). This strategy is employed by a number of viruses, which are restricted to the herpes virus and poxvirus families (McFadden *et al.*, *Semin. Cell. Dev. Biol.*, 9:359-368, 1996). Over

time, the definition of virokine has expanded to encompass cytokine analogs and agonists, growth factors, and inhibitors, such as secreted serine proteinase inhibitors, of the poxvirus family (McFadden (1995) Austin (TX): *R. G. Landes Company*, incorporated herein by reference). Several sequences disclosed herein, including
5 M141, M118, M135 and M144, may be classified as virokines. M135 and M144 can be more specifically identified as anti-inflammatories.

M141/mVOX-2

The cDNA sequence M141 (or mVOX) (SEQ ID NO:11) (see Figure 11), has
10 significant homology to the mammalian OX-2 gene. Specifically, M141 is predicted to encode a protein (SEQ ID NO:31; Figure 31) having approximately 25% identity and 43% similarity to the human and rat isoforms OX-2. OX-2 is expressed in the brain, thymus, ovary and fallopian tubes, glomerulus, smooth muscle, as well as follicular dendritic cells in lymphoid organs, and the endothelium of the postcapillary
15 venules (Borriello *et al.*, *J. Immunol.* 158(10):4548-4554,1997). This widespread tissue distribution suggests a diverse role for OX-2. Previous studies have demonstrated that mammalian OX-2 receptors mediate costimulation of T cells in a B7-independent pathway. However, the mVOX-2 protein lacks a cytoplasmic domain that would presumably function in delivering intracellular signals.

20 It is currently thought that the immune response consists of two major components: a cellular immune response (mediated by T cells) and a humoral immune response (mediated by B cells). B cells recognize antigen via surface bound antibody that acts as a receptor. In contrast, T cells only recognize antigens through specific T cell receptors (TCR) expressed on the surface of T cells. TCR molecules only
25 recognize linear epitopes that have been processed and presented onto the surface of an antigen presenting cell (APC). These linear epitopes have been processed intercellularly and presented on the surface of the APC in association with major histocompatibility complex MHC molecules.

Activation of T cells requires two distinct types of signals. The first signal is the antigen dependent signal and results from the engagement of the TCR by major histocompatibility (MHC)-antigen complex on the surface of the APC. The second signal is antigen independent, and is mediated by interaction of one of a number of ligands on APCs with their cognate receptor(s) on T cells. It is only when these two distinct signals are delivered together to the T cell, that T cell proliferation and cytokine production ensue. This important control point in T cell activation relies on the ligand B7 and the receptor CD28. The ligands of the B7/CD28 pathway (B7-1 and B7-2) are expressed on a variety of APCs and can provide costimulation through the CD28 receptor on T cells.

It has been demonstrated that OX-2 is also capable of providing a potent second signal to T cells by costimulation through OX-2 receptors on T cells (in the presence of antigen), (Borriello *et al.*, *J. Immunol.*, 158(10):4548-4554, 1997). Signaling through OX-2 results in T cell proliferation and antigen specific tolerance. OX-2 can also provide costimulation to T cells in an antigen-independent manner using an anti-CD3 antibody to provide the primary signal (Borriello *et al.*, *J. Immunol.*, 158(10):4548-4554, 1997). Furthermore, it has been shown that OX-2 costimulation prevents a Th1 type of immune response and thereby mediates transplant tolerance (Gorczynski *et al.*, *Transplantation*, 65(8):1106-1114, 1999).

We believe that mVOX-2 expressed during myxoma infection can have one or both of the following effects: 1) suppression of the Th1 immune response needed for viral clearance and cytotoxic T lymphocyte activity; and 2) inhibition of T cell costimulatory signals due to the lack of an intracellular signaling domain. In this scenario, mVOX-2 acts in a dominant negative fashion. Therefore, mVOX-2 expression most likely plays an immunosuppressive role during myxoma infection of mammalian organisms.

In one aspect of the invention, the polypeptide encoded by M141, the mVOX-2 gene, is administered *in vivo* as an immunosuppressant. For example, in one preferred embodiment, a therapeutic preparation of mVOX-2 polypeptide can be used

to modulate cytotoxic immune responses. Alternatively, in another preferred embodiment of the invention, administration of mVOX-2 *in vivo* disrupts T cell stimulation.

5 *M118/ Mig Homolog*

12 The DNA sequence referred to herein as M118 (SEQ ID NO:12) (see Figure 12) has a protein sequence (SEQ ID NO:32) (see Figure 32) that demonstrates considerable homology to a mammalian chemokine known as “monokine induced by interferon-g” (Mig). As mentioned above, chemokines are a large family of small (67
10 to 103 amino acids) secreted proteins that play an important role in the selective recruitment of leukocytes (Baggiolini *et al.*, *Annu. Rev. Immunol.* 15:675-705, 1997). Generally, a chemokine is a chemotactic cytokine that ensures migration of leukocytes to the right tissue or compartment at the right time. Chemokines are rapidly produced in blood and tissue cells upon induction by pro-inflammatory
15 cytokines and other stimuli (Baggiolini *et al.*, *supra*; Moser *et al.*, *Int. Rev. Immunol.*, 16:323-344, 1997; Murphy, *Cytokine Growth Fact. Rev.* 7:47-64, 1996; Gerard *et al.*, *Curr. Opin. Immunol.* 6:140-145, 1996). While the mammalian Mig contains two conserved cysteine residues separated by an amino acid (and hence is a member of the CXC family of chemokines), the myxoma M118 homolog does not retain such
20 cysteines. Furthermore, M118 homology to Mig is limited to the C-terminal region of the protein.

Thousands of chemokine receptors are expressed on the surface of a single leukocyte. Upon ligand binding, leukocytes respond by chemotaxis, enzyme and mediator release and various effector functions. All known chemokine receptors are
25 members of the large family of seven-transmembrane domain receptors that require G proteins for signal transduction. As mentioned previously, the chemokine receptors can be further classified into two distinct families, CC and CXC, based on which family of chemokines they bind (Baggiolini *et al.*, *supra*). Based on this complexity, it will be apparent to one of ordinary skill in the art, that the cellular infiltrate is

largely defined by the composition of locally produced chemokines as well as the diversity of circulating leukocytes that express the relevant receptors.

The amino acid sequence homology of M118 to mammalian Mig provides insight into its role during myxoma infection of mammalian hosts. Mig is known to be upregulated in response to secretion of interferon- γ IFN- γ (Luster *et al.*, *Nature* 215:272-276, 1985; Farber, *Proc. Natl. Acad. Sci. U.S.A.* 87, 5238-5242, 1998; Farber, *Biochem. Biophys. Res. Commun.* 192:223-230, 1993). Previous studies have demonstrated that mammalian Mig binds the CXC Receptor 3 (CXCR3) (Piali *et al.*, *Eur. J. Immunol.* 28(3):961-972, 1998; Goebeler *et al.*, *J. Pathol.*, 184(1):89-95, 1998) and acts primarily as a potent chemoattractant on activated T and natural killer (NK)-cells (Luster *et al.*, *J. Exp. Med.*, 178:1057-1066, 1993; Farber, *J. Leukocyte Biol.* 61:246-257, 1997). Hence, it is suggested that Mig is involved in the recruitment of lymphocytes during inflammation and mediates the progression of interferon dependent pathologies. Lymphocyte participation is prominently associated with delayed-type hypersensitivity, autoimmune and antiviral responses. For example, it is likely that Mig is expressed during myxoma infection of mammalian cells. By way of further example, expression of Mig also correlates with psoriatic lesions (Weng *et al.*, *J. Biol. Chem.*, 272(29):18288-18291, 1998).

We believe that the M118 protein antagonizes the chemotactic function of Mig, since it only represents a C-terminal fragment of the mammalian Mig and does not contain the two cysteine residues conserved within the CXC subfamily of chemokines. A chemokine antagonist could be used by the virus to prevent the local recruitment of leukocytes. We believe that M118 may disrupt Mig function by blocking the Mig binding site upon CXCR3. Alternatively or additionally, M118 may otherwise abrogate CXCR-mediated signaling. As a result, M118 may provide an anti-inflammatory role during myxoma infection of mammalian organisms. We also propose that the *in vivo* administration of M118 gene products shall reduce Mig-CXCR3 mediated signaling and therefore decrease or interrupt lymphocyte recruitment and inflammatory symptoms associated with any of a variety of

inflammatory diseases. Therefore, preferred embodiments of the present invention provide the polypeptide encoded by the M118 gene for administration *in vivo* as an immunomodulatory compound with anti-inflammatory effects.

5 *M135 and M144/Anti-Inflammatories*

We believe that the M135 and M144 sequences disclosed herein will mediate anti-inflammatory mechanisms *in vivo* upon myxoma infection through the proteins encoded therein. The predicted amino acid sequences of M135 and M144 are homologous to important known mammalian anti-inflammatory genes.

10 Upon analysis, M135 appears to be a hybrid between the IL-1b and the IL-6 receptor. M135 shares 29% identity (47% similarity) with the known sequence of the IL-1b receptor and shares homology with the IL-6 receptor. In addition to the activity of activated T cells in mediating cellular immune responses, cellular immunity is also mediated by lymphocyte products, including interleukins and lymphokines, that are
15 released by the T cells and other immunomodulatory cells (*e.g.*, monocytes, dendritic cells, B cells, fibroblasts and epithelial cells) upon contact with antigen. Receptors for IL-1b transduce signals that regulate inflammations and are found on a number of different cells including, thymocytes, monocytes, T cells, B cells and monocytes. IL-6 responding cells include thymocytes, B cells and NK cells. The IL-6 receptor
20 mediates signals that promote differentiation.

It is apparent from the diversity in function of the homologous proteins listed above that any of a variety of immunomodulatory activities could be affected by the gene products of the M135. For example, without wishing to be bound to any particular theory, M135 may function as a dominant negative IL-1b receptor that
25 binds the IL-1 or IL-6 ligand and prevents intracellular signaling. In preferred embodiments, the invention provides a polypeptide encoded by M135 that can be administered *in vivo* as an immunomodulatory protein with immunosuppressant effects.

M144 shares 27% identity (42% similarity) with CD46, a known complement regulator that mediates the lysis of infected cells. As mentioned previously, a humoral immune response is carried out by B cells in their production of antibodies that specifically recognize a particular antigen. Although antibody alone may in some instances be protective *in vivo*, much of the ability of antibodies to protect against infection is dependent on the complement system. On reaction of an antibody with its antigens a collection of blood serum proteins (referred to herein as "complement") are activated. As a result of this activation, organisms expressing a particular antigen may be lysed and in the process, phagocytic cells are called to remove the debris. As an example, lysis of antibody-coated bacteria may occur as a result of the complement-mediated pathway.

In addition to the antibody initiated sequence of complement events, there is an alternate pathway for the activation of complement components. This system involves a series of components that interact with polysaccharides and lipopolysaccharides on bacteria or virus particles, or with parasites. This alternate pathway for the activation of complement is important for control of infection in the absence of specific immunity. Thus, many different organisms are eliminated as a result of their activation of the alternate pathway.

Inappropriate or excessive activation of the complement system can lead to harmful, potentially life-threatening consequences due to severe inflammatory tissue destruction. These consequences are clinically manifested in various disorders, including septic shock, multiple organ failure, and hyper-acute graft rejection. Genetic complement deficiencies or complement depletion have been proven to be beneficial in reducing tissue injury in a number of animal models of severe complement-dependent inflammation. It is therefore believed that therapeutic inhibition of complement is likely to arrest the process of certain diseases.

Attempts to efficiently inhibit complement include the application of endogenous soluble complement inhibitors, the administration of antibodies, and either blockage of key proteins of the cascade reaction, neutralizing the action of the

complement-derived anaphylatoxin, or interfering with complement receptor 3 (CR3, CD18/11b)-mediated adhesion of inflammatory cells to the vascular endothelium. In addition, incorporation of membrane-bound complement regulators (DAF-CD55, MCP-CD46, CD59) has become possible by transfection of the correspondent cDNA into xenogeneic cells. Protection against complement-mediated inflammatory tissue damage could be achieved in various animal models of sepsis, myocardial as well as intestinal ischemia/reperfusion injury, adult respiratory distress syndrome, nephritis, and graft rejection. Thus, complement inhibition appears to be a suitable therapeutic approach to control inflammation (Kirschfink *et al.*, *Immunopharmacology* Dec;38(1-2):51-62, 1997)

Human CD46 has been identified as 1) a measles virus receptor protein; and 2) a regulator of the complement pathway. During measles virus (MV) infection, lymphopenia and immune suppression are observed in humans. CD46 (also known as membrane cofactor protein (MCP)) acts as a receptor for MV, accelerating entry of the virus into host cells. As a regulator of the complement cascade, CD46 acts to protect host cells from the autologous complement system. CD46, in addition to CD55 (decay-accelerating factor) and CD59 (protectin), has also been shown to protect tumor cells against lysis by activated complement (Schmitt *et al.*, (1999) *Eur. J. Cancer*, Jan;35(1):117-24). Thus, CD46 encompasses both complement-related and MV-mediated immunomodulation (Seya, *Int. J. Hematol.* Aug;64(2):101-9, 1996; Devaux *et al.*, *Eur. J. Immunol.*, Mar;29(3):815-22, 1999).

We believe that M144 encodes a dominant negative form of CD46 that prevents the proper formation of the complement complex and lysis of infected cells. We believe that *in vivo* administration of the M144 gene product will reduce inflammatory symptoms. Alternatively, the M144 gene product may be employed to inhibit viral entry into cells.

Viroceptors

As mentioned above, cytokine receptors have been evolutionarily acquired by poxviruses. The term viroceptor includes secreted soluble virus-encoded cytokine receptors. Viroceptors function 1) by binding host cytokines, thereby preventing subsequent interactions with their true cellular receptors; and 2) as virus-encoded transmembrane proteins with significant homology to cellular cytokine receptors. Several of the sequences disclosed in the present invention can be classified as viroceptors, including M121, M122, M154, M104, M107, and M128, which are described in more detail below. M121, M122 and M154 are immunoreceptor-related genes, whereas M104, M107 and M128 are multi-transmembrane receptor-related genes.

Immunoreceptor-Related Genes

As previously mentioned, the DNA sequences M121, M122, and M154 (SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17) (see Figure 15-17) are predicted to encode immunoreceptor-related proteins (SEQ ID NO: 35, SEQ ID NO: 36 and SEQ ID NO:37) (see Figures 35-37) that are expressed by myxoma-infected cells.

Immunoreceptors are key response molecules that receive and respond to signals embodied as receptor ligands. Immunoreceptors receive information from the extracellular milieu and transmit that information to the intracellular environment enabling coordination of the many complex interactions required to modulate an immune response. It is the theory of the present invention that the proteins encoded by the novel myxoma genes M121, M122, and M154 function to interrupt the normal function of the homologous immunoreceptor proteins expressed by immune cells, thereby inhibiting immunostimulation.

The M121 protein demonstrates high homology (24% identity) to the CD69 protein, a C-type lectin receptor that mediates recognition of carbohydrate molecules. A lectin is a protein with binding sites that recognize specific sugar residues. Such specific protein-carbohydrate interactions serve multiple functions in the immune

system. For example, many animal lectins mediate both pathogen recognition and cell-cell interactions. In addition, the broad selectivity of the sugar-binding site on a lectin contributes to the immune system's ability to discriminate between self and non-self (Weiss *et al.*, *Immunol Rev* 1998 Jun;163:19-34, 1998). Specific C-type lectin receptors can distinguish amongst a wide variety of lectins. We believe that expression of M121 protein by myxoma-infected cells competes with the CD69 receptor for specific carbohydrate ligands and thereby interrupts CD69-mediated responses of immune cells.

In preferred embodiments, the present invention provides the polypeptide encoded by the M121 gene. In particularly preferred embodiments, the M121 polypeptide is administered *in vivo* as an immunosuppressant. For example, in one aspect embodiment, the present invention provides a therapeutic preparation of M121 polypeptide that may be used to modulate pathogen recognition. Alternatively, in another aspect of the invention, administration of M121 *in vivo* may promote discrimination between self and non-self.

The M122 protein also shares (22%) identity to a C-type lectin receptor, specifically LY49C (herein referred to as NKR), over a 127 amino acid region. NKR mediates natural killer (NK) cell immune responses (Accession # G11330631). The M122 protein may therefore be secreted by myxoma infected cells to disrupt the function of NK cells within the immune system and provide protection against an NK mediated inflammatory response. Therefore, in preferred embodiments, the present invention provides the M122 protein as a therapeutic immunosuppressant agent.

The M154 protein exhibits homology to other viral proteins, including the gp120 protein of the Human Immunodeficiency Virus (HIV) (21%). It is well known that HIV infects CD4+ T cells. The tropism of HIV for these cells is determined through the envelope protein gp120, which binds the CD4 receptor (along with additional co-receptor molecules) (Paxton *et al.*, *Semin. Immunol.*, Jun;10(3):187-194, 1998) and enables the virus to fuse with the cell membrane, thereby being taken up by the cell. Binding of gp120 to CD4 also plays a major role in downregulating

CD4+ T cells, leading to the characteristic decline in the number of CD4+ T cells in HIV infected patients. One theory is that gp120 binding to CD4+ T cells plays a role in activating a cell death pathway in T cells (Peter *et al.*, *Br. Med. Bull.*, 53(3):604-16, 1997). Due to the known role of the gp120 protein in downregulating CD4+ T cells, we believe that *in vivo* expression of M154 binds and disrupts immunoreceptor function to persist myxoma infection. Thus, certain preferred embodiments of the invention include preparations of the M154 polypeptide that can be used as suppressors of immunoreceptor function.

Multi-Transmembrane Receptors

As previously mentioned, the DNA sequences M104, M107, and M128 (SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20) (see Figure 18-20) are predicted to encode homologs of several mammalian receptor proteins that contain multiple transmembrane regions. Multi-transmembrane receptor proteins are amphipathic proteins having multiple hydrophobic regions that span the lipid bilayer of the cell membrane from the cytoplasm to the cell surface interspersed between hydrophilic regions that are exposed to water on both sides of the membrane. The number of hydrophobic regions in an amphipathic protein is often proportional to the number of times that proteins spans the lipid bilayer. Many multi-transmembrane receptor-related proteins act as receptors for various ligands (*e.g.*, cytokines) that initiate transduction of a signal from the cell surface, where the ligand is binding, to the interior of the cell. This initiation is often in the form of a conformational change in the multi-transmembrane receptor upon ligand binding. Such complex formation is an important event in transducing immunomodulatory signals that are important in initiating or suppressing certain immune functions.

The M104 protein (SEQ ID NO: 38) (Figure 38) is a short polypeptide containing high sequence similarity to the ORF-74 IL-8 receptor encoded by Ateline herpesvirus (Rosenkilde *et al.*, *J. Biol. Chem.*, Jan 6;274(2):956-961, 1999). ORR-74 is a CXC chemokine receptor encoded by many γ -herpesviruses (*e.g.*, human

herpesvirus 8 and Kaposi's sarcoma-associated herpesvirus). ORF-74 is a seven transmembrane (7TM) protein that binds the chemokine IL-8 with high affinity, although it has limited homology to mammalian IL-8 receptors (CXCR-1 and CXCR-2).

5 7TM protein receptors frequently signal through G proteins (for reviews see Kelvin *et al.*, *J. Leukocyte Biol.*, 54:604-612, 1993; Murphy, *Ann. Rev. Imm.*, 12:593-633, 1994; Horuk, *Imm. Today*, 15:169-174, 1994). Some G proteins (G_s and G_i) couple receptors to the adenylate cyclase cascade, whereas others (G_p) couple receptors to the phospholipase C signaling pathway. Most 7TM chemokine receptors
10 preferentially signal through the G_i pathway, however ORF-74 activates the phospholipase C pathway, leading to constitutively high turnover of various mitogenic proteins (*e.g.*, phosphatidylinositol, cJun, N-terminal kinase, and p38 mitogen activated protein kinase). Therefore, ORF-74 also functions as an oncogene that induces cellular transformation. It has been proposed that ORF-74 could be
15 causally involved in the development of Kaposi's sarcoma lesions and lymphomas associated with herpesvirus infection (Rosenkilde *et al.*, *supra*).

While the wild type ORF74 protein consists of seven transmembrane regions, the M104 polypeptide disclosed herein only demonstrates one or two C-terminal transmembrane domain linked to a short cytosolic tail. Hence, without wishing to
20 limit the theory of the invention, we suggest that upon expression of M104 by infected cells, M104 polypeptide molecules interfere with IL-8 mediated signal transduction and act as dominant negative versions of the IL-8 receptor or other chemokine receptors. Thus, in one aspect of the invention, M104 is used as an immunosuppressant. Given the potential role of ORF-74 in cellular transformation
25 and malignancy, another aspect of the invention provides antagonists to ORF-74 that can be used as treatments for herpesvirus-associated malignancies. Such treatments are particularly desirable because it is well known that 7TM receptors are classically good drug targets.

The M107 protein (SEQ ID NO:39) (Figure 39) is predicted to contain four transmembrane regions and demonstrates high homology to multi-transmembrane receptors, particularly the 7TM receptor of *C. elegans*. Since, as noted above, such 7TM receptors are found among numerous chemokine receptors, including CXCR1, CCR2b, CXCR4, CCR4 and CCR5, it is herein hypothesized that the expression of M107 among infected cells leads to the disruption of chemokine receptor function. Therefore, the present invention provides the M107 polypeptide as a general immunomodulator of chemokine receptor function.

Sequence analysis of the M128 polypeptide (SEQ ID NO:40) (Figure 40) demonstrates at least five transmembrane regions with significant homology to CD47 (also known as the integrin-associated protein; IAP). Previous research has demonstrated that CD47 provides an adhesion-dependent costimulation pathway to T cells that is independent of CD28 molecules (Walclavicek *et al.*, *J. Immunol.*, 159(11):5345-5354, 1997). Therefore, without wishing to be bound by any particular theory, we propose the M128 disrupts adhesion mediated costimulation of T cells during myxoma infection and prevents CD47 function. In preferred embodiments of the present invention, M128 protein is provided as an immunosuppressant. More specifically, the M128 protein is provided as a T cell specific immunosuppressor.

Leporipox Virus Protein Expression

In general, *leporipox* virus proteins according to the invention, may be produced by transformation of a suitable host cell with all or part of a *leporipox* virus protein-encoding cDNA fragment (*e.g.*, the cDNAs described above) in a suitable expression vehicle.

Those skilled in the field of molecular biology will understand that any of a wide variety of expression systems may be used to provide the recombinant protein. The precise host cell used is not critical to the invention. The *leporipox* virus protein may be produced in a prokaryotic host (*e.g.*, *E. coli*) or in a eukaryotic host (*e.g.*, *Saccharomyces cerevisiae*, insect cells, *e.g.*, Sf21 cells, or mammalian cells, *e.g.*, COS

1, NIH 3T3, or HeLa cells). Such cells are available from a wide range of sources (e.g., the American Type Culture Collection, Rockland, MD; also, see, e.g., Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1994). The method of transformation or transfection and the choice of expression
5 vehicle will depend on the host system selected. Transformation and transfection methods are described, e.g., in Ausubel *et al.* (*supra*); expression vehicles may be chosen from those provided, e.g., in *Cloning Vectors: A Laboratory Manual*, P.H. Pouwels *et al.*, 1985, Supp. 1987).

One preferred expression system is the baculovirus system (using, for example,
10 the vector pBacPAK9) available from Clontech (Pal Alto, CA). If desired, this system may be used in conjunction with other protein expression techniques, for example, the myc tag approach described by Evan *et al.* (*Mol. Cell Biol.* 5:3610-3616, 1985).

Alternatively, a *leporipox* virus protein is produced by a stably-transfected
15 mammalian cell line. A number of vectors suitable for stable transfection of mammalian cells are available to the public, e.g., see Pouwels *et al.* (*supra*); methods for constructing such cell lines are also publicly available, e.g., in Ausubel *et al.* (*supra*). In one example, cDNA encoding the *leporipox* virus protein is cloned into an expression vector which includes the dihydrofolate reductase (DHFR) gene.
20 Integration of the plasmid and, therefore, the *leporipox* virus protein-encoding gene into the host cell chromosome is selected for by inclusion of 0.01-300 μ M methotrexate in the cell culture medium (as described in Ausubel *et al.*, *supra*). This dominant selection can be accomplished in most cell types. Recombinant protein expression can be increased by DHFR-mediated amplification of the transfected gene.
25 Methods for selecting cell lines bearing gene amplifications are described in Ausubel *et al.* (*supra*); such methods generally involve extended culture in medium containing gradually increasing levels of methotrexate. DHFR-containing expression vectors commonly used for this purpose include pCVSEII-DHFR and pAdD26SV(A) (described in Ausubel *et al.*, *supra*). Any of the host cells described above or,

preferably, a DHFR-deficient CHO cell line (*e.g.*, CHO DHFR⁻ cells, ATCC Accession No. CRL 9096) are among the host cells preferred for DHFR selection of a stably-transfected cell line or DHFR-mediated gene amplification.

Once the recombinant *leporipox* virus protein is expressed, it is isolated, *e.g.*,
5 using affinity chromatography. In one example, an anti-*leporipox* virus protein antibody (*e.g.*, produced as described herein) may be attached to a column and used to isolate the *leporipox* virus protein. Lysis and fractionation of *leporipox* virus protein-harboring cells prior to affinity chromatography may be performed by standard methods (see, *e.g.*, Ausubel *et al.*, *supra*). In another example, *leporipox*
10 virus proteins may be purified or substantially purified from a mixture of compounds such as an extract or supernatant obtained from cells (Ausubel *et al.*, *supra*). Standard purification techniques can be used to progressively eliminate undesirable compounds from the mixture until a single compound or minimal number of effective compounds has been isolated.

15 Once isolated, the recombinant protein can, if desired, be further purified, *e.g.*, by high performance liquid chromatography (see, *e.g.*, Fisher, *Laboratory Techniques In Biochemistry And Molecular Biology*, eds., Work and Burdon, Elsevier, 1980).

Polypeptides of the invention, particularly short *leporipox* virus protein fragments, can also be produced by chemical synthesis (*e.g.*, by the methods described
20 in *Solid Phase Peptide Synthesis*, 2nd ed., 1984 The Pierce Chemical Co., Rockford, IL).

These general techniques of polypeptide expression and purification can also be used to produce and isolate useful *leporipox* virus protein fragments or analogs (described herein).

25 In certain preferred embodiments, the *leporipox* protein might have attached any one of a variety of tags. Tags can be amino acid tags or chemical tags and can be added for the purpose of purification (for example a 6-histidine tag for purification over a nickel column). In other preferred embodiments, various labels can be used as means for detecting binding of a *leporipox* protein to another protein, for example to

a chemokine or a chemokine receptor. Alternatively, *leporipox* DNA or RNA may be labeled for detection, for example in a hybridization assay. *Leporipox* virus nucleic acids or proteins, or derivatives thereof, may be directly or indirectly labeled, for example, with a radioscope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator or an enzyme. Those of ordinary skill in the art will know of other suitable labels or will be able to ascertain such, using routine experimentation. In yet another preferred embodiment of the invention, the proteins disclosed herein, or derivatives thereof, are linked to toxins. Proteins linked to toxins can be used, for example to target toxic drugs to malignant tumors if the protein has the ability localize to the tumor.

Anti-Leporipox Virus Protein Antibodies

To generate *leporipox* virus protein-specific antibodies, a *leporipox* virus protein coding sequence (*i.e.*, mVOX-2) may be expressed, for example, as a C-terminal fusion with glutathione S-transferase (GST) (Smith *et al.*, *Gene* 67:31-40, 1988). The fusion protein may then be purified on glutathione-Sepharose beads, eluted with glutathione cleaved with thrombin (at the engineered cleavage site), and purified to the degree necessary for immunization of rabbits. Primary immunizations are carried out with Freud's complete adjuvant and subsequent immunizations with Freud's incomplete adjuvant. Antibody titres are monitored by Western blot and immunoprecipitation analyzes using the thrombin-cleaved *leporipox* virus protein fragment of the GST-*leporipox* virus fusion protein. Immune sera are affinity purified using CNBr-Sepharose-coupled *leporipox* virus protein. Antiserum specificity is determined using a panel of unrelated GST proteins (including GSTp53, Rb, HPV-16 E6, and E6-AP) and GST-trypsin (which was generated by PCR using known sequences).

As an alternate or adjunct immunogen to GST fusion proteins, peptides corresponding to relatively unique hydrophilic *leporipox* virus proteins may be generated and coupled to keyhole limpet hemocyanin (KLH) through an introduced

C-terminal lysine. Antiserum to each of these peptides is similarly affinity purified on peptides conjugated to BSA, and specificity tested in ELISA and Western blots using peptide conjugates, and by Western blot and immunoprecipitation using *leporipox* virus protein expressed as a GST fusion protein.

5 Alternatively, monoclonal antibodies may be prepared using the *leporipox* virus proteins described above and standard hybridoma technology (see, *e.g.*, Kohler *et al.*, *Nature*, 256:495, 1975; Kohler *et al.*, *Eur. J. Immunol.* 6:511, 1976; Kohler *et al.*, *Eur. J. Immunol.* 6:292, 1976; Hammerling *et al.*, In *Monoclonal Antibodies and T Cell Hybridomas*, Elsevier, NY, 1981; Ausubel *et al.*, *supra*). Once produced,
10 monoclonal antibodies are also tested for specific *leporipox* virus protein recognition by Western blot or immunoprecipitation analysis (by the methods described in Ausubel *et al.*, *supra*). Antibodies which specifically recognize *leporipox* virus proteins are considered to be useful in the invention; such antibodies may be used, *e.g.*, in an immunoassay to monitor the level of *leporipox* virus proteins produced by
15 a mammal (for example, to determine the amount or location of a *leporipox* virus protein).

 Preferably, antibodies of the invention are not only produced using the whole *leporipox* virus polypeptide, but using fragments of the *leporipox* virus polypeptide which lie outside highly conserved regions and appear likely to be antigenic, by
20 criteria such as high frequency of charged residues may also be used. In one specific example, such fragments are generated by standard techniques of PCR and cloned into the pGEX expression vector (Ausubel *et al.*, *supra*). Fusion proteins are expressed in *E. coli* and purified using a glutathione agarose affinity matrix as described in Ausubel *et al.* (*supra*). To attempt to minimize the potential problems of
25 low affinity or specificity of antisera, two or three such fusions are generated for each protein, and each fusion is injected into at least two rabbits. Antisera are raised by injections in a series, preferably including at least three booster injections.

Identification of Molecules that Modulate Leporipox Virus Biological Activity or
Whose Biological Activity is Modulated by Leporipox Virus

Isolation of the *leporipox* virus cDNA (as described herein) also facilitates the identification of molecules that increase or decrease a *leporipox* virus polypeptide biological activity. Similarly, molecules whose activity is modulated by a *leporipox* virus polypeptide biological activity can be identified. According to one approach, candidate molecules are added at varying concentrations to the culture medium of cells expressing *leporipox* virus mRNA. *Leporipox* virus polypeptide biological activity is then measured using standard techniques. The measurement of biological activity can include the measurement of *leporipox* virus polypeptide protein and nucleic acid molecule levels, or the effect of *leporipox* virus polypeptide on immunomodulation

If desired, the effect of candidate modulators on expression can, in the alternative, be measured at the level of *leporipox* virus protein production using the same general approach and standard immunological detection techniques, such as western blotting or immunoprecipitation with a *leporipox* virus polypeptide-specific antibody (see below).

Candidate modulators can be purified (or substantially purified) molecules or can be one component of a mixture of compounds (*e.g.*, an extract or supernatant obtained from cells; Ausubel *et al.*, *supra*). In a mixed compound assay, *leporipox* virus polypeptide expression is tested against progressively smaller subsets of the candidate compound pool (*e.g.*, produced by standard purification techniques, *e.g.*, HPLC or FPLC) until a single compound or minimal compound mixture is demonstrated to modulate *leporipox* virus polypeptide expression.

Alternatively, or in addition, candidate compounds can be screened for those that modulate *leporipox* virus polypeptide activity. In this approach, the level of immunomodulation in the presence of a candidate compound is compared to the level

of immunomodulation in its absence, under equivalent conditions. Again, such a screen can begin with a pool of candidate compounds, from which one or more useful modulator compounds is isolated in a step-wise fashion.

The screening assays described above can be carried out in a variety of ways that are well known to those skilled in this art. These include using *leporipox* virus polypeptide variants or by using fragments of a *leporipox* virus polypeptide.

A test compound that can be screened in the methods described above can be a chemical, be it naturally-occurring or artificially-derived. Such compounds can include, for example, polypeptides, synthesized organic molecules, naturally occurring organic molecules, nucleic acid molecules, and components thereof. Candidate *leporipox* virus polypeptide modulators include peptide as well as non-peptide molecules (*e.g.*, peptide or non-peptide molecules found, *e.g.*, in a cell extract, mammalian serum, or growth medium in which mammalian cells have been cultured).

In general, novel drugs for prevention or treatment of immunomodulatory diseases are identified from large libraries of both natural products, synthetic (or semi-synthetic) extracts, and chemical libraries using methods that are well known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening methods of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using these methods. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic-, or animal-based extracts, fermentation broths, and synthetic compounds, as well as modifications of existing compounds.

Numerous methods are also available for generating random or directed synthesis (*e.g.*, semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid molecule-based compounds. Synthetic compound libraries are commercially available from Brandon Associates (Merrimack, NH) and Aldrich Chemical

(Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA).

5 In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, *e.g.*, by standard extraction and fractionation methods. Furthermore, if desired, any library or compound can be readily modified using standard chemical, physical, or biochemical methods.

10 In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (*e.g.*, taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their therapeutic activities for immunological disorders can be employed whenever possible.

15 When a crude extract is found to regulate immunomodulation, further fractionation of the positive lead extract can be carried out to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having a desired activity. The same assays described herein for the detection of activities in mixtures of
20 compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value can be subsequently analyzed using, for example, any of the animal
25 models described herein.

Testing and Administration of Immunomodulatory Molecules

Leporipox immunomodulatory polypeptides of the present invention may be screened for immunomodulatory activity. For example, chemotaxis activity in the

presence of a candidate compound is compared to chemotaxis activity in its absence, under equivalent conditions. Such a screen may begin with a pool of candidate compounds, from which one or more useful immunomodulator compounds are isolated in a step-wise fashion. Chemotaxis (of eosinophil or other leukocyte) activity may be measured by any standard assay, for example, those described herein.

Candidate *leporipox* virus encoded modulators include peptide as well as non-peptide molecules (*e.g.*, peptide or non-peptide molecules found, *e.g.*, in a cell extract, mammalian serum, or growth medium on which mammalian cells have been cultured). Particularly useful are modulators of *leporipox* virus protein expression.

A molecule which promotes an increase in *leporipox* virus protein expression or a decrease in leukocyte chemotaxis activity is considered particularly useful in the invention; such a molecule may be used, for example, as a therapeutic to decrease the immunoreactivity in a individual. In addition, *leporipox* virus proteins identified in the present invention (or modifications and derivatives thereof) that exhibit these activities are also particularly desirable. For example, these polypeptides may be used to treat an individual that has rheumatoid arthritis. Other human diseases that may be treated using a molecule that act as an immunosuppressant or otherwise reduces the immune function include, acute inflammation, allergic reactions, asthmatic reactions, inflammatory bowel diseases (*i.e.*, Crohn's Disease and ulcerative colitis), transplant rejection, and restenosis.

A molecule which enhances or induces apoptosis may alternatively be used in the treatment of tumors.

Immunomodulators of this invention and other polypeptides found to be effective at the level of *leporipox* virus protein expression or activity may be confirmed as useful in animal models. The animal models that may be used in the present invention will test drug candidates for efficacy in treating autoimmune and inflammatory diseases. Target therapeutic areas include acute inflammation, rheumatoid arthritis, transplant rejection, asthma, inflammatory bowel disease, uveitis, restenosis, multiple sclerosis, psoriasis, wound healing, lupus erythematosus and any

other autoimmune or inflammatory disorder that can be recognized by one of ordinary skill in the art.

For example, other diseases related to inflammation that may be treated by methods the present invention include, for example, allergic rhinitis, atopic dermatitis and food allergies. Examples of other autoimmune disorders, where the immune system attacks the host's own tissues, include, but are not limited to type 1 insulin-dependent diabetes mellitus, deramatitis, meningitis, thrombotic thrombocytopenic purpura, Sjogren's syndrome, encephalitis, leukocyte adhesion deficiency, rheumatic fever, Reiter's syndrome, psoriatic arthritic, progressive systemic sclerosis, primary biliary cirrhosis, pemphigus, pemphigoid, necrotizing vasculitis, mayasthenia gravis, lupus erythmatusus, polymyositis, sarcoidosis, granulomatorsis, vasculitis, pernicious anemia, CNS inflammatory disorder antigen-antibody complex mediated diseases, autoimmune hemolytic anemia, Hashimoto's thyroiditis, Graves disease, habitual spontaneous abortions, Reynard's syndrome, glomerulonephritis, dermatomyositis, chronic active hepatitis, celiac disease, autoimmune complications of AIDS, atrophic gastritis, ankylosing spondylitis and Addison's disease.

Other diseases related to non-malignant or immunological-related cell-proliferative diseases that may be treated by methods the present invention include for example psoriasis, penphigus vularis, Behcet's syndrome, acute respiratory distress syndrome (ARDS), ischemic heart disease, atherosclerosis, post-dialysis syndrome, leukemia, acquired immune deficiency syndrome septic shock and other type of acute inflammation, and lipid histiocytosis.

If successful, the identified *leporipox* virus polypeptide may be used as anti-inflammatory or anti-cancer therapeutics (*e.g.*, a mouse tumor model)

Animal models for testing the immunomodulatory effects of candidate compounds are well known in the art. Therefore, the present invention merely refers to a selection of animal models that can be used to test the candidate compounds o the

invention and omits what is well known in the art. Animal models proposed for use in the present invention to test candidate compounds for their efficacy in treating autoimmune and inflammatory disorders include, but are not limited to:

5 *Acute inflammation:*

Animal models of acute inflammation are targeted for initial, fast drug efficacy screening and for their potential predicative value of outcomes in chronic inflammatory diseases. The following animal models may be used to test the candidate compounds of the present invention for their efficacy in treating acute
10 inflammation: 1) carrageenin induced inflammation 2) turpentine induced inflammation 3) transgenic HLAB-27 inflammatory and 4) ear-scratch model of inflammation.

Rheumatoid arthritis; rat, mouse and rabbit

Efficacy in Rheumatoid Arthritis evaluated in 1) various antigen induced
15 arthritis models in rabbit, rat and mouse; and 2) in transgenic rheumatological models.

The molecular and cellular mechanisms of action of the candidate compounds will be evaluated by testing their efficacy in influencing key intracellular mechanisms that regulate degradative processes involved in joint disease. Important molecular
20 and cellular mechanisms that will receive particular focus include signaling events regulating disease processes such as increased angiogenesis, synovial hyperplasia and matrix metalloprotease expression. These processes are thought to be involved in cartilage degradation in arthritic diseases.

25 1. Collagen induced arthritis; rat, mouse and rabbit

Autoimmune-mediated polyarthritis can be induced in certain strains of rodents (rat, mouse and rabbit) and non-human primates by immunizing them with native type II collagen. The collagen induced arthritis model is widely used and well characterized. Collagen induced arthritis is mediated by susceptibility to

autoantibodies which bind to a particular region of type II collagen. The mechanism of induction is linked to MHC-class II molecules but also depends on the species of type II collagen used for immunization.

5 2. Ovalbumin induced arthritis; rabbit

Candidate compounds are tested for efficacy in decreasing signs and symptoms of ovalbumin arthritis. Polyarthritis is induced in rabbits by immunizing them with Ovalbumin.

10 3. Adjuvant induced arthritis; rat, mouse and rabbit

Candidate compounds are tested for the efficacy in decreasing signs and symptoms of adjuvant induced arthritis. Polyarthritis is induced in certain strains of rodents by immunizing them with Freud's Adjuvant.

15 4. Streptococcal cell wall-induced arthritis; rat

Candidate compounds are tested for efficacy in decreasing signs and symptoms of streptococcal cell wall-induced arthritis. Chronic, erosive polyarthritis is induced by intraperitoneal-injection of aqueous suspension of cell wall fragments, isolated from group A streptococci.

20

Transplant rejection (acute and chronic)

Efficacy in transplant rejection is evaluated in various models of graft vascular disease (GVD). GVD is the most common cause of late graft failure in solid organ transplantation. GVD or graft atherosclerosis is characterized by plaque formation and fibrosis in small vessels. The development of graft vascular disease has been
25 associate with acute allograft rejection, ischemia-reperfusion injury and bacterial or viral infections. The common pathway of these postoperative insults results in perivascular inflammation which triggers migration of mesenchymal cells into the vessel wall eventually resulting in occlusion or partial occlusion of the vessel lumen.

1. *Aortic allograft model; rat, rabbit, monkey*

Candidate compounds are tested for efficacy in reducing graft atherosclerosis and transplant rejection in a model of vascular injury after transplantation of aortic segments performed in certain strains of MHC mismatched rats, and rabbits.

5

2. *Tracheal allograft model; rat, rabbit, monkey*

Candidate compounds are tested for efficacy in reducing graft atherosclerosis and transplant rejection in a model of vascular injury after transplantation of tracheal segments performed in certain strains of MHC mismatched rats, rabbits, and monkeys.

10

3. *Heterotopic heart transplant; mouse, rat, monkey*

A heterotopic heart transplantation is performed in MHC mismatched rats. In this model, rodents are treated with cyclosporine A for only the first 7 days after transplantation, are allowed to develop graft vascular disease, and are then analyzed after sacrifice at postoperative day 90.

15

4. *Orthotopic kidney transplant; mouse, rat, monkey*

An orthotopic kidney transplantation is performed in MHC mismatched rats. In this model, animals receiving subtherapeutic doses of cyclosporine A for the first 10 days after transplantation, are allowed to exhibit features of chronic renal allograft rejection in 70% of cases, and are then analyzed after sacrifice at postoperative day.

20

5. *Orthotopic lung transplant; rat, monkey*

Candidate compounds are tested for effectiveness in delaying or reducing signs and symptoms of organ rejection after lung whole organ transplantation in rats and monkeys .

25

6. *Reperfusion injury; rat*

The immediate postoperative course in clinical lung transplantation is often severely impaired by delayed graft function as a result of ischemia and reperfusion injury. Preventive efficacy of drug candidates in ischemia-reperfusion injury is evaluated using a model of acute, *in vivo* double lung transplantation in the rat
5 (Hausen *et al.*, *Ann Thorac Surg* 61:1714-9,1996 incorporated herein by reference).

Restenosis

Candidate compounds will be tested for efficacy in reducing atherosclerotic plaque deposition in a model of coronary restenosis after balloon angioplasty.

10 Atherosclerotic plaque formation is critically involved in vascular occlusion and has been linked to excessive inflammatory and thrombotic response to arterial injury.

Asthma; rodent

The effectiveness of candidate compounds in reduction of signs and symptoms
15 of asthma is evaluated in rodent models of antigen induced experimental airways inflammation. The models include:

1. Ovalbumin induced experimental airways inflammation; rodent

Candidate compounds are tested for efficacy in reducing inflammatory cell
20 components in the bronchoalveolar lavage of the lungs after aerosol challenge in ovalbumin sensitized rodent models of experimental airways inflammation.

2. Ovalbumin induced allergic sensitization in presence of GM-CSF transgene expression; mice

25 Candidate compounds are tested for efficacy in reducing inflammatory cell components in the bronchoalveolar lavage of the lungs of mice after ovalbumin aerosol challenge in the context of local expression of GM-CSF (Staempfli *et al.*, *J. Clin. Invest.*, Vol. 102:9, 1704-1714).

Inflammatory bowel disease (IBD); mice and rats

Drug candidates are evaluated for their potential therapeutic efficacy in ulcerative colitis or Crohn's disease utilizing various models of antigen induced and genetically mediated spontaneous chronic intestinal inflammation in mice and rats.

5 Examples include:

1. Dextran sulfate sodium induced IBD; mice

Chronic, irreversible clinical symptoms of IBD are induced by treating mice with an oral administration of dextran sulfate sodium.

10

2. Gene deletion and transgenic models for IBD; rodent

Compound efficacy will be tested in transgenic rodent lines which develop symptoms closely resembling the human elements of inflammatory bowel disease. Models include, the targeted deletion of the genes encoding IL-2, IL-10, TGF beta, T-cell receptor alpha/beta, keratin 8, Gi2 alpha. In addition, animals expressing transgenes for the human WA-B27 and HLA-B27 as well as a dominant negative construct which functionally blocks N-cadherin will be tested.

15

Uveitis

20

Drug candidates will be evaluated for efficacy in various animal models of uveitis. Key models include both, experimental autoimmune uveitis and adoptively transferred experimental autoimmune uveitis.

1. Experimental autoimmune uveitis (EAU)

25

EAU is a T-cell mediated inflammatory eye disease that can be induced in several mammalian species by immunization with ocular-specific antigens (Gery *et al.*, *Invest. Ophthalmol. Vis. Sci.*, 27: 1296-1300, 1986,. Sanui *et al.*, *J. Exp. Med.*,

169:1947-1989, incorporated herein by reference). This experimental disease is considered a model for a family of inflammatory eye diseases in humans and has been used to examine numerous modalities before their human testing.

5 2. Adoptively transferred experimental autoimmune uveitis

Adoptively transferred EAU is induced through injection of lymphocytes presensitized against the retinal antigen are injected into naive syngenic recipients (McAllister *et al.*, *J. Immunol.*, 138:1416-1420, 1987 incorporated herein by reference)

10 Once identified, a *leporipox* virus immunomodulator or anticarcinogen may be administered with a pharmaceutically-acceptable diluent, carrier, or excipient, at a pharmaceutically effective dose. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer *leporipox*
15 virus proteins to patients suffering from presymptomatic carcinoma. Any appropriate route of administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral administration. Therapeutic formulations may be in the form of liquid solutions or
20 suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are found in, for example, "Remington's Pharmaceutical Sciences." Formulations for parenteral
25 administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral

delivery systems for NES1 modulatory compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

If desired, treatment with a NES1 modulatory compound may be combined with more traditional cancer therapies such as surgery, radiation, or chemotherapy.

Detection of Specific Conditions

Leporipox virus polypeptides and nucleic acid sequences find diagnostic use in the detection or monitoring of inflammatory, autoimmune and other conditions. For example, because *leporipox* virus proteins are involved in leukocyte chemotaxis and because a decrease in the number of leukocytes correlates with immunosuppression, an alteration in the level of particular *leporipox* virus protein production provides an indication of the prognosis of the condition. Levels of *leporipox* virus protein expression may be assayed by any standard technique. For example, its expression in a biological sample (*e.g.*, a biopsy) may be monitored by standard Northern blot analysis or may be aided by PCR (see, *e.g.*, Ausubel *et al.*, *supra*; *PCR Technology: Principles and Applications for DNA Amplification*, ed., H.A. Ehrlich, Stockton Press, NY; and Yap and McGee, *Nucl. Acids. Res.* 19:4294, 1991).

In yet another approach, immunoassays are used to detect or monitor *leporipox* virus protein in a biological sample. *Leporipox* virus protein-specific polyclonal or monoclonal antibodies (produced as described above) may be used in any standard immunoassay format (*e.g.*, ELISA, Western blot, or RIA assay) to measure *leporipox* virus polypeptide levels; again comparison is to wild-type *leporipox* virus protein levels. A change in *leporipox* virus protein production may be indicative of a particular prognosis. Examples of immunoassays are described, *e.g.*, in Ausubel *et*

al., supra. Immunohistochemical techniques may also be utilized for *leporipox* virus protein detection. For example, a tissue sample may be obtained from a patient, and a section stained for the presence of *leporipox* virus protein using an anti-*leporipox* virus protein antibody and any standard detection system (*e.g.*, one which includes a secondary antibody conjugated to horseradish peroxidase). General guidance regarding such techniques can be found in, *e.g.*, Bancroft and Stevens (*Theory and Practice of Histological Techniques*, Churchill Livingstone, 1982) and Ausubel *et al.* (*supra*).

Leporipox Virus Gene Therapy

Because expression of *leporipox* virus protein may correlate with autoimmune, inflammatory or tumor prognosis, the *leporipox* virus gene also finds use in immunomodulatory or anti-cancer gene therapy. For example, to enhance leukocyte infiltration of a tumor, a functional *leporipox* virus gene may be introduced into cells at the site of a tumor. In addition, *leporipox* virus polypeptides that are shown to reverse autoimmune reactions may also be used in gene therapy. Alternatively, *leporipox* virus polypeptides which alter inflammatory responses may be administered via gene therapy for the treatment of eosinophil mediated inflammatory conditions.

Retroviral vectors, adenoviral vectors, adeno-associated viral vectors, or other viral vectors with the appropriate tropism for *leporipox* virus protein-expressing cells may be used as a gene transfer delivery system for a therapeutic *leporipox* virus gene construct. Numerous vectors useful for this purpose are generally known (Miller, *Human Gene Therapy* 15-14, 1990; Friedman, *Science* 244:1275-1281, 1989; Eglitis and Anderson, *BioTechniques* 6:608-614, 1988; Tolstoshev and Anderson, *Current Opinion in Biotechnology* 1:55-61, 1990; Sharp, *The Lancet* 337:1277-1278, 1991; Cornetta *et al.*, *Nucleic Acid Research and Molecular Biology* 36:311-322, 1987; Anderson, *Science* 226:401-409, 1984; Moen, *Blood Cells* 17:407-416, 1991; and Miller and Rosman, *Biotechniques* 7:980-990, 1989; Le Gal La Salle *et al.*, *Science*

259:988-990, 1993; and Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg *et al.*, *N. Engl. J. Med* 323:370, 1990; Anderson *et al.*, U.S. Pat. No. 5,399,346).

Non-viral approaches may also be employed for the introduction of therapeutic
5 DNA into cells. For example, *leporipox* virus gene may be introduced into a tumor cell by the techniques of lipofection (Felgner *et al.*, *Proc. Natl. Acad. Sci. USA* 84:7413, 1987; Ono *et al.*, *Neuroscience Lett* 117:259, 1990; Brigham *et al.*, *Am. J. Med. Sci.* 298:278, 1989; Staubinger and Papahadjopoulos, *Meth. Enz.* 101:512, 1983); asialorosonucoid-polylysine conjugation (Wu and Wu, *J. Biol. Chem.*
10 263:14621, 1988; Wu *et al.*, *J. Biol. Chem.* 264:16985, 1989); or, less preferably, microinjection under surgical conditions (Wolff *et al.*, *Science* 247:1465, 1990).

For any of the above approaches, the therapeutic *leporipox* virus DNA construct is preferably applied to the site of the malignancy or inflammation and cytotoxic damage (for example, by injection), but may also be applied to tissue in the
15 vicinity of the malignancy or inflammation and cytotoxic damage or even to a blood vessel supplying these areas.

In the gene therapy constructs, *leporipox* virus cDNA expression is directed from any suitable promoter (*e.g.*, the human cytomegalovirus, simian virus 40, or metallothionein promoters), and its production is regulated by any desired mammalian
20 regulatory element. For example, if desired, enhancers known to direct preferential gene expression in endothelial or epithelial cells may be used to direct *leporipox* virus protein expression. Such enhancers include, without limitation, the lung specific promoters (*e.g.* surfactant), and gut specific regulatory sequences.

Alternatively, if a *leporipox* virus genomic clone is utilized as a therapeutic
25 construct (for example, following its isolation by hybridization with the *leporipox* virus cDNA described above), *leporipox* virus protein expression is regulated by its cognate regulatory sequences or, if desired, by regulatory sequences derived from a heterologous source, *e.g.*, any of the promoters or regulatory elements described above.

Less preferably, *leporipox* virus gene therapy is accomplished by direct administration of the *leporipox* virus mRNA to a tumor. This mRNA may be produced and isolated by any standard technique, but is most readily produced by *in vitro* transcription using a *leporipox* virus cDNA under the control of a high efficiency promoter (*e.g.*, the T7 promoter). Administration of *leporipox* virus mRNA to malignant cells is carried out by any of the methods for direct nucleic acid administration described above.

Ideally, the production of *leporipox* virus protein by any gene therapeutic approach described above results in a cellular level of *leporipox* virus protein that is at least equivalent to the normal, cellular level of NES1 in an unaffected individual. Treatment by any NES1-mediated gene therapy approach may be combined with more traditional cancer therapies (*e.g.*, surgery, radiation, or chemotherapy for treatment of tumors).

Another therapeutic approach included within the invention involves direct administration of recombinant *leporipox* virus protein, either to the site of a malignancy (for example, by injection) or systemically by any conventional recombinant protein administration technique for treatment of an autoimmune or inflammatory disorder. The actual dosage of *leporipox* virus protein depends on a number of factors, including the size and health of the individual patient, but, generally, between 0.1mg and 100mg inclusive are administered per day to an adult in any pharmaceutically-acceptable formulation.

The above approaches may also be used to inhibit the activity of the candidate compound by substituting an altered *leporipox* virus polypeptide having *leporipox* virus protein blocking activity (*e.g.*, have a deletion or insertion at the amino terminus) for the *leporipox* virus polypeptide described above.

Transgenic Animals

Transgenic animals may be made using standard techniques. For example, a *leporipox* virus gene may be provided using endogenous control sequences or using

constitutive, tissue-specific, or inducible regulatory sequences. Transgenic animals lacking functional *leporipox* virus polypeptide may also be made using standard techniques. This may be done by engineering knock-out mutations in the *leporipox* virus gene using DNA sequences provided herein.

5

Leporipox Virus Gene Sequences

In general, the present invention relates to *leporipox* virus nucleic acid. In some preferred embodiments the nucleic acid is genomic DNA. In other preferred embodiments the nucleic acid is cDNA. In yet other preferred embodiments, the nucleic acid is mRNA. In certain preferred aspects of the invention the *leporipox* virus nucleic acid encodes an immunomodulatory polypeptide. Preferably the immunomodulatory polypeptide is of the myxoma species or alternatively the Shope fibroma species of *leporipox* viruses. The immunomodulatory polypeptide may be an immunosuppressor or an immunostimulator. Preferably the invention relates to a polypeptide that is substantially identical (at least 80% identity) with the polypeptides disclosed herein. For example, the polypeptide may be any one, or a combination of a cytokine, an anti-inflammatory, an immunoreceptor, a multi-transmembrane receptor protein or a secreted protein.

20 *Myxoma Virus Knockouts*

Poxviruses are among the largest eukaryotic DNA viruses and have the unusual capacity to replicate autonomously in the cytoplasm of infected cells. Many poxvirus proteins have been defined as virulence factors on the basis that, when present, they confer increased pathogenicity and improve viral replication within immunocompetent hosts. When genes that encode these virulence factor proteins are deleted, the resulting virus strain generally exhibits an attenuated or altered disease phenotype (Turner, Curr. Top. Microbiol. Immunol., 163:125-151, 1990; Buller Microbiol. Rev., 55:80-122, 1991; Smith, J. Gen. Virol., 74:1725-1740; McFadden, Austin (TX): R. G. Landes Company, 1995, incorporated herein by reference). Such

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“knockout” myxoma viruses may assist in the elucidation of the immunomodulatory or other role of viral proteins.

Using standard virological assays (Nash *et al.*, (1999) Immunological Review, 57:731 to end), one of ordinary skill in the art may establish the contribution of each gene to myxoma virus infection and the general biochemical and physiological progression of myxomatosis. Knockout myxoma viruses lacking a particular gene may be generated using standard molecular biological techniques (see Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY, 1989; Innis *et al.*, *PCR Protocols: A Guide to Methods and Applications*, Academic Press, San Diego, CA, 1990; Erlich *et al.*, *PCR Technology: Principles and Applications for DNA Amplification*, Stockton Press, New York, NY, 1989 each of which is incorporated herein by reference). The virulence of these knockout viruses may be assessed using standard infectivity assays well known in the art (see Nash *et al.*, (1999) Immunological Review, 57:731 to end). For example, as mentioned above, the OX-2 homolog M141 (mVox-2) (SEQ ID NO: 9) might be useful in elucidating the mechanism used by myxoma virus and other poxviruses to disrupt T cell stimulation. Such a discovery may lead to a method of modulating T cell stimulation in humans.

Examples

Cloning Additional Leporipox Virus Genes. Based on the amino acid sequences provided by the present invention degenerate oligonucleotide primers containing restriction sites will be synthesized. First strand cDNA will be synthesized from RNA prepared from a tissue of interest and PCR will be performed with an initial five cycles, for example, at 37° for 60s, followed by 25 cycles at 50° for 60s (denaturation at 95° for 30s and extension at 72° for 90s) in order to amplify a *leporipox* virus cDNA fragment that can be subsequently subcloned into Bluescript II KS (Stratagene). Construction of a cDNA library using poly A RNA isolated from the selected tissue will be performed using Stratagene ZAP Express Vector according to

the directions of the manufacturer. Potential clones will be subsequently amplified and an aliquot of this cDNA library containing phage will be screened with the *leporipox* virus cDNA that has been ³²P- labeled with Klenow enzyme. Isolated phagemids will be subsequently subjected to automated sequencing on both strands using Applied Biosystems Instrumentation (model 373a) and the dye- terminator protocol. Sequence analysis will be performed using software developed by the University of Wisconsin genetics computer group (Altschul, *et al. J. Mol. Biol.* 215:403-410, 1990).

DNA and RNA analysis. RNA will be isolated by CsCl centrifugation in guanidine isothiocyanate (Chirgwin, *et al. (1979) Biochemistry.* 18:5294-9). Biologically active ribonucleic acid will be isolated from sources enriched in ribonuclease. DNA will be isolated from these gradients as well. In some cases, RNA will be isolated using RNazol (Biotech Lab, Inc.) according to the directions of the manufacturer. Poly A RNA will be enriched by elution through an oligo dT column (Pharmacia). For example, 10 mcg of total RNA, 2 mcg of poly A RNA, or 10 mcg of restriction endonuclease cut DNA will be electrophoresed in agarose, and transferred to Gene Screen (NEN Dupont) membranes. Membranes will be hybridized with ³²P labeled full length cDNA or a fragment encoding the translated protein. High stringency hybridization will be performed, for example, in 50% formamide, 10% dextran sulfate, 5X SSC, 1X Denhardt's solution (0.0002% (w/v) polyvinylpyrrolidone, 0.0002% (w/v) BSA, 0.0002% (w/v) Ficoll 400), 1% (w/v) SDS, 100 mcg/ml denatured herring sperm DNA, and 20mM Tris at 42oC and blots will be washed with 0.2X SSC, 0.5% SDS at 65oC. Low stringency hybridization will be performed, for example, in 0.6M NaCl, 80mM TrisCl, 4mM EDTA, 0.1% (w/v) sodium pyrophosphate, 0.1% (w/v) SDS, 10X Denhardts, 100mcg/ml denatured herring sperm DNA at 50oC and washed with 1XSSC, 0.05% SDS at 50oC. Quantitation of the intensity of band hybridization will be determined using a Phosphor-Imager (Molecular Dynamics).

Leporipox Virus Gene Analysis. A cDNA probe from the coding region of the *Leporipox* virus cDNA will be ³²P-labeled with Klenow enzyme and used to screen approximately 1 X 10⁶ plaques from a mammalian genomic library (e.g., a variety of libraries are available from Stratagene, La Jolla, CA) under conditions of low stringency (hybridization in 0.6 M NaCl, 80mM TrisCl, 4mM EDTA, 0.1% sodium pyrophosphate, 0.1% SDS, 10X DenhardtOs solution (0.002% polyvinylpyrrolidone, 0.002% BSA, 0.002% Ficoll 400), 100mcg/ml denatured herring sperm DNA at 50°C and blots washed with 1X SSC, 0.05% SDS at 50°C). Plaques that hybridize strongly will be purified. The genomic DNA will be liberated from the phage DNA by restriction digestion with the appropriate enzymes and sub-cloned into pBlue- Script SK II (Stratagene). Any positively identified genomic fragment that hybridizes with the probe will be subcloned into, for example, pBlue-Script KS II, and subjected to automated sequencing on both strands using Applied Biosystems Instrumentation (model 373a) and the dye-terminator protocol. Sequence analysis will be performed using software developed by the University of Wisconsin genetics computer group Altschul, *et al.* (1990) J. Mol. Biol. 215, 403-410.

The *leporipox* virus gene homolog chromosomal localization will be determined by the analysis of any identified polymorphisms in the gene. PCR primers flanking this polymorphism will be constructed and genomic DNA will be amplified by PCR. Using these primers, a size polymorphism will be identified (For example, see Rowe, *et al.*, *Mamm. Gen.* 5, 253-274, 1994).

Murine Leporipox cDNA Analysis. The identified genomic fragment will be used to screen a mammalian cDNA expression library (Stratagene) under conditions of high stringency (hybridization in 50% formamide, 10% dextran sulfate, 5X SSC, 1X DenhardtOs solution, 1% SDS, 100 mcg/ml denatured herring sperm DNA, and 20mM Tris at 42°C and blots were washed with 0.2X SSC, 0.5% SDS at 65°C). Positive plaques will be identified, purified, and phagemids will be prepared according to the instructions of the library manufacturer. The inserts will be

completely sequenced on both strands by automated sequencing. Alignment analysis will be determined by the Clustal method using MegAlign software (DNASTAR Inc) (Higgins, *et al.* (1988) Gene 73, 237-244).

5 *Construction and Transfection of Protein Expression Vectors.* PCR primers will be designed to amplify the coding region of the *leporipox* gene, or homolog or derivative thereof, flanked by convenient restriction sites for subsequent sub-cloning. PCR will be performed under standard conditions using *leporipox* cDNA-pBlueScript as a template. The resulting PCR products will be subsequently
10 subcloned using, for example, a TA cloning kit (Invitrogen, San Diego, CA) and confirmatory sequencing will be performed. *Leporipox* cDNA will be subcloned into the available restriction sites of pcDNA-I/Amp (Invitrogen). Approximately 4 mcg of the *leporipox* -pcDNA-I construct will be transfected into 100 mm plates containing ~30% confluent COS cells using DEAE-Dextran (Lopata, *et al.*, *Nucl. Acids Res.* 12,
15 5707-5717, 1984). In order to measure transfection efficiency, a replicate sample of COS cells will be transfected with a CMV promoter-placental alkaline phosphatase control plasmid (Fields-Berry, *et al.*, *Proc. Nati. Acad. Sci. U.S.A.* 89, 693-697, 1992). RNA expression will be confirmed by Northern analysis using the *leporipox* cDNA as a probe. *Leporipox* -pcDNA-I transfected or mock transfected COS cell
20 supernatant will be obtained after 72 hrs of culture and stored at 4°C. In another set of transfection experiments, *leporipox* cDNA will be similarly subcloned into the available site of MoLTR-SV40 I/PA expression vector (for example, see Luster, *et al.*, *J. Exp. Med.* 178, 1057-1065, 1993). 20 mcg of linearized *leporipox* -MoLTR construct and 1 mcg of linearized neomycin resistance plasmid pSV7Neo will be used
25 to transfect J558L cells by electroporation. G418 resistant cells from single wells will be analyzed for *leporipox* mRNA expression by Northern analysis. Cells expressing *leporipox* virus protein or control untransfected cells (that do not express *leporipox* virus protein) will be expanded in large cultures. In order to optimize the concentration of *leporipox* virus protein in the supernatant, the cells will be grown at

high density (1×10^6 cells/ml) in RPMI without FCS, cultured for 72 hrs, and the conditioned medium will be concentrated 5-fold with Centricon 3000 microconcentrators (Amicon, Beverly, MA) before being stored.

5 *Chemotaxis Assays.* Murine leukocytes, for example eosinophils, will be isolated. Eosinophils in particular will be isolated from IL-5 transgenic mice (Dent, *et al.* (1990) *J. Exp. Med.* 172, 1425-1431). These mice develop splenomegaly with eosinophils accounting for ~30% of the splenocytes. Eosinophils will be purified from the spleen using immuno-magnetic separation to remove the contaminating
10 splenocytes. Briefly, splenocytes will be labeled with anti-Thy-1 (M5/49), anti-B220 (6B2), and anti-Lyt-2 (53-6.7). Hybridoma cell lines will be obtained, for example, from American Type Culture Collection and hybridoma cell supernatants will be used as a source of antibodies. The antibody labeled cells will be treated with, anti-serum coated-magnetic beads, the anti-serum having specificity for the isotype of the
15 primary antibody, (M450, Dynal, Great Neck, NY) and eosinophils will be enriched by negative selection through a magnetic field. Macrophage cells will be isolated from the peritoneal cavity of mice that had been pre-treated (2 days prior) with intraperitoneal injection of 2.9% thioglycollate (Difco, Detroit, CA). Peritoneal neutrophils will be isolated from mice pre-treated with sodium casein (Luo, *et al.*, *J.*
20 *Immun.* 153, 4616-4624, 1994). Macrophages and neutrophils will be purified by Percoll gradients (Luo, *et al.*, *J. Immun.* 153, 4616-4624, 1994. Eosinophils or macrophages will be suspended in HBSS with 0.05% BSA at 2×10^6 cells/ml, respectively, and 50 ml of replicate cells will be placed in the top well of a 48 well micro-chemotaxis chamber (Neuro Probe, Inc, Cabin John, MD). A polycarbonate
25 filter with 5- μ m pores will be used to separate the cells from buffer (30 ml) alone or buffer containing recombinant COS cell supernatant and a positive (for example MCP-1 (Rollins, & Pober, *Am. J. Path.*, 138, 1315-1319, 1991)) and negative control (for example, supernatant from mock-transfected COS cells) so that a comparison can be made and the immunosuppressive (inhibition of chemotaxis) properties of the

leporipox virus protein assessed. Cells will be incubated at 37°C for 60 minutes (eosinophils and neutrophils) or 90 minutes (macrophages) and the cells that migrate across the filter and adhere to the bottom side of the filter will be stained with Diff-Quick (Baxter Scientific, McGaw Park, IL). The number of cells per 400X field will be counted.

Statistical Analysis. The statistical significance of differences between means will be determined by analysis of variance (ANOVA). $P < 0.05$ will be considered significant. When ANOVA indicates a significant difference, the Newman-Keuls test will be used to determine which groups are significantly different from each other.

Analysis of Leporipox cDNA. Using degenerate oligonucleotide primers based upon the amino acid sequence of the *leporipox* gene sequences disclosed herein, a cDNA will be amplified by PCR from single stranded cDNA from a selected mammalian tissue. This PCR product will encode a peptide identical to the *leporipox* gene and will be used to screen an amplified cDNA library made from selected mammalian tissue. Positive plaques will be subsequently purified. Sequence analysis of the plaques will then be performed as described herein above.

Leporipox mRNA Expression in Different Organs. Northern blot analysis of total RNA isolated from different mammalian tissue samples may reveal detectable expression of any *leporipox* virus gene, homolog or derivative. Mammalian tissues including the brain, bone marrow, skin, intestines, stomach, heart, thymus, lymph node, mammary gland, skeletal muscle, tongue, spleen, liver, testes, and kidney will be analyzed. Likewise, cell lines such as macrophages isolated and cultured from the spleen, a lung epithelial cell line, and a colon adenocarcinoma cell, will be analyzed for expression of *leporipox* or homologous mRNA.

Other Embodiments

In other preferred embodiments, the invention includes any protein which is substantially identical to a leporipox virus polypeptide (preferably sequences of Figures 21-40); such homologs include other substantially pure naturally occurring mammalian homologs of leporipox proteins as well as allelic variations; natural mutants; induced mutants; proteins encoded by DNA that hybridizes to the *leporipox* sequences of Figures 1-20 under high stringency conditions or low stringency conditions (*e.g.*, washing at 2X SSC at 40°C with a probe of at least 40 nucleotides); and polypeptides or proteins specifically bound by antisera directed to a *leporipox* polypeptide. The term also includes chimeric polypeptides that include a *leporipox* fragment.

The invention further includes analogs of the *leporipox* virus polypeptides. Analogs can differ from the naturally occurring *leporipox* protein by amino acid sequence differences, by post-translational modifications, or by both. Analogs of the invention will generally exhibit at least 70%, more preferably 80%, even more preferably 90%, and most preferably 95% or even 99%, identity with all or part of a naturally occurring *leporipox* sequence. The length of comparison sequences will be at least 8 amino acid residues, preferably at least 24 amino acid residues, and more preferably more than 35 amino acid residues. Modifications include *in vivo* and *in vitro* chemical derivatization of polypeptides, *e.g.*, acetylation, carboxylation, phosphorylation, or glycosylation; such modifications may occur during polypeptide synthesis or processing or following treatment with isolated modifying enzymes. Analogs can also differ from the naturally occurring *leporipox* polypeptide by alterations in primary sequence. These include genetic variants, both natural and induced (for example, resulting from random mutagenesis by irradiation or exposure to ethanemethylsulfate or by site-specific mutagenesis as described in Sambrook, Fritsch and Maniatis, *Molecular Cloning: A Laboratory Manual* (2d ed.), CSH Press, 1989, hereby incorporated by reference; or Ausubel *et al.*, *supra*, hereby incorporated by reference). Also included are cyclized peptides molecules and analogs which

contain residues other than L-amino acids, *e.g.*, D-amino acids or non-naturally occurring or synthetic amino acids, *e.g.*, β or γ amino acids.

In addition to full-length polypeptides, the invention also includes *leporipox* polypeptide fragments. As used herein, the term "fragment" means at least 10
5 contiguous amino acids, preferably at least 30 contiguous amino acids, more preferably at least 50 contiguous amino acids, and most preferably at least 60 to 80 or more contiguous amino acids. Fragments of *leporipox* virus proteins can be generated by methods known to those skilled in the art or may result from normal protein processing (*e.g.*, removal of amino acids from the nascent polypeptide that are
10 not required for biological activity or removal of amino acids by alternative mRNA splicing or alternative protein processing events).

Preferable fragments or analogs according to the invention are those which exhibit biological activity (for example, the ability to act as an immunomodulator as described herein). Preferably, a *leporipox* polypeptide, fragment, or analog exhibits
15 at least 10%, more preferably 30%, and most preferably, 70% or more of the biological activity of a full length naturally occurring *leporipox* virus polypeptide.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the
20 invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

25 What is claimed is:

CLAIMS

1. A substantially pure *leporipox* virus immunomodulatory polypeptide.
2. The polypeptide of claim 1, wherein said polypeptide is derived from myxoma virus or Shope Fibroma virus.
3. The polypeptide of claim 1, wherein said polypeptide comprises an amino acid sequence encoding a chemokine, a cytokine, an immunomodulator, an anti-inflammatory polypeptide, an immunoreceptor, or multi-transmembrane receptor protein.
4. The polypeptide of claim 1, wherein said polypeptide comprises an amino acid sequence that encodes an identifiable signal sequence.
5. The polypeptide of claim 1, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40.
6. The polypeptide of claim 5 wherein said polypeptide comprises an amino acid sequence substantially identical to SEQ ID NO:31.
7. The polypeptide of claim 5, wherein said cytokine comprises an amino acid sequence substantially identical to SEQ ID NO:32.

8. A substantially pure *leporipox* virus nucleic acid molecule comprising a sequence encoding a *leporipox* virus polypeptide.
9. The nucleic acid molecule of claim 8, wherein said nucleic acid molecule encodes a myxoma virus polypeptide or a Shope fibroma virus polypeptide.
10. The nucleic acid molecule of claim 8, wherein said nucleic acid molecule encodes a polypeptide comprising an amino acid sequence that is substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40.
11. The nucleic acid molecule of claim 8, wherein said nucleic acid molecule is selected from the group consisting of genomic DNA, cDNA, and mRNA.
12. The nucleic acid molecule of claim 8, wherein said nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide with an identifiable signal sequence.
13. The nucleic acid molecule of claim 8, wherein said nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide selected from the group consisting of a chemokine, a cytokine, an immunomodulator, an anti-inflammatory polypeptide, an immunoreceptor, or a multi-transmembrane receptor protein.
14. The nucleic acid of claim 13, wherein said cytokine is substantially identical to M118 (SEQ ID NO: 32).

15. A nucleic acid molecule having at least 50% nucleotide sequence identity to a sequence encoding a *leporipox* virus polypeptide or fragment thereof, wherein said fragment comprises at least six amino acids, and said nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.
16. The nucleic acid molecule of claim 17, wherein said nucleic acid molecule has 100% complementarity to a nucleotide sequence encoding a *leporipox* virus polypeptide or fragment thereof, wherein said fragment comprises at least six amino acids, and said nucleic acid molecule hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.
17. A nucleic acid molecule, wherein said nucleic acid molecule comprises a sequence that is antisense to the coding strand of a *leporipox* virus nucleic acid molecule or a fragment thereof.
18. A vector comprising the nucleic acid molecule of claim 8.
19. The vector of claim 18, wherein said vector is a gene therapy vector.
20. A cell comprising the vector of claim 18.
21. The vector of claim 18, wherein said nucleic acid molecule is operably linked to regulatory sequences for expression of a *leporipox* virus polypeptide and wherein said regulatory sequences comprise a promoter.
22. The cell of claim 20, wherein said cell is selected from the group consisting of a human cell and a rodent cell.

23. A non-human transgenic animal comprising the nucleic acid molecule of claim 8.
24. A cell from the non-human transgenic animal of claim 23.
25. A non-human transgenic animal having a knockout mutation in one or both alleles encoding a polypeptide substantially identical to a *leporipox* virus polypeptide.
26. An antibody that specifically binds to a *leporipox* virus polypeptide.
27. The antibody of claim 26, wherein said polypeptide comprises an amino acid sequence that is substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40.
28. A probe for analyzing a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof, said probe having at least 50% nucleotide sequence identity to a sequence encoding a *leporipox* virus polypeptide or fragment thereof, wherein said fragment comprises at least six amino acids, and said probe hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.

29. The probe of claim 28, wherein said probe has 100% complementarity to a nucleic acid molecule encoding a *leporipox* virus polypeptide or fragment thereof, wherein said fragment comprises at least six amino acids, and said probe hybridizes under high stringency conditions to at least a portion of a *leporipox* virus nucleic acid molecule.

30. A method of detecting a *leporipox* virus polypeptide in a sample, said method comprising contacting said sample with the antibody of claim 26, and assaying for the binding of said antibody to said polypeptide.

31. A method of detecting a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof in a cell, said method comprising contacting the nucleic acid molecule of claim 8 or a fragment thereof, wherein said fragment is greater than about 18 nucleotides in length, with a preparation of genomic DNA from said cell, under hybridization conditions providing detection of DNA sequences having about 50% or greater nucleotide sequence identity to a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20.

32. A method of identifying a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof comprising:

- (a) providing a mammalian cell sample;
- (b) introducing by transformation into said cell sample a candidate gene;
- (c) expressing said candidate gene within said cell sample; and
- (d) determining whether said sample elicits an altered level of immune function whereby an alteration in the level of immune function identifies a *leporipox* virus gene or a *leporipox* virus gene homolog or fragment thereof.

33. A method for identifying a test compound that modulates the expression or activity of a *leporipox* virus polypeptide, said method comprising contacting said *leporipox* virus polypeptide with said test compound, and determining the effect of said test compound on said *leporipox* virus polypeptide.

34. A method of targeting proteins for secretion from a cell, comprising attaching an identifiable signal sequence selected from a *leporipox* virus polypeptide to a protein of interest, wherein said protein of interest is secreted from said cell.

35. A method of immunomodulation in a mammal, said method comprising: administering to said mammal a therapeutically effective amount of a *leporipox* virus polypeptide or fragment thereof, wherein said polypeptide has an immunomodulatory effect in said mammal.

36. A method of immunomodulation in a mammal, said method comprising: administering to said mammal a therapeutically effective amount of a compound that modulates the activity of a *leporipox* virus polypeptide, wherein said compound has an immunomodulatory effect in said mammal.

37. A method of treating a mammal having an immunomodulatory disorder, said method comprising:

administering to said mammal a therapeutically effective amount of a compound that modulates the activity of a *leporipox* virus polypeptide, wherein said compound has an immunomodulatory effect in said mammal.

38. A pharmaceutical composition comprising at least one dose of a therapeutically effective amount of a *leporipox* virus polypeptide or fragment thereof, in a pharmaceutically acceptable carrier, said composition being formulated for the treatment of an immunomodulatory disorder.

39. The method of claims 33 to 38, wherein the *leporipox* virus polypeptide comprises an amino acid sequence substantially identical to an amino acid sequence selected from the group consisting of SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40, and fragments and analogs thereof.

40. The method of claims 33 to 38, wherein said polypeptide comprises an amino acid sequence substantially identical to SEQ ID NO: 31 or fragments and analogs thereof.

41. The method of claims 33 to 38, wherein said polypeptide comprises an amino acid sequence substantially identical to SEQ ID NO: 32 or fragments and analogs thereof.

42. The method of claims 35 and 36, wherein said immunomodulation is selected from the group consisting of immunosuppression, immunostimulation, cell proliferation, apoptosis, decreasing T cell stimulation, and decreasing inflammation in a mammal.

43. The method of claims 35 to 37, wherein said mammal is a human.

44. The method of claims 35 to 37, wherein said mammal is diagnosed with a tumor.

45. The method of claim 44, wherein said human has a tumor selected from the group consisting of a carcinoma, a plasmacytoma, a lymphoma, and a sarcoma.

46. The method of claim 35, wherein said *leporipox* virus polypeptide is a multi-transmembrane receptor related protein.

47. The method of claim 35, wherein said polypeptide comprises an amino acid sequence substantially identical to the sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40 and fragments and analogs thereof.

48. The method of claim 35, wherein said mammal has a condition selected from the group consisting of acute inflammation, rheumatoid arthritis, transplant rejection, restenosis, asthma, allergies, inflammatory bowel disease, uveitis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis, systemic lupus erythematosus, nephrotic syndrome lupus, multiple sclerosis, myasthenia gravis, type I and type II diabetes mellitus, glomerulonephritis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, microbial infection, malignancy and metastasis, autoimmune disease, cirrhosis, endotoxemia, atherosclerosis, reperfusion injury and inflammatory responses, AIDS, cirrhosis of the liver, neurodegeneration, myelodysplastic syndrome, and ischemic injury.

FIGURE 1**M035: DNA**

ATGAACCCGAAGTACTGGGGGAGAGCTATATGGACCGTTATTTTTATAATTCTATCGAA
GGCGAAAGCGTCCGGTAATATAGAACTATGTAAACGACAACTGTATACGATCGTGGAGA
CTTTACCATGTCCCTCGTGTAGATTGCATGCGAAAAAGGCTATACAGGAGAACGATATA
ATGTCTAGCGACGATTTAAACTATATTTACTTTTTCTTTATTAGTTTATTTAACAATCT
AGCGTCAGATCCCGCGTATAAAATAGATTTAAACAGAGTTAGTCCACTTATTTAA
(SEQ ID NO: 1)

FIGURE 2**M037: DNA**

ATGATCGTATTTGTGATATTTATTATTGCGTTCGTTTTCTGCGGATGGATCTCGTACGG
TTTTTTAAAACCGTATATGTTTTTAAACCGGAAACATTGAA (SEQ ID NO: 2)

FIGURE 3**M046: DNA**

ATGGCATCTCCTTTAATATACTTGTTATTTTTCATAATATTTTGGTACTTACTTATTA
TTTCAACAAGCATCCTACGAATAAGTTGGAGCTATCCGTAGACAAGTTAAACAGAGAAA
ATAAAATAATAAAACAACGCGACGATGCATTTCCCGTGGTGCTTAACACGACCGTGTTT
ACCCGACCCGAGACGCCCGTTCCACGAAGGTACACACGTACTACGACTCGGCCACGGG
GGTTGTCACGATGCTATCCAATAATAAAAAACGTATTTTAGATTAGACTTTGACGACG
ACGTACGAACTTTGTTACCTATTTTACTCCTTAGTAAATGA (SEQ ID NO: 3)

FIGURE 4**M102: DNA**

ATGATTAGCGAATTACTTTTGTTTGCCGTATGTGTCATTATAATAGGACTCATCATATA
CGGTATATACACGAGAAAGGCCACGCAACAACACACTCCTCCCTCCTCCGAACGATACG
AGAAAATGGAAAACCTAAAAACGGGGTACGTAGATAAATTGAAATCCGCCCATTCAAG
TCGTTTATATAAATTATTTTCGGGTAATAA (SEQ ID NO:4)

FIGURE 5**M103: DNA**

ATGGACACGATGACGATTCTCAGTAACTACTTCAACACAGCACTTATAGGAGGTATCGT
CTTACTCGCGACGGCGTGTGTGTTTCGCGTTTATAGATTTCTCTAAGAACAAGTCTACCG
TGACAAACGCATGGAGAGCCCTAAGCGGCATCACGTTTGTACTAGGGATCGTGATCACG
GTGGGTATGCTTATTTATTCCATGTGGGGTAGATATTGTAAACCTCCGACTAAGACGAC
CGTCGTAGAAAACGGACGATATAACTCTAGCCCTATCGAACTAAACGGACAATAG
(SEQ ID NO: 5)

FIGURE 6**M110: DNA**

ATGATAACCCTCTTTCTAGTTTTATGTTATTTTCATTCTTATTTTTTAACATCATCGTTCC
GGCGATCTCCGAAAAGATGCGAAAGGAATACGACGCGTACCTAAAATACGCCCACTTGA
AGAAAGACGCCGTGTGTGTTGACGATAGATTGTTTACCTACGATTTTAAAACGTCTGGA
GTCGTCGCAAAAATGTTTCATAGACTCCAACGGAAAACCGTTACCGTGTTTCGAGGACGCG
CGATATACGTAGCAACAACGCGATATACTGCGACAACGACGAAAACGTATTAGATTTTA
GAAAATCGTGTTCTAAGGCATATTTAGATTTATTTTTTTACTACTTAA (SEQ ID NO:
6)

FIGURE 7**M116: DNA**

ATGAACCCCGTTACTGTTTTTTTCGTCGTCGTCGTTACGGTCGCCGTATGTATGATTTT
GTTCCAGGTGTATTCTATTTACTTAACTACGACAATATAAAAGAATTTAACGCGATGC
ATTCGCCCTTGGAGTACTCTAAAATGGTAAACGTTACAGCCATAGACAGACGGGTACAG
GACGCGAACGACGACATATACGACGCTAAACAAAAATGGCGATGTGTTAAGTTTCGATGA
TTCGTACGTGTCGCTGTCGATGTTTGGATATAAGGCGGACGGTGTAGGCATACGCCGAT
TTCGCACACTCAACGGGTGCATCGATTATACTTTTTCTACATCCACTCATTCCAGTATC
CTGAATCCGTGCATACCCCCAAACGATCCAAAAAGCAGAGAGTGTACGTTTTTAAAATC
TGCGCTTTAAA (SEQ ID NO:7)

FIGURE 8**M125: DNA**

ATGATTGTCGTGGCGTATATGGGACTGTTGTTTTCTTTTGTTCGTTGTCCGCTTATTT
ACTATCTGTGTACAAACACCAGATTAAAAAATGTTTGCATCGGCCGACGAAACGGACCA
AATGCATCCGATTGAATTCTATTACGTATTCCGCGGACGATATCGTACACCAAATTCCA
GAAACGGTAGAATCAGACGACGAATTTGATTGAGAATGGTCTTCGGACGAGGACGATGG
AGAAGTGTACGAGAACTACACGAGCAAGAGCGAGAATAATTTTGTGGCACGAACAGACG
ACGACGTGGCCGTGGACGTTCTCGTGGAACGGAGGACGAACCCAACTGGGATCCCCT
ATCTACGACGCGAATACATCGAACGTGTATGAGATACCCGACGACGGAGAGAGTTTCGA
CGACGTACAGATAGACCGTAACGTATCGGATAAGAAGTATTTTACGTATTTTACAGAAA
CGGCCGTATCTTAG (SEQ ID NO:8)

FIGURE 9A**M134: DNA**

ATGTATCGAACGTTATTTATTCTAATAATGATAGGATACGCGTATCCCGAGGAAGTCTG
TTACAGAAAACTGGGTCTCTACGGAGTATATCACGATGACAGTAAATACAGAACTCCGT
TGGATGTAAAAACGATGACTCAGAACTACGAAAACGTAATCATCGCTAACGCCATGTTG
CTAGAATCAAAAATAAACTGGACGGTTATCATGTGCGGAAGTGAACGAGACGTTTCGTCCA
AAACTGTTTCGAGCTCCGACTACCTGTACAATGGTTCGGATTAACGAAACGTTTATCTTAA
CGTTCCAGCGCGGGTACGTAGACGCGGATCACGAACTCTTATTCGTTCGAACCGACCTCG
TTGGATGAGATGCCTAATACGAACGTGTCCGTAGTATACAAAAACGACACGGGTACGAA
CATTACAACGTCCGCGCCACCGACGACCGCCCCCTACCCCAACTCCCGAAGTCAGCAACG
ACACGACACAATTGCGATTATCGTTCAATGAGTCGAGTATGATCATTACGTTTAAACAAC
ATAACCGTCGTGTTAAACAACACCTGTATAACGACGAGTGTAGAACGGGTCCGTGTACG
ACTGGTTAACGATTCTCTGATAGTAAGCGCCACATCGTATCCTTTTTTCCACGAGTCCTC
CGTTTATGGAGAAGGAATACTTCGACAATTGTACGTTGACGCTACCCGTGTCCATCCAT
CAAGGGTCCAAGTTCGAAGAACAACGGGTAGAGGAATCCAAGTGTACGGTCGAGTATAA
CGTCACAGACTATAACTCTACCGCGGACAATAACACGTCGGTAAACGCCACAACGGGCT
TAAACTACACGTGTATGACGAATACGACGTTTCGATCCTACTAAAAACATTACGTACGTG
TACAACAACGAGACCCGGGTAGTATTGATAGAACAACAAAACGATCTATTTACAAACAT
TACCATTATCACGGATTTTCTGAACGAATGCAACGCCTCGAGTATGGAGACGAAAATAT
ACGCCGTGGGTATACCCAACGTATATAACGAAATACTAACCAACTTAAGCGTGGAGATT
ACGAACGACACAGTTACTTCAATTGTAAGTTAATGGGAACGGGTGATTGTGGATT
GGGTATATTCTCGAGCGCGGACGACCATGATCCTAGAAGAGAAAACGAAATCAAAAA
CTAAATCTAGTTCTAGACACGCCAGGTCCGTTCGTTCGATCTAGAGGACGCCTTCTGTCTA
CATATGAGACACGGTTTACATCACGACGTAGACTGTCGGTCCCGTCTCATACCCGAGGA
AGAACCAACCCAGCCGACCAGGACACGTAATCGACGGTCTCCTCCAAAAGGAGAGAAAC
CCCCCGTACCTCCTAAAAGCGATCTCGTCCTAATGAGCGCCGAGGAATTAGGAGCTCGA
CCCAAGATACGGAAGAACACAGATACGATACAACTAGGTGCCTCGGGAACGGACGGTCC
TGTGTCGGGAAGCGATCAAATCTACGCGGACCTCAAACAGAAAATAGAAACGCGGCTTA
AGAAACTCACGATCGATGAGGGCGGACTTACCGCGTCGAGACTGCCACCGTCTACAAAA
GCTCTCCTGGAGGAGGCGATCGGTAGAAAGGCGAGGTCCGTTTCAGGTATCTAAAGACAT
TACTCGTCAGATAATAGACCAACAACAGGGGGCTACGGGAGACCCCATATCGGGTAGAC
AGTTTAAAGGTAAATGTACGAACACAAACGCGTCCTTCTACGACCGTAACCGTCGACACT
AGTAGCGGCGTGTACGCGAACGTTCTGAGAACTCCTAAAGATGTGGAGGTGACCGCTCC
GAAAGACGTCACCGTTGTGAAAACACCGTCTACGGGGGACGAGACGACACGTAATTCT
TAGAACCCCGACGATCCTCGTCGGCGTCCGAGTCTCCGTACTTCTTAGAACCCCGACGA
TCCTCGTCGGCGTCGGACGTAGGATCCGCATCTCCTTACTTCTTACAACCGGGAGACGA
AGACGTATTCTGATAGGTGAGGAGTATGCGCAAGTAAACAAACGCGTCTACCGAGCGATG
GGGTACATAATCCGTTGAGAAGACATTCATCTAGCGATTACGAAACGATTAAAGAAAGA
CAACGATCTATAAAATATCACCGTGAGAATTACTACGAGTCCGTAGACGATAGTAACCT
GTACGCGCTTGCCGGGCGACCTACCCCCAGGCGACCAAAACCCCCGGGAAGGCGTTCCTC
TTCCACCCATTCCGAGGAAAGATTTACCTCTTCTCCTATTCCGGGCAACGATCCGTTT
AACACAAAGACGAAAAAGATGATCGACAAAATATGCGACAGTCAAGGCGCCGCTTCCAT
CTGCGGTATCCGAGGAACCGACGCCTTATACGAGTCTGTGGACGATGTGGACACTCGTC

FIGURE 9B

ATCTTAAGCGTAACCCCATCTACGAACCGTTTAAACGAACGAGAGTATTCCACAAACCCG
TTGTATCAGCCTTTAGAAGAGGGGGCAAACCCCAAATCGGCTCTAACGAGGAAGAACGC
CATTAGGAGACGTCCCGGACAGGACTCCGACACACTCGTCATAGAAACGAGGTATTCCG
AAGGCCCCGAACCAGGAAATGACAATTATGCGGCGAACAACGTCAAGAATAACGCAGAC
GGTCGTTCCACGAATATCTATTCCGCGGAGCCTAAAAATGGAAATACCGGAGGTGGAGG
AACGGGTACGGATGTGGCGAATACGAAGGACGGACAAGCCAAGAAGGTGAAAACCTCCCA
AAGGTAATAAGCATAAGAAGTTGTCCATGGGCGGTGCCTACGAGAACAATAAAATGAAC
TCCATGATTAAGGCTATCGCCCTATCTAGTTACCTATCCACGACGAATTCTAGAATTTT
GTCGATTATGGCGAGCGCCGGATCTCAACCGAAAGAACTCGCGATAGTGAACATCGTAT
CCTCTGTGTTATCTCAAATAGGAGGTACCATAGCTATCGCGGGAAGCAATAGCCCTACG
GCGGCAGCTGCCGGGTTAGCCCTGCAAGGGATATCTGGACTCATCGACGCGGCGACGTC
CATCTACTACATACTGGCGGGGTGCGAGCCGTACAAAGATCCAGCCATCGAAAAGTTTT
CCAATTACGCTAATTACATGTCTAGAACGGAAGCGGGTGCCCGGGTGTGTATGATGCC
GACTCGGACATTACCATTACGTTGGCGTACAGACACAGCAAAATGAACACGGACGCTGA
AAAAACAGAGGTGAATACACGGACGTTATACCCAGTAAAGTGTACTATTTGAAGAATA
ACTACATCAGTTACACCGTGAAGGTAACCTCTGGTCTGTCCAATAGGTCAGTTACGTCTG
TTAGAGGCGGATGTTAACACGTACGCTACGTTAATAAGAGAAGAGAATAACGGAGCCAA
GTACTACCTCGTACACGGCATTTTAGAACTATTATCGTATCATTGACGGTTACGTTTA
CGTGCGGGAACGAACCCGGGGTCATCTTTACACCGTTTCGAGCAAAAATTACGAGACATG
CAACTGCTTCGTATATCGACTCCGGGAGAACCCAAAGAGGCCGAAGACATGCCGTCGAA
CGTGTGCGATCTTTACCCGCTTAAACGATTCTATGTATTGGCCGGAAACTGTCCGTACG
ATATGAGTAGAAAGTCCGTGCGATACGTTACGTGTAGTACGCTATTGAGGATGTCTACC
TACGAAGCCACGAAACATCGTTGGATCTTGATGAACCCGTTCTCGGAAGACGAACACGA
CAACATTCAACTGTTTACGTTTAAAGAAGTACGATTTCAAAGGCTCGGTAATAAATCTAA
ACGAGATAGGACATAGCGACACCGTATGTAGTCAGTCCGATACGAGCACGTGTTACTGG
TCCGATGCGATGATTCTAGAAGACGTTACGGCGTGTACGTCTAGAATACGAAAACCTCTA
CGTAAAACCTGAGCACGTGTTGGGGAAGGGATACAACAGCTTTGTTCTAACGTGTCCGT
ACGGGTCCACGCCTTTCTACATCTCGAACGGAACCATCGTAGACATCCCCATCAATACA
CGAAGGACGACGGTTCCGGTTTACGGCCAGTCGGACACGACGGCCCTGGTATCGTGTAT
TCATAACACGAATCCCGCGTACAAGTCGGACATCATCCAACGTGTCATTTGTTACGGAGG
ACGCTCGGTCTAATTACCTGGACTTTAGATACTTCAAGTACAGACAAAACCTGTTCAAT
GTATTCAGCGACCCAATGCCGTTGAGATCTAAGAAATGTAAACGTTATGAGGAAAACAG
ACGATGTAAAACTATTACCACGTGAAACACATACCCAAAATAGACTACAAAGTAGTGA
TGCAACGACTTCCCATGGTCAAACGTGTCCACGAGTTACACGGGCCCCGTTGAATGACAAA
ACGATTACGAAGATATCGTTCGTATTACGCGTCTCCCATCAGTCTATCCATCGACGTGAG
TTCCTTGTGAGCGGTGTACGACGTACCGCACCACTTTTGGAATATGCGAAGGAGGGCG
TCCGGACGTTACGCGCCATCGCCGTAACGATGTTTCGCGTGTTCGGTTGTTGCGGGAAAC
GTGAACGTGAACCCAGGGATCGGGGGCAGGACAGATACGTACGGTAGGAACGCCAAATA
CATCTTCTTGGAACCAAGCGGTCTCCGTCCAACAACCGTATACCGTTTCGATTTTCGTAT
ACGACAGTTACTATCAGACGACCAACTACCCGTACGAGAAATGCGATGTCTACCTGGAC
TTGGTTACGCAACGCTTGGAGATACGATGTCCGGAACCTCACGATTCCTCAGAAGCCTTT
CAACTCTCCTCTAGTGAACAGTTTATGCGTATTAGTTGCCACGTCCAGAGATCATTGCG
CGTTAGTGACAGAAAACCTGGGACAGAACCTACGGGTACAGCTACGCCGACGCGTATACA
GAATTCGACTCCTGTAAAAACGGATATTATCCATCTCGACCCATTGATAACTTCTGCTA

FIGURE 9C

TTACTGGCACCTGAGCACCTACTGGCCTCCCGATTACGACCCGTGCGTGTCCGCCATGG
TTCTGGCACATAGTTACATCTTCCCGGACAATAAGATCGTAAATCCTCCGTACATCAAG
GAATTCGGATACGATCCCGATAAAAACGAATACGTGACCGAACTCTGTACGTGAAACT
TCAGGCGCTCTACGACCAGTACAATAAACTGGTAGAATACTCCATGAATCCCATGGTCG
ATATTTCAAATAATCTAGCTTCCGCGATGACTCCGGAGGCTCGCGAGATCTTCCGATTG
AAGTACAGCGGGGCCGAGATGGAAACGGAGATTACTCTGAATAAACGCAAGGCCGAGAA
AGTAAAAGAGGACATAGAGGATCTCCTGAACGAGATATACGCCAACACGCTAACGTATT
CGGAGGCTACGGCTATGTTACGATCCGCCATCTCTACCCGGTGTTGTGTGCTGAATGGA
ACCGATGTGTACAAATACTTCCGGTTGGAACATTATCTGTGTGGAACGTACGAGGATTA
CCTGGTCTATATAGATAACAAAACCTACGTACGTATAAACGAGACCGTTGTACCGGAGA
ACGAGTATCTGGCAGCGAAGGCCCGCGAGTGACCTGTTTCCACACGGACTTGATCCCC
ATTACGGACGAAGAGACACAACGACGTTTTTGAGAAAATGATTGTACAGGCGGCGTTAGA
GGACGCCCTAACGAGCATCTTTGAGGAGCACGACAATAACGTAACCGATTACTTCGCGG
AATACATGCGATCCCTCCAAATGGCGAATAAAAGTCATACGAATAATATTATCGCGGTC
GCTTTAGCGGGGATAATCGTCATTGTAACGACCTACGTGTTTACTAGATTACGCACTAA
GCAAAAAAAGGAAATTATAACGTACGTAATAAGATAGATAATTCCATACAGAAAGAGA
TTCAGTTGGACGGTGTATATACTACTGACAACGTTTTTATATAA (SEQ ID NO:9)

FIGURE 10**M153: DNA**

ATGGGTCCATTTATGGTATCCGCATTAACCATGGTACGTGCGTGTATAGACTGTCGTAC
CTACTTCATAGCTACTCGTGAACGTAATACGATTCACGAGGTGGCAGAGATGGAAGATG
TGGAGGAGGTGGAGGAGGTGAACGATGACGACGGCGATGAATACGTCGACGCTGTCGAG
GAAATCGTCGTGGAGTCACCCGCTTAG (SEQ ID NO:10)

FIGURE 11**M141: DNA**

ATGCGTGTGTTAAGTATTTTAGCGTTATTATCTACAGTAGCCTACGCTTACTCCGTTTCG
CTGTACAAATACAACGACGGTAGCCGAACATGTAAACGTTACTATTAGTTGCAATAAAA
CTAGCAGTAGTAGTAGTTTGTTCATCTTATAACGTGGAAAAAATAATGAAACGACT
ATAGCGGGGTACGGACCAAGTGGCGCAACCATTAAAGATGCGAGCAAAATAGAGTATTT
ATCCACTGGATACAACACGTCCACTATCTTGATAAAAAATGTAAGCGCGGAAGATAGCG
GACTTTACTACTGTATATTCAACTCGTTCTCTACCGAACCTAGCGAAGAAGGAACGGTA
CGGGTAAACGTAACGACATCTAGTGCAACGACTACTTTACAACAACCTCAACCTCAGGC
TTTACGAACGACCCGTGGTCGATCGACTAATCGATCGACGTCGCGTCACGTATCGCGTA
CCTCGACGCATCACGTAGGTGACGGATCCTTAACGGTGGAAACGAGACAGTATAAATAC
TCATCTTCGTCCTCTTCCTCATCCTCCAGCTGGACGAGTAGCGCAGGATCTCGTAACGT
ACCGAGCTTATTTAACTCATTTTCGTAATAAAAATGATTTTTTTATATCCCAAATTTAA
TCGGATAA (SEQ ID NO:11)

FIGURE 12**M118: DNA**

ATGAGTGACGAGGATATTAACGAGTCTAATTTTCATGCACCTATTGTGCGACGTTATTGAC
CAACAAAGACATTGACCTGGATACGGAATCTGCCGCTACGTTATCCGCCATAAAAGAAC
TCATTTCCCAGATCAACCTTAAGGTATTAGCCTTAAACAAAAAATCGAAAAAAATATA
CGAACGAACGAACCGTTAAGTTATGTATCGAAACGAGAAGGAACTAGAACTTAA (SEQ
ID NO:12)

FIGURE 13**M135: DNA**

ATGGTGTTTATATTTATTATCACCTGTGTATGTTTGGTGACGAGATCCTGTGGGGGTGG
GTTAGAAGACGATATAGATCGCATATTTCAAAAACGATACAACGAACTGAGCCAGCCGA
TTAAGCGCAATATGCGTACACTGTGCAAGTTTAGAGGAATTACCGCGACTATGTFTACG
GAAGGAGAATCTTACCTTATTCAATGTCCCATAATTCACGATTACGTGCTACGGGCGCT
GTATGACTTAGTGGAAGGAAGTTACACGGTACGCTGGGAACGCGAAACGGAAGACGATG
TTGAGTCGGTAGATCCGAAGTTAGTCAAAGGGACGCTATTATACCTCCAACCTAACGCG
TCCAGTATAGGAACGTATCTATGTACCTTACACGATAACCGAGGTATGTGTTATCAATC
TGTCGCGCACGTCATCCGACGTCCGAAGATGCAATGCGTGAAACATGCACATACGACAT
CGGACAGCAACCTGTGGATATACCTCGCCATTTTAGCAGTTTTGATATCCTTAGGCGTC
CTGTAA (SEQ ID NO: 13)

FIGURE 14**M144: DNA**

ATGCGCGCTACATTATGGACCGTGTACGTAGCGTCGTTGTTACAGTCGTATGTACTAGC
CGATTGTAAGAACGATTTTAAGTCGAACGTTCAAGCTGTGAATAAGAAACAGACGTACA
AACAAGACGAGGTAACGGAATTACAATGCGTTCCGGGGTATCAGAAGAAGTCCAACGTA
ACTATTTCCGCCACGTGCGGAAAAGATAATACGTGGCGCATAAGTAACGAATACGTATG
CGTTCGTAGAGAATGTCCCGATCCACCCACGATAGAAAACGGAAGAGTACATACCCCTA
AAATTATGTATCATCGACACGACGCGGTACGTTACGTGTGTAACGAGAACCATAAGAGC
ATTCCTTATTCGTTGGTGGAAGACGTCGTTTCGATGTATTAATGAAACGACGTGGTA
TCCTTCTCCTCCACGTGTAAGATGATCGTGTGTAGGTTCCCGCTCTTCAAAACGGAT
ACGTTACGGAGTTCCCTTCATTAAACGATTCTGTTATAAAAACAGGGTACGTTTACG
TGCAATCCCGACTTTTACACTGGTGGGTGCGTCGTACGCGACGTGTACGTTAAACGCTAC
TTGGTCGCCCCGATGTTCTAAATGTGTTTCGACGCGCGCACGATAGTAATACGCGCAATA
TATTCGCCTTTGTGGAATATGACGACTTTGAAGATCTAGACGACGAAGACGCGGTAAAC
GAAAACTGACGGATACGAGCACTCGCCCCGACGACGCTACCTCCGATCGTCCGTCTCA
TGTCTTTGTCGCGCTCGTTATTCTAGGCACCATCTTGTTTATATTTACGTTAGGTGTGA
TATTATTATTTTGTTTCGTGTACTAGTTCAAATATTTTACATCCTAATAAATTGTCTTAT
ACTAAGTTGAGTGATATAA (SEQ ID NO: 14)

FIGURE 15**M121: DNA**

ATGTCGTTACACGCCAACGACGCGGACGAGTCGAAGGACGAAGAAGCTGCGTTCATCGG
TTCCACAATTTACGGCAAGAACTAAAGAAGAAACACCTGCTCAAAAAAGTCAGATGTA
TCGTGATCCTGCTGCGTGTAAGCATCGTTACGTCCATCGTGTCGCTTATGGCAATTGCC
GCCATGTTAGCATTACAGTGCAGTAACTGCGAGGTCATTACGACATCGGCTCGTATATC
GACGTATTCTTCCATTGCCCATTACGAGGCGAGTACGTGCAAAGGGATCGTCTTCGACG
CGAGCTGTTATATGTTTCACAAAGAACCCAAAACGTTCTACGAGGCCGGGGCGGATTGC
GCCAATCAAAGTGCCGTATTGCCTTTCAAAACACCTAAGGAGCATTGGATGTGGGATTA
TCTGGAAGGTACCTGGGGGGTGGACGGATACGGAATCGTTGACTCGGTGGACCTTCGGA
CCTACGACGTGAGTACAGAAATGAGAAAATATTTTTGCGTAAATCATTCTTTATAG
(SEQ ID NO: 15)

FIGURE 16**M122: DNA**

ATGAAAACGTTAAACAGACAAACGGTGGGCAAAATTAAAAAATGTCTACGCCCCGCGGC
CATTTTTATGATTATATCGACTATAGTAAGCGGAATCGGTACGGTATTACGCTATAAGG
ACGATCTCTTCCCCAACGCGTGCGATAGGGGTTGGATGTCGTACGATAACTATTGTTAT
CTCAATACAAAAATCCAACTATCTGTGTACGGAGGAGCCGTATTATGCGCGAACCACAA
GGCTAGGATTCCGAAGGCCAACTTTCGTCATTTGAAAGTGATATCGCTAACGTACGGGA
GAGACTTCTGGGTGAGTCTGACGAAACAAAAAGACGGTCGTTGGATAGATATAAATACG
AATAAGACGGTTAATATGGATAGTAGTAGAGAGTTGGCCGAGATTAAGAAAAAAAACAC
GGGCGCTACAGACGCGTCATGTTACGTATATAAGTTGAACGGTATACAGGAGATACTGT
GCAACGTCGTAAACTACGTTATATGTATGAAAAGATTCTATAAGTGA (SEQ ID NO:
16)

FIGURE 17**M154: DNA**

ATGGCGCGGTATATTATCATCGTGCTCGCCTGCCTCGTCGCAACCTCAACATGTGCGAC
GTATCCAAAAAGTACTGGCACTTAGCCGCCGAGCTAACCATCGGGTTAAATCGGTACG
TCGAAACGGTTATGGGAGAATGTCACATGAAGGAACGATACGATCATAAAACGTCCACG
CTCATATTAACCGGGTACGGGCTTATGATAAACATTACGATTACTAACGTGGTACAACG
ATTTGTGGCGGCCAGTGCTGGTGCAGGAGATGGGAACAAGCTATCCATCATGTTATTTA
CGACTCATCCGTTGACGAAGTATTCGGATATATACCTAACCATTACGTGTCTGGAACCG
GAGGCGACGTGGGCAACTACCGGCAATCAACTTCCCGACTCGTTACATCACAACAAGGA
TGTGTCCATAACCATCTTAGGATCCTGTGTAACATGTGTTAACCTAGAAACCAATCCGA
TTAAAGTGAATCCTCATTTACGCATCCGATTAGTATGTTTGTGTACGACAACAAGGAG
GATGTCCGAGGCAGTTACGGTGTTACGTTTGAGGATGAACTAAACGTATGTTTTCTCGA
TATAAAAAGGTCAGTTACGATCTTTGTTATAGACAAACGAGATACCTTATATAA
(SEQ ID NO:17)

FIGURE 18**M104: DNA**

ATGATAACTAATTACGAACCGGTAATCTTGCTGGGAATTATTTGTTTTACCGTGTTGGT
CAATTTCAAACCTATCGACCAAAGCGAAGATAGACGTGATATTTTCATCCAATCCATAT
TATTTATGTGGTTTATATTCCACTTTGTACATTCAGTGTTTTAA (SEQ ID NO:18)

FIGURE 19**M107: DNA**

ATGAGTTATTTAAGTTATTACAATATGTTTACGGATTTTAGCGCGGGAGCGGGCGTGTC
CGAGCCGGAACTGTTACCAAAGAAGAAGAAGATCGTTTTTTCCCGTTTAGGAAGCG
ATGCTTCTGGGGGCAAAGACACGAGTCATTTACCGCATCTGTCGCTACCGACCAGTCTT
AAAGGATTGATTCCGAATATACTTATGAGAAACGATATTAAGTCGTTAATCGGGTTAAT
TCTTTTTTGTGTTGGCTATCACAACGCCGCCTTATATTTCCGTAATTATGCTAGGGATCG
CCTCTATATTGATCCCTTTTCCGTCTCTCGTAATCGCGTATTGTTTGTGTTACAGATC
GTGAACACAACGAGTTACGGAACGATCGGAATGACCATCGTGTGTGTGTTTATGTCCTT
CTTTACAATGGCTATGCAAACCGTGTCCCGTACAGTGTATACGATCTCGTACATTATTT
TAGCAATTTTATTTTGCGTATACGTGTTTAATATAACTCGTGCCAGGTCCCAGTCGTCG
GAGCCTACGAAGTGCGCGGTTAAAGAAGGGATACGTAGATGCGCCGAAAACCTAGCTT
CTACGAAGATTAA (SEQ ID NO:19)

FIGURE 20**M128: DNA**

ATGATAGGTTTATTGTTCTTCGTATACGTAGTTCCTCTGGCCGCCGAAAACGAAGTAAC
CGTAACGCCCTACACGGTGTGTAATAAGACGGTTACGTTGGAGTGTAACCTAGACGCGT
TAATTTACAAAGATATAAATTCTGTCCACGTAAAGTGGTTATTTCGACACGATGTATGAT
ACGATTTTGAATAAAACGAACGGGTCGTCTATCACGTTTCGATTTTCGCGAACAACCTGAC
GGGGAACCTACACGTGCGAGGCGTATAGCGAGTTCAACTCGGTGAAACACGTTATCGCGC
TAACTTTCGTACACCAATGGTTTAGTCGCGAAGAGATTCAGTTTATTCTGTCTTTACTT
ACTATTTACATTATATTGTTGTGGGGAAACGTGTGTACGATAACGTTTAAAATAAACA
CGTATCCAAGTTGATTCACGTGTATTCTATCGCTTTATGGATGACGCTTATTATGTTTCG
TAGGACAGTATATGATCGGTATAGATACGGATATGTTATACGTAAAGGTAAACGGAATC
ATTCTTATTCAGCTGTCTATTTTCTCATCAATTTTCTTACAGCGTATTCTTCACAAAAA
ACTAATACCTTCGTACTTACTAAATATCGTTTTGGGGTTGAAGGCCGTCTCGTATACGG
GGTCTACGGTCGTTATCGCGTTATCCTTCATCGGATGTTACAATAAAGCGTACGGGTAC
ACATACATGTATAAACTCTTGTTTCGCGGATATATTAGAGTTAATTAGTTTAATCGCGTT
GTACACGCTACCCTTGGGCACTCAGGCGACGTATAAAAAGTTATACCTCCAATCGGACG
AAACCTTCACGTTTCTATAA (SEQ ID NO:20)

FIGURE 21

M035: Protein

MNPKYWGRAIWTVIFIILSKAKASGNIELCKRQLYTIVETLPCPSCRLHAKKAIQENDI
MSSDDLNYIYFFFIISLFNNLASDPAYKIDLNRVSPLI (SEQ ID NO:21)

FIGURE 22

M037: Protein

MIVFVIFIIAFVFCGWISYGFLKPYMFLNRKH (SEQ ID NO:22)

FIGURE 23**M046: Protein**

MASPLIYLLFFIIFLVLTYYFNKHPTNKLKLSVDKLNRENKIIKQRDDAFPVVLNTTVF
TRPETPVPTKVHTYYDSATGVVTMLSNNKKRIFRLDFDDDVRTLTPILLLSK (SEQ
ID NO:23)

FIGURE 24

M102: Protein

MISELLLFAVCVIIIGLIYGIYTRKATQQHTPPSSERYEKMENLKTGYVDKLKSAHFK
SFYKLFSGN (SEQ ID NO:24)

FIGURE 25**M103: Protein**

MDTMTILSNYFNTALIGGIVLLATACVFAFIDFSKNKSTVTNAWRALSGITFVLGIVIT
VGMLIYSMWGRYCKPPTKTTVENGRYNSSPIELNGQ (SEQ ID NO:25)

FIGURE 26**M110: Protein**

MITLFLVLCYFILIFNIIVPAISEKMRKEYDAYLKYAHLKKDAVCVDDRLFTYDFKTSG
VVAKMFIDSNGKPLPCSRTRDIRSNNAIYCDNDENVLDFRKSCSKAYLDLFFTT (SEQ
ID NO:26)

FIGURE 27**M116: Protein**

MNPVTVFFVVVVTVAVCMILFQVYSIYLNVDNIKEFNAMHSPLYSKMVNVTAIDRRVQ
DANDDIYDAKQKWRCVKFDDSYVSLSMFGYKADGVGIRRFRTLNGCIDYTFSTSTHSSI
LNPCIPPNDPKSRECTFLKSAL (SEQ ID NO:27)

FIGURE 28**M125: Protein**

MI V V A Y M G L L F S F C S L S A Y L L S V Y K H Q I K K C L H R P T K R T K C I R L N S I T Y S A D D I V H Q I P
E T V E S D D E F D S E W S S D E D D G E V Y E N Y T S K S E N N F V A R T D D D V A V D V L V E T E D E P N W D P T
I Y D A N T S N V Y E I P D D G E S F D D V Q I D R N V S D K K Y F T Y F T E T A V S (SEQ ID NO: 28)

FIGURE 29

M134: Protein

MYRTLFIIMIGYAYPEEVCYRKLGLYGVYHDDSKYRTPLDVKTMTQNYENVIIANAML
LESKINWTVIMSEVNETFVQNCSSSDYLYNGRINETFILTFQRGYVDADHELLFVEPTS
LDENPNTNVSVVYKNDTGTNITTSAPPTTAPTPTPEVSNDTTQLRLSFNESSMIITFNN
ITVVLNNTCITTSVERVRVRLVNDLSIVSATSYPFSTSPPFMEKEYFDNCTLTLTPVSIH
QGSKFEEQ RVEESNCTVEYNVTDYNSTADNNTSVNATTGLNYTCMTNTTTFDPTKNITYV
YNNETRVVLI EQQNDLFTNITIIITDFLNECNASSMETKIYAVGIPNVYNEILTNLSEI
TNDTVTYFNCKLMGTGDCGLGIFLERATTMILEEKT KSKTKSSSRHARSVDLEDAFCL
HMRHGLHHDVDCRSRLIPEEPTQPTRTRNRSPPKGEKPPVPPKSDLVLMSAEELGAR
PKIRKNTDTIQLGASGTDGPVSGSDQIYADLKQKIETRLK KLTIDEGGLTASRLPPSTK
ALLEEAI GRKARSVQVSKDITRQIIDQQOGATGDPISGRQFKVNVRTQTRPSTTVTVDT
SSGVYANVLRTPK DVEVTAPKDVTVVKT TVYGGRDDTYFLEPRRSSSASESPYFLEPRR
SSSASDVGSASPYFLQPGDEDVFGQEY AQVNKRRLPSDGVHNPLRRHSSSDYETIKER
QRSIKYHRENYYESVDDSNLYALAGRPTPRRPNPREGVPLPPIPRKDLPLPPIPGNDPF
NTKTKKMIDKICDSQGAASICGIRGTDALYESVDDVDTRHLKRNP IYEPFNEREYSTNP
LYQPLEEGAKPKSALTRKNAIRRRPGQSDTLVIETRYSEGPEPGNDNYAANNVKNNAD
GRSTNIYSAEPKNGNTGGGGTGTDVANTKDGQAKKVTPKGNKHKKLSMGGAYENNMN
SMIKAIALSSYLSTTNSRISSIMASAGSQPKELAI VNI VSSVLSQIGGTIAIAGSNSPT
AAAAGLALQGISGLIDAATSIYYILAGSQPYKDP AIEKFSNYANYMSRTEAGARVCMMP
DSDITITL AYRHSKMNTDAEKNRGEYTDVIPSKVYYLKNNYISYTVKVTLVCPIGQLRL
LEADVNTYATLIREENNGAKYYLVHGILELLSYHSTVTFTCGNEPGVIFTPFEQKL RDM
QLLRISTPGEPKEAEDMP SNVCDLYPLKRFYVLAGNCPYDMSRKSVAYVTCSTLLRMST
YEATKHRWILMNPFS EDEHDNIQLFTFKKYDFKGSVINLNEIGHSDTVCSQSDTSTCYW
SDAMILEDVTACTSRIRKLYVKLSTSLGKGYN SFVLTCPYGSTPFYISNGTIVDIPINT
RRTTVRFTAQSDTTALVSCIHNTNPAYKSDIIQLSFVTE DARSNYLDFRYFKYRQKLFN
VFSDPMP LRSKKCKRYEENRRCKNYYHV KHIPKIDYKVV MQRLPMVKLSTSYTGPLNDK
TITKISSYASPI SLSDVSSLSSVYDVPHHFWKYAKEGVRTFSAIAVTMFACSVVAGN
VNVNPGIGGRTD TYGRNAKYIFLGTKRSPSNRI PFDFVYDSYYQTTNYPYEKCDVYLD
LVTQRLEIRCELTIPQKPFNSPLVNSLCVLVATSRDH CALVTENWDR TYGYSYADAYT
EFDSCKN GYPSRPIDNFCYYWHLSTYWPPDYDPCVSAMVLAHSYIFPDNKIVNPPYIK
EFGYDPDKNEYVDRTLYVKLQALYDQYNKLVEYS MNPMVDISNNLASAMTPEAREIFRL
KYSGAEMETEITLNKRKA EKVKEDIEDLLNEIYANTLT YSEATAMLRSAISTRCCVLNG
TDVYKYFRLEHYLCGTYEDYLVIYIDNKTYVRINETV VPENEYLAAKAPRVTCFHTDLIP
ITDEETQRRFEKMIVQA ALEDALTSIFEEHDNNVTDYFAEYMRSLQ MANKSHTNNIIAV
ALAGIIVIVTTYVFTRLRTKQKKNYNVRNKIDNSIQKEIQLDGVYTTDNVFI (SEQ
ID NO: 29)

FIGURE 30

M153: Protein

MGPFMVSALTMVRACIDCRTYFIATRERNTIHEVAEMEDVEEVEEVNDDDGDEYVDAVE
EIVVESPA (SEQ ID NO: 30)

FIGURE 31**M141: Protein**

MRVLSILALLSTVAYAYSVRCTNTTTVAEHVNVTTISCNKTSSSSSLFHLITWKKNNETT
IAGYGPSGATIKDASKIEYLSTGYNTSTILIKNVSAEDSGLYYCIFNSFSTEPSEEGTV
RVNVTSSATTTLQQPQPQALRTTRGRSTNRSTSRRHVSRTSTHHVGDGSLTVETRQYKY
SSSSSSSSSSWTSSAGSRNVPSLFLKLFVIKMFYIPNLIG (SEQ ID NO:31)

FIGURE 32

M118: Protein

MSDEDINESNFMHLLSTLLTNKDIDLDTESAATLSAIKELISQINLKVLALNKKSKKNI
RTNEPLSYVSKREGTRT (SEQ ID NO: 32)

FIGURE 33**M135: Protein**

MVFIFIITCVCLVTRSCGGGLEDDIDRIFQKRYNELSQPIKRNMR TLCKFRGITATMFT
EGESYLIQCPIIH DYVLRALYDLVEGSYTVRWERETEDDVESVDPKLVKG TLLYLQPN A
SSIGTYLCTLHDNRGMCYQSVAHVIRRPKMQCVKHAHTTSDSNLWIYLAILAVLISLGV
L (SEQ ID NO:33)

FIGURE 34**M144: Protein**

MRATLWTVYVASLLQSYVLADCKNDFKSNVQAVNKKQTYKQDEVTELQCVPGYQKKS
NV TISATCGKDNTWRISNEYVCVRRECPDPPTIENGRVHTPKIMYHRHDAVRYVCNENHKS
IPYSLVGEDVVRGINETTWYSPPTCKMIVCRFPALQNGYVHGVPFIKRFCYKNRVRFT
CNPDFTLVGASYATCTLNATWSPDVPKCVRAHDSNTRNIFAFVEYDDFEDLDDEDAVN
EKLTDSTRPDDATSDRPSHV FVALVILGTILFIFTLGVILLFCSTSSNILHPNKLSY
TKLSV (SEQ ID NO: 34)

FIGURE 35**M121: Protein**

MSLHANDADESKDEEAAFIGSTIYGKKLKKKHLLKKVRCIVILLRVSIVTSIVSLMAIA
AMLALQCSNCEVITTSARISTYSSIAHYEASTCKGIVFDASCYMFHKEPKTFYEAGADC
ANQSAVLPFKTPKEHWMWDYLEGTWGVGDGYGIVDSVDLRTYDVSTEMRKYFCVKSFTL
(SEQ ID NO: 35)

FIGURE 36**M122: Protein**

MKTLNRQTVGKIKKMSTPAAIFMIISTIVSGIGTVLRYKDDLFPNACDRGWMSYDNYCY
LNTKIQLSVYGGAVLCANHKARIPKANFRHLKVISLTYGRDFWVSLTKQKDGRWIDINT
NKTVMNMDSSRELAIEIKKKNTGATDASCYVYKLNGIQEILCNVVNYVICMKRFYK (SEQ
ID NO:36)

FIGURE 37**M154: Protein**

MARYIIIIVLACLVATSTCATYPKKYWHLAAELTIGLNRYVETVMGECHMKERYDHKTST
LILTGyGLMINITITNVVQRFVAASAGAGDGNKLSIMLFTTHPLTKYSDIYLTITCLEP
EATWATTGNQLPDSLHHNKDVSITILGSCVTCVNLETNPIKVNPHFTHPISMfVYDNKE
DVRGSYGVTFEDELNVCFLDIKKVSYDLCYRQTRYLI (SEQ ID NO: 154)

FIGURE 38

M104: Protein

MITNYEPVILLGIICFTVLVNFKLSTKAKIDVIFFIQSILFMWFIFHFVHSVF (SEQ
ID NO: 38)

FIGURE 39**M107: Protein**

MSYLSYYNMFTDFSAGAGVSEPELFTKEEEESFFPRLGSDASGGKDTSHLPHLSLPTSL
KGLIPNILMRNDIKSLIGLILFVLAITTPPYISVIMLGIASILIPFPSLVIAAYCLLLQI
VNTTSYGTIGMTIVCVFMSFFTMMAMQTVSRTVYTISYIILAILFCVYVFNITRARSQSS
EPTKCAVKEGIRRCAEKPSFYED (SEQ ID NO:39)

FIGURE 40**M128: Protein**

MIGLLFFVYVPLAAENEVTVTPYTVCNKTVTLECNLDALIYKDINSVHVKWLFDTMYD
TISNKTNGSSITFDFANNLTGNYTCEAYSEFNSVKHVIALTFVHQWFSREEIQFILSLL
TIYIILLWGNVCTITFKINNVSKLIHVYSIALWMTLIMFVGQYMIGIDTDMLYVKVNGI
ILIQLSIFSSIFLQRILHKKLIPSYLLNIVLGLKAVSYTGSTVVIALSFIGCYNKAYGY
TYMYKLLFADILELISLIALYTLPLGTQATYKKLYLQSDFTFTFL (SEQ ID
NO: 40)

1.

SEQUENCE LISTING

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<140>

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<212> DNA

<213> Myxoma Virus

<400> 2

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<211> 336

<212> DNA

<213> Myxoma Virus

<400> 3

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cgacccgaga cgcccggtcc cacgaaggta cacacgtact acgactcggc cacgggggtt	240
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<211> 207

<212> DNA

<213> Myxoma Virus

<400> 4

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aaaatggaaa	acttaaaaac	ggggtagcgt	gataaattga	aatccgcca	tttcaagtcg	180
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<210> 5

<211> 291

<212> DNA

<213> Myxoma Virus

<400> 5

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<211> 342

<212> DNA

<213> Myxoma Virus

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<210> 7

<211> 424

<212> DNA

<213> Myxoma Virus

<400> 7

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taaa						424

<210> 8

<211> 486

<212> DNA

<213> Myxoma Virus

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<210> 9

<211> 6003

<212> DNA

<213> Myxoma Virus

<400> 9

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 <212> DNA
 <213> Myxoma Virus

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<210> 11
 <211> 657
 <212> DNA
 <213> Myxoma Virus

<400> 11
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<210> 12
 <211> 231
 <212> DNA
 <213> Myxoma Virus

<400> 12
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<210> 13
 <211> 537
 <212> DNA
 <213> Myxoma Virus

<400> 13
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<210> 14
 <211> 903
 <212> DNA
 <213> Myxoma Virus

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 taa 903

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 <211> 531
 <212> DNA
 <213> Myxoma Virus

<400> 15
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<210> 16
 <211> 519
 <212> DNA
 <213> Myxoma Virus

<400> 16
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<210> 17
 <211> 645

<212> DNA

<213> Myxoma Virus

<400> 17

atggcgcggt	atattatcat	cgtgctcgcc	tgcctcgctc	caacctcaac	atgtgcgacg	60
tatccaaaaa	agtactggca	cttagccgcc	gagctaacca	tcgggttaaa	tcggtacgtc	120
gaaacggtta	tgggagaatg	tcacatgaag	gaacgatacg	atcataaaac	gtccacgctc	180
atattaaccg	ggtacgggct	tatgataaac	attacgatta	ctaacgtggt	acaacgattt	240
gtggcgggcca	gtgctgggtc	aggagatggg	aacaagctat	ccatcatggt	atttacgact	300
catccgttga	cgaagtattc	ggatatatac	ctaaccatta	cgtgtctgga	accggaggcg	360
acgtgggcaa	ctaccggcaa	tcaacttccc	gactcggtac	atcacaacaa	ggatgtgtcc	420
ataaccatct	taggatcctg	tgtaacatgt	gttaacctag	aaaccaatcc	gattaaagtg	480
aatcctcatt	tcacgcatcc	gattagtatg	tttgtgtacg	acaacaagga	ggatgtccga	540
ggcagttacg	gtgttacgtt	tgaggatgaa	ctaaacgtat	gttttctcga	tataaaaaag	600
gtcagttacg	atctttgtta	tagacaaacg	agatacctta	tataa		645

<210> 18

<211> 162

<212> DNA

<213> Myxoma Virus

<400> 18

atgataacta	attacgaacc	ggtaatcttg	ctgggaatta	tttgttttac	cgtgttggtc	60
aatttcaaac	tatcgaccaa	agcgaagata	gacgtgatat	ttttcatcca	atccatatta	120
tttatgtggg	ttatattcca	ctttgtacat	tcagtgtttt	aa		162

<210> 19

<211> 603

<212> DNA

<213> Myxoma Virus

<400> 19

atgagttatt	taagttatta	caatatgttt	acggatttta	gcgcggggagc	gggcgtgtcc	60
gagccggaac	tgttcaccaa	agaagaagaa	gaatcgtttt	ttccccgttt	aggaagcgat	120
gcttctgggg	gcaaagacac	gagtcattta	ccgcactctgt	cgctaccgac	cagtcttaaa	180
ggattgattc	cgaatatact	tatgagaaac	gatattaagt	cgttaatcgg	gttaattcctt	240
tttgtgttgg	ctatcacaac	gccgccttat	atttcgtaa	ttatgctagg	gatcgccctc	300
atattgatcc	cttttccgtc	tctcgtaatc	gcgtattgtt	tggtgttaca	gatcgtgaac	360
acaacgagtt	acggaacgat	cggaatgacc	atcgtgtgtg	tgtttatgtc	cttctttaca	420
atggctatgc	aaaccgtgtc	ccgtacagtg	tatacgatct	cgtacattat	tttagcaatt	480
ttatttttgcg	tatacgtgtt	taatataact	cgtgccagggt	cccagtcgtc	ggagcctacg	540
aagtgcgcgg	ttaaagaagg	gatacgtaga	tgccgcgaaa	aacctagctt	ctacgaagat	600
taa						603

<210> 20

<211> 846

<212> DNA

<213> Myxoma Virus

<400> 20

atgatagggt	tattgttctt	cgtatacgta	gttcctctgg	ccgccgaaaa	cgaagtaacc	60
gtaacgccct	acacggtgtg	taataagacg	gttacgttgg	agtgtaacct	agacgcgtta	120
atttacaag	atataaattc	tgtccacgta	aagtggttat	tcgacacgat	gtatgatacg	180
atttcgaata	aaacgaacgg	gtcgtctatc	acgttcgatt	tcgcgaacaa	cctgacgggg	240
aactacacgt	gcgaggcgta	tagcgagtgc	aactcgggtg	aacacgttat	cgcgctaact	300
ttcgtacacc	aatgggtttag	tcgcgaagag	attcagttta	ttctgtcttt	acttactatt	360
tacattatat	tggttggtggg	aaacgtgtgt	acgataacgt	ttaaaataaa	caacgtatcc	420

```

aagttgattc acgtgtattc tatcgcttta tggatgacgc ttattatggt cgtaggacag      480
tatatgatcg gtatagatac ggatatgtta tacgtaaagg taaacggaat cattcttatt      540
cagctgtcta ttttctcatc aattttctta cagcgtattc ttcacaaaaa actaatacct      600
tcgtacttac taaatatcgt tttgggggtg aaggccgtct cgtatacggg gtctacggtc      660
gttatcgcggt tatecttcat cggatgttac aataaagcgt acgggtacac atacatgtat      720
aaactcttgt tcgcggatat attagagtta attagtttaa tcgcgttgta cacgctaccc      780
ttgggcactc aggcgacgta taaaaagtta tacctccaat cggacgaaac cttcacgttt      840
ctataa

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<210> 21
 <211> 96
 <212> PRT
 <213> Myxoma Virus

```

<400> 21
Met Asn Pro Lys Tyr Trp Gly Arg Ala Ile Trp Thr Val Ile Phe Ile
 1             5             10            15
Ile Leu Ser Lys Ala Lys Ala Ser Gly Asn Ile Glu Leu Cys Lys Arg
      20             25            30
Gln Leu Tyr Thr Ile Val Glu Thr Leu Pro Cys Pro Ser Cys Arg Leu
      35             40            45
His Ala Lys Lys Ala Ile Gln Glu Asn Asp Ile Met Ser Ser Asp Asp
      50             55            60
Leu Asn Tyr Ile Tyr Phe Phe Phe Ile Ser Leu Phe Asn Asn Leu Ala
      65             70            75            80
Ser Asp Pro Ala Tyr Lys Ile Asp Leu Asn Arg Val Ser Pro Leu Ile
      85             90            95

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<210> 22
 <211> 32
 <212> PRT
 <213> Myxoma Virus

```

<400> 22
Met Ile Val Phe Val Ile Phe Ile Ile Ala Phe Val Phe Cys Gly Trp
 1             5             10            15
Ile Ser Tyr Gly Phe Leu Lys Pro Tyr Met Phe Leu Asn Arg Lys His
      20             25            30

```

<210> 23
 <211> 111
 <212> PRT
 <213> Myxoma Virus

```

<400> 23
Met Ala Ser Pro Leu Ile Tyr Leu Leu Phe Phe Ile Ile Phe Leu Val
 1             5             10            15
Leu Thr Tyr Tyr Phe Asn Lys His Pro Thr Asn Lys Leu Glu Leu Ser
      20             25            30
Val Asp Lys Leu Asn Arg Glu Asn Lys Ile Ile Lys Gln Arg Asp Asp
      35             40            45
Ala Phe Pro Val Val Leu Asn Thr Thr Val Phe Thr Arg Pro Glu Thr
      50             55            60
Pro Val Pro Thr Lys Val His Thr Tyr Tyr Asp Ser Ala Thr Gly Val
      65             70            75            80
Val Thr Met Leu Ser Asn Asn Lys Lys Arg Ile Phe Arg Leu Asp Phe
      85             90            95

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Asp Asp Asp Val Arg Thr Leu Leu Pro Ile Leu Leu Leu Ser Lys
 100 105 110

<210> 24
 <211> 68
 <212> PRT
 <213> Myxoma Virus

<400> 24
 Met Ile Ser Glu Leu Leu Leu Phe Ala Val Cys Val Ile Ile Ile Gly
 1 5 10 15
 Leu Ile Ile Tyr Gly Ile Tyr Thr Arg Lys Ala Thr Gln Gln His Thr
 20 25 30
 Pro Pro Ser Ser Glu Arg Tyr Glu Lys Met Glu Asn Leu Lys Thr Gly
 35 40 45
 Tyr Val Asp Lys Leu Lys Ser Ala His Phe Lys Ser Phe Tyr Lys Leu
 50 55 60
 Phe Ser Gly Asn
 65

<210> 25
 <211> 96
 <212> PRT
 <213> Myxoma Virus

<400> 25
 Met Asp Thr Met Thr Ile Leu Ser Asn Tyr Phe Asn Thr Ala Leu Ile
 1 5 10 15
 Gly Gly Ile Val Leu Leu Ala Thr Ala Cys Val Phe Ala Phe Ile Asp
 20 25 30
 Phe Ser Lys Asn Lys Ser Thr Val Thr Asn Ala Trp Arg Ala Leu Ser
 35 40 45
 Gly Ile Thr Phe Val Leu Gly Ile Val Ile Thr Val Gly Met Leu Ile
 50 55 60
 Tyr Ser Met Trp Gly Arg Tyr Cys Lys Pro Pro Thr Lys Thr Thr Val
 65 70 75 80
 Val Glu Asn Gly Arg Tyr Asn Ser Ser Pro Ile Glu Leu Asn Gly Gln
 85 90 95

<210> 26
 <211> 113
 <212> PRT
 <213> Myxoma Virus

<400> 26
 Met Ile Thr Leu Phe Leu Val Leu Cys Tyr Phe Ile Leu Ile Phe Asn
 1 5 10 15
 Ile Ile Val Pro Ala Ile Ser Glu Lys Met Arg Lys Glu Tyr Asp Ala
 20 25 30
 Tyr Leu Lys Tyr Ala His Leu Lys Lys Asp Ala Val Cys Val Asp Asp
 35 40 45
 Arg Leu Phe Thr Tyr Asp Phe Lys Thr Ser Gly Val Val Ala Lys Met
 50 55 60
 Phe Ile Asp Ser Asn Gly Lys Pro Leu Pro Cys Ser Arg Thr Arg Asp
 65 70 75 80
 Ile Arg Ser Asn Asn Ala Ile Tyr Cys Asp Asn Asp Glu Asn Val Leu
 85 90 95

Asp Phe Arg Lys Ser Cys Ser Lys Ala Tyr Leu Asp Leu Phe Phe Thr
 100 105 110

Thr

<210> 27

<211> 140

<212> PRT

<213> Myxoma Virus

<400> 27

Met Asn Pro Val Thr Val Phe Phe Val Val Val Val Thr Val Ala Val
 1 5 10 15
 Cys Met Ile Leu Phe Gln Val Tyr Ser Ile Tyr Leu Asn Tyr Asp Asn
 20 25 30
 Ile Lys Glu Phe Asn Ala Met His Ser Pro Leu Glu Tyr Ser Lys Met
 35 40 45
 Val Asn Val Thr Ala Ile Asp Arg Arg Val Gln Asp Ala Asn Asp Asp
 50 55 60
 Ile Tyr Asp Ala Lys Gln Lys Trp Arg Cys Val Lys Phe Asp Asp Ser
 65 70 75 80
 Tyr Val Ser Leu Ser Met Phe Gly Tyr Lys Ala Asp Gly Val Gly Ile
 85 90 95
 Arg Arg Phe Arg Thr Leu Asn Gly Cys Ile Asp Tyr Thr Phe Ser Thr
 100 105 110
 Ser Thr His Ser Ser Ile Leu Asn Pro Cys Ile Pro Pro Asn Asp Pro
 115 120 125
 Lys Ser Arg Glu Cys Thr Phe Leu Lys Ser Ala Leu
 130 135 140

<210> 28

<211> 161

<212> PRT

<213> Myxoma Virus

<400> 28

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

<210> 29
 <211> 2000
 <212> PRT
 <213> Myxoma Virus

<400> 29

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

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385		390		395		400
Ala Arg Ser Val	Val Asp Leu Glu Asp	Ala Phe Cys Leu His Met Arg				
	405	410		415		
His Gly Leu His	His Asp Val Asp Cys Arg Ser Arg Leu Ile Pro Glu					
	420	425		430		
Glu Glu Pro Thr	Gln Pro Thr Arg Thr Arg Asn Arg Arg Ser Pro Pro					
	435	440		445		
Lys Gly Glu Lys	Pro Pro Val Pro Pro Lys Ser Asp Leu Val Leu Met					
	450	455		460		
Ser Ala Glu Glu	Leu Gly Ala Arg Pro Lys Ile Arg Lys Asn Thr Asp					
465	470	475		480		
Thr Ile Gln Leu	Gly Ala Ser Gly Thr Asp Gly Pro Val Ser Gly Ser					
	485	490		495		
Asp Gln Ile Tyr	Ala Asp Leu Lys Gln Lys Ile Glu Thr Arg Leu Lys					
	500	505		510		
Lys Leu Thr Ile	Asp Glu Gly Gly Leu Thr Ala Ser Arg Leu Pro Pro					
	515	520		525		
Ser Thr Lys Ala	Leu Leu Glu Glu Ala Ile Gly Arg Lys Ala Arg Ser					
	530	535		540		
Val Gln Val Ser	Lys Asp Ile Thr Arg Gln Ile Ile Asp Gln Gln Gln					
545	550	555		560		
Gly Ala Thr Gly	Asp Pro Ile Ser Gly Arg Gln Phe Lys Val Asn Val					
	565	570		575		
Arg Thr Gln Thr	Arg Pro Ser Thr Thr Val Thr Val Asp Thr Ser Ser					
	580	585		590		
Gly Val Tyr Ala	Asn Val Leu Arg Thr Pro Lys Asp Val Glu Val Thr					
	595	600		605		
Ala Pro Lys Asp	Val Thr Val Val Lys Thr Thr Val Tyr Gly Gly Arg					
	610	615		620		
Asp Asp Thr Tyr	Phe Leu Glu Pro Arg Arg Ser Ser Ser Ala Ser Glu					
625	630	635		640		
Ser Pro Tyr Phe	Leu Glu Pro Arg Arg Ser Ser Ser Ala Ser Asp Val					
	645	650		655		
Gly Ser Ala Ser	Pro Tyr Phe Leu Gln Pro Gly Asp Glu Asp Val Phe					
	660	665		670		
Val Gly Gln Glu	Tyr Ala Gln Val Asn Lys Arg Arg Leu Pro Ser Asp					
	675	680		685		
Gly Val His Asn	Pro Leu Arg Arg His Ser Ser Ser Asp Tyr Glu Thr					
	690	695		700		
Ile Lys Glu Arg	Gln Arg Ser Ile Lys Tyr His Arg Glu Asn Tyr Tyr					
705	710	715		720		
Glu Ser Val Asp	Asp Ser Asn Leu Tyr Ala Leu Ala Gly Arg Pro Thr					
	725	730		735		
Pro Arg Arg Pro	Asn Pro Arg Glu Gly Val Pro Leu Pro Pro Ile Pro					
	740	745		750		
Arg Lys Asp Leu	Pro Leu Pro Pro Ile Pro Gly Asn Asp Pro Phe Asn					
	755	760		765		
Thr Lys Thr Lys	Lys Met Ile Asp Lys Ile Cys Asp Ser Gln Gly Ala					
	770	775		780		
Ala Ser Ile Cys	Gly Ile Arg Gly Thr Asp Ala Leu Tyr Glu Ser Val					
785	790	795		800		
Asp Asp Val Asp	Thr Arg His Leu Lys Arg Asn Pro Ile Tyr Glu Pro					
	805	810		815		
Phe Asn Glu Arg	Glu Tyr Ser Thr Asn Pro Leu Tyr Gln Pro Leu Glu					
	820	825		830		
Glu Gly Ala Lys	Pro Lys Ser Ala Leu Thr Arg Lys Asn Ala Ile Arg					
	835	840		845		

Arg Arg Pro Gly Gln Asp Ser Asp Thr Leu Val Ile Glu Thr Arg Tyr
 850 855 860
 Ser Glu Gly Pro Glu Pro Gly Asn Asp Asn Tyr Ala Ala Asn Asn Val
 865 870 875 880
 Lys Asn Asn Ala Asp Gly Arg Ser Thr Asn Ile Tyr Ser Ala Glu Pro
 885 890 895
 Lys Asn Gly Asn Thr Gly Gly Gly Gly Thr Gly Thr Asp Val Ala Asn
 900 905 910
 Thr Lys Asp Gly Gln Ala Lys Lys Val Lys Thr Pro Lys Gly Asn Lys
 915 920 925
 His Lys Lys Leu Ser Met Gly Gly Ala Tyr Glu Asn Asn Lys Met Asn
 930 935 940
 Ser Met Ile Lys Ala Ile Ala Leu Ser Ser Tyr Leu Ser Thr Thr Asn
 945 950 955 960
 Ser Arg Ile Ser Ser Ile Met Ala Ser Ala Gly Ser Gln Pro Lys Glu
 965 970 975
 Leu Ala Ile Val Asn Ile Val Ser Ser Val Leu Ser Gln Ile Gly Gly
 980 985 990
 Thr Ile Ala Ile Ala Gly Ser Asn Ser Pro Thr Ala Ala Ala Gly
 995 1000 1005
 Leu Ala Leu Gln Gly Ile Ser Gly Leu Ile Asp Ala Ala Thr Ser Ile
 1010 1015 1020
 Tyr Tyr Ile Leu Ala Gly Ser Gln Pro Tyr Lys Asp Pro Ala Ile Glu
 1025 1030 1035 1040
 Lys Phe Ser Asn Tyr Ala Asn Tyr Met Ser Arg Thr Glu Ala Gly Ala
 1045 1050 1055
 Arg Val Cys Met Met Pro Asp Ser Asp Ile Thr Ile Thr Leu Ala Tyr
 1060 1065 1070
 Arg His Ser Lys Met Asn Thr Asp Ala Glu Lys Asn Arg Gly Glu Tyr
 1075 1080 1085
 Thr Asp Val Ile Pro Ser Lys Val Tyr Tyr Leu Lys Asn Asn Tyr Ile
 1090 1095 1100
 Ser Tyr Thr Val Lys Val Thr Leu Val Cys Pro Ile Gly Gln Leu Arg
 1105 1110 1115 1120
 Leu Leu Glu Ala Asp Val Asn Thr Tyr Ala Thr Leu Ile Arg Glu Glu
 1125 1130 1135
 Asn Asn Gly Ala Lys Tyr Tyr Leu Val His Gly Ile Leu Glu Leu Leu
 1140 1145 1150
 Ser Tyr His Ser Thr Val Thr Phe Thr Cys Gly Asn Glu Pro Gly Val
 1155 1160 1165
 Ile Phe Thr Pro Phe Glu Gln Lys Leu Arg Asp Met Gln Leu Leu Arg
 1170 1175 1180
 Ile Ser Thr Pro Gly Glu Pro Lys Glu Ala Glu Asp Met Pro Ser Asn
 1185 1190 1195 1200
 Val Cys Asp Leu Tyr Pro Leu Lys Arg Phe Tyr Val Leu Ala Gly Asn
 1205 1210 1215
 Cys Pro Tyr Asp Met Ser Arg Lys Ser Val Ala Tyr Val Thr Cys Ser
 1220 1225 1230
 Thr Leu Leu Arg Met Ser Thr Tyr Glu Ala Thr Lys His Arg Trp Ile
 1235 1240 1245
 Leu Met Asn Pro Phe Ser Glu Asp Glu His Asp Asn Ile Gln Leu Phe
 1250 1255 1260
 Thr Phe Lys Lys Tyr Asp Phe Lys Gly Ser Val Ile Asn Leu Asn Glu
 1265 1270 1275 1280
 Ile Gly His Ser Asp Thr Val Cys Ser Gln Ser Asp Thr Ser Thr Cys
 1285 1290 1295
 Tyr Trp Ser Asp Ala Met Ile Leu Glu Asp Val Thr Ala Cys Thr Ser

1300	1305	1310
Arg Ile Arg Lys Leu Tyr Val	Lys Leu Ser Thr Ser	Leu Gly Lys Gly
1315	1320	1325
Tyr Asn Ser Phe Val Leu Thr	Cys Pro Tyr Gly Ser Thr	Pro Phe Tyr
1330	1335	1340
Ile Ser Asn Gly Thr Ile Val	Asp Ile Pro Ile Asn Thr	Arg Arg Thr
1345	1350	1355
Thr Val Arg Phe Thr Ala Gln	Ser Asp Thr Thr Ala Leu	Val Ser Cys
1365	1370	1375
Ile His Asn Thr Asn Pro Ala	Tyr Lys Ser Asp Ile Ile	Gln Leu Ser
1380	1385	1390
Phe Val Thr Glu Asp Ala Arg	Ser Asn Tyr Leu Asp Phe	Arg Tyr Phe
1395	1400	1405
Lys Tyr Arg Gln Lys Leu Phe	Asn Val Phe Ser Asp Pro	Met Pro Leu
1410	1415	1420
Arg Ser Lys Lys Cys Lys Arg	Tyr Glu Glu Asn Arg Arg	Cys Lys Asn
1425	1430	1435
Tyr Tyr His Val Lys His Ile	Pro Lys Ile Asp Tyr Lys	Val Val Met
1445	1450	1455
Gln Arg Leu Pro Met Val Lys	Leu Ser Thr Ser Tyr Thr	Gly Pro Leu
1460	1465	1470
Asn Asp Lys Thr Ile Thr Lys	Ile Ser Ser Tyr Tyr Ala	Ser Pro Ile
1475	1480	1485
Ser Leu Ser Ile Asp Val Ser	Ser Ser Leu Ser Ser Val	Tyr Asp Val Pro
1490	1495	1500
His His Phe Trp Lys Tyr Ala	Lys Glu Gly Val Arg Thr	Phe Ser Ala
1505	1510	1515
Ile Ala Val Thr Met Phe Ala	Cys Ser Val Val Ala Gly	Asn Val Asn
1525	1530	1535
Val Asn Pro Gly Ile Gly Gly	Arg Thr Asp Thr Tyr Gly	Arg Asn Ala
1540	1545	1550
Lys Tyr Ile Phe Leu Gly Thr	Lys Arg Ser Pro Ser Asn	Asn Arg Ile
1555	1560	1565
Pro Phe Asp Phe Val Tyr Asp	Ser Tyr Tyr Gln Thr Thr	Asn Tyr Pro
1570	1575	1580
Tyr Glu Lys Cys Asp Val Tyr	Leu Asp Leu Val Thr Gln	Arg Leu Glu
1585	1590	1595
Ile Arg Cys Pro Glu Leu Thr	Ile Pro Gln Lys Pro Phe	Asn Ser Pro
1605	1610	1615
Leu Val Asn Ser Leu Cys Val	Leu Val Ala Thr Ser Arg	Asp His Cys
1620	1625	1630
Ala Leu Val Thr Glu Asn Trp	Asp Arg Thr Tyr Gly Tyr	Ser Tyr Ala
1635	1640	1645
Asp Ala Tyr Thr Glu Phe Asp	Ser Cys Lys Asn Gly Tyr	Tyr Pro Ser
1650	1655	1660
Arg Pro Ile Asp Asn Phe Cys	Tyr Tyr Trp His Leu Ser	Thr Tyr Trp
1665	1670	1675
Pro Pro Asp Tyr Asp Pro Cys	Val Ser Ala Met Val Leu	Ala His Ser
1685	1690	1695
Tyr Ile Phe Pro Asp Asn Lys	Ile Val Asn Pro Pro Tyr	Ile Lys Glu
1700	1705	1710
Phe Gly Tyr Asp Pro Asp Lys	Asn Glu Tyr Val Asp Arg	Thr Leu Tyr
1715	1720	1725
Val Lys Leu Gln Ala Leu Tyr	Asp Gln Tyr Asn Lys Leu	Val Glu Tyr
1730	1735	1740
Ser Met Asn Pro Met Val Asp	Ile Ser Asn Asn Leu Ala	Ser Ala Met
1745	1750	1755
		1760

Thr Pro Glu Ala Arg Glu Ile Phe Arg Leu Lys Tyr Ser Gly Ala Glu
 1765 1770 1775
 Met Glu Thr Glu Ile Thr Leu Asn Lys Arg Lys Ala Glu Lys Val Lys
 1780 1785 1790
 Glu Asp Ile Glu Asp Leu Leu Asn Glu Ile Tyr Ala Asn Thr Leu Thr
 1795 1800 1805
 Tyr Ser Glu Ala Thr Ala Met Leu Arg Ser Ala Ile Ser Thr Arg Cys
 1810 1815 1820
 Cys Val Leu Asn Gly Thr Asp Val Tyr Lys Tyr Phe Arg Leu Glu His
 1825 1830 1835 1840
 Tyr Leu Cys Gly Thr Tyr Glu Asp Tyr Leu Val Tyr Ile Asp Asn Lys
 1845 1850 1855
 Thr Tyr Val Arg Ile Asn Glu Thr Val Val Pro Glu Asn Glu Tyr Leu
 1860 1865 1870
 Ala Ala Lys Ala Pro Arg Val Thr Cys Phe His Thr Asp Leu Ile Pro
 1875 1880 1885
 Ile Thr Asp Glu Glu Thr Gln Arg Arg Phe Glu Lys Met Ile Val Gln
 1890 1895 1900
 Ala Ala Leu Glu Asp Ala Leu Thr Ser Ile Phe Glu Glu His Asp Asn
 1905 1910 1915 1920
 Asn Val Thr Asp Tyr Phe Ala Glu Tyr Met Arg Ser Leu Gln Met Ala
 1925 1930 1935
 Asn Lys Ser His Thr Asn Asn Ile Ile Ala Val Ala Leu Ala Gly Ile
 1940 1945 1950
 Ile Val Ile Val Thr Thr Tyr Val Phe Thr Arg Leu Arg Thr Lys Gln
 1955 1960 1965
 Lys Lys Gly Asn Tyr Asn Val Arg Asn Lys Ile Asp Asn Ser Ile Gln
 1970 1975 1980
 Lys Glu Ile Gln Leu Asp Gly Val Tyr Thr Thr Asp Asn Val Phe Ile
 1985 1990 1995 2000

<210> 30

<211> 67

<212> PRT

<213> Myxoma Virus

<400> 30

Met Gly Pro Phe Met Val Ser Ala Leu Thr Met Val Arg Ala Cys Ile
 1 5 10 15
 Asp Cys Arg Thr Tyr Phe Ile Ala Thr Arg Glu Arg Asn Thr Ile His
 20 25 30
 Glu Val Ala Glu Met Glu Asp Val Glu Glu Val Glu Glu Val Asn Asp
 35 40 45
 Asp Asp Gly Asp Glu Tyr Val Asp Ala Val Glu Glu Ile Val Val Glu
 50 55 60
 Ser Pro Ala
 65

<210> 31

<211> 218

<212> PRT

<213> Myxoma Virus

<400> 31

Met Arg Val Leu Ser Ile Leu Ala Leu Leu Ser Thr Val Ala Tyr Ala
 1 5 10 15
 Tyr Ser Val Arg Cys Thr Asn Thr Thr Thr Val Ala Glu His Val Asn

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

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<210> 32

<211> 76

<212> PRT

<213> Myxoma Virus

<400> 32

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

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<210> 33

<211> 178

<212> PRT

<213> Myxoma Virus

<400> 33

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Met Val Phe Ile Phe Ile Ile Thr Cys Val Cys Leu Val Thr Arg Ser
1      5      10      15
Cys Gly Gly Gly Leu Glu Asp Asp Ile Asp Arg Ile Phe Gln Lys Arg
      20      25      30
Tyr Asn Glu Leu Ser Gln Pro Ile Lys Arg Asn Met Arg Thr Leu Cys
      35      40      45
Lys Phe Arg Gly Ile Thr Ala Thr Met Phe Thr Glu Gly Glu Ser Tyr
      50      55      60

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Leu Ile Gln Cys Pro Ile Ile His Asp Tyr Val Leu Arg Ala Leu Tyr
65          70          75          80
Asp Leu Val Glu Gly Ser Tyr Thr Val Arg Trp Glu Arg Glu Thr Glu
          85          90          95
Asp Asp Val Glu Ser Val Asp Pro Lys Leu Val Lys Gly Thr Leu Leu
          100         105         110
Tyr Leu Gln Pro Asn Ala Ser Ser Ile Gly Thr Tyr Leu Cys Thr Leu
          115         120         125
His Asp Asn Arg Gly Met Cys Tyr Gln Ser Val Ala His Val Ile Arg
          130         135         140
Arg Pro Lys Met Gln Cys Val Lys His Ala His Thr Thr Ser Asp Ser
145          150         155         160
Asn Leu Trp Ile Tyr Leu Ala Ile Leu Ala Val Leu Ile Ser Leu Gly
          165         170         175
Val Leu

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<210> 34
<211> 300
<212> PRT
<213> Myxoma Virus

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<400> 34
Met Arg Ala Thr Leu Trp Thr Val Tyr Val Ala Ser Leu Leu Gln Ser
1          5          10          15
Tyr Val Leu Ala Asp Cys Lys Asn Asp Phe Lys Ser Asn Val Gln Ala
          20          25          30
Val Asn Lys Lys Gln Thr Tyr Lys Gln Asp Glu Val Thr Glu Leu Gln
          35          40          45
Cys Val Pro Gly Tyr Gln Lys Lys Ser Asn Val Thr Ile Ser Ala Thr
          50          55          60
Cys Gly Lys Asp Asn Thr Trp Arg Ile Ser Asn Glu Tyr Val Cys Val
65          70          75          80
Arg Arg Glu Cys Pro Asp Pro Pro Thr Ile Glu Asn Gly Arg Val His
          85          90          95
Thr Pro Lys Ile Met Tyr His Arg His Asp Ala Val Arg Tyr Val Cys
          100         105         110
Asn Glu Asn His Lys Ser Ile Pro Tyr Ser Leu Val Gly Glu Asp Val
          115         120         125
Val Arg Cys Ile Asn Glu Thr Thr Trp Tyr Pro Ser Pro Pro Thr Cys
          130         135         140
Lys Met Ile Val Cys Arg Phe Pro Ala Leu Gln Asn Gly Tyr Val His
145          150         155         160
Gly Val Pro Phe Ile Lys Arg Phe Cys Tyr Lys Asn Arg Val Arg Phe
          165         170         175
Thr Cys Asn Pro Asp Phe Thr Leu Val Gly Ala Ser Tyr Ala Thr Cys
          180         185         190
Thr Leu Asn Ala Thr Trp Ser Pro Asp Val Pro Lys Cys Val Arg Arg
          195         200         205
Ala His Asp Ser Asn Thr Arg Asn Ile Phe Ala Phe Val Glu Tyr Asp
          210         215         220
Asp Phe Glu Asp Leu Asp Asp Glu Asp Ala Val Asn Glu Lys Leu Thr
225          230         235         240
Asp Thr Ser Thr Arg Pro Asp Asp Ala Thr Ser Asp Arg Pro Ser His
          245         250         255
Val Phe Val Ala Leu Val Ile Leu Gly Thr Ile Leu Phe Ile Phe Thr
          260         265         270

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Leu Gly Val Ile Leu Leu Phe Cys Ser Cys Thr Ser Ser Asn Ile Leu
 275 280 285
 His Pro Asn Lys Leu Ser Tyr Thr Lys Leu Ser Val
 290 295 300

<210> 35

<211> 176

<212> PRT

<213> Myxoma Virus

<400> 35

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

<210> 36

<211> 172

<212> PRT

<213> Myxoma Virus

<400> 36

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

19

130		135		140
Cys Tyr Val Tyr Lys	Leu Asn Gly Ile Gln Glu Ile Leu Cys Asn Val			
145	150	155		160
Val Asn Tyr Val Ile	Cys Met Lys Arg Phe Tyr Lys			
	165	170		

<210> 37
 <211> 214
 <212> PRT
 <213> Myxoma Virus

<400> 37
 Met Ala Arg Tyr Ile Ile Ile Val Leu Ala Cys Leu Val Ala Thr Ser
 1 5 10 15
 Thr Cys Ala Thr Tyr Pro Lys Lys Tyr Trp His Leu Ala Ala Glu Leu
 20 25 30
 Thr Ile Gly Leu Asn Arg Tyr Val Glu Thr Val Met Gly Glu Cys His
 35 40 45
 Met Lys Glu Arg Tyr Asp His Lys Thr Ser Thr Leu Ile Leu Thr Gly
 50 55 60
 Tyr Gly Leu Met Ile Asn Ile Thr Ile Thr Asn Val Val Gln Arg Phe
 65 70 75 80
 Val Ala Ala Ser Ala Gly Ala Gly Asp Gly Asn Lys Leu Ser Ile Met
 85 90 95
 Leu Phe Thr Thr His Pro Leu Thr Lys Tyr Ser Asp Ile Tyr Leu Thr
 100 105 110
 Ile Thr Cys Leu Glu Pro Glu Ala Thr Trp Ala Thr Thr Gly Asn Gln
 115 120 125
 Leu Pro Asp Ser Leu His His Asn Lys Asp Val Ser Ile Thr Ile Leu
 130 135 140
 Gly Ser Cys Val Thr Cys Val Asn Leu Glu Thr Asn Pro Ile Lys Val
 145 150 155 160
 Asn Pro His Phe Thr His Pro Ile Ser Met Phe Val Tyr Asp Asn Lys
 165 170 175
 Glu Asp Val Arg Gly Ser Tyr Gly Val Thr Phe Glu Asp Glu Leu Asn
 180 185 190
 Val Cys Phe Leu Asp Ile Lys Lys Val Ser Tyr Asp Leu Cys Tyr Arg
 195 200 205
 Gln Thr Arg Tyr Leu Ile
 210

<210> 38
 <211> 53
 <212> PRT
 <213> Myxoma Virus

<400> 38
 Met Ile Thr Asn Tyr Glu Pro Val Ile Leu Leu Gly Ile Ile Cys Phe
 1 5 10 15
 Thr Val Leu Val Asn Phe Lys Leu Ser Thr Lys Ala Lys Ile Asp Val
 20 25 30
 Ile Phe Phe Ile Gln Ser Ile Leu Phe Met Trp Phe Ile Phe His Phe
 35 40 45
 Val His Ser Val Phe
 50

<210> 39

<211> 200
 <212> PRT
 <213> Myxoma Virus

<400> 39

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

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<210> 40
 <211> 281
 <212> PRT
 <213> Myxoma Virus

<400> 40

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Met Ile Gly Leu Leu Phe Phe Val Tyr Val Val Pro Leu Ala Ala Glu
 1           5           10           15
Asn Glu Val Thr Val Thr Pro Tyr Thr Val Cys Asn Lys Thr Val Thr
          20           25           30
Leu Glu Cys Asn Leu Asp Ala Leu Ile Tyr Lys Asp Ile Asn Ser Val
          35           40           45
His Val Lys Trp Leu Phe Asp Thr Met Tyr Asp Thr Ile Ser Asn Lys
          50           55           60
Thr Asn Gly Ser Ser Ile Thr Phe Asp Phe Ala Asn Asn Leu Thr Gly
65           70           75           80
Asn Tyr Thr Cys Glu Ala Tyr Ser Glu Phe Asn Ser Val Lys His Val
          85           90           95
Ile Ala Leu Thr Phe Val His Gln Trp Phe Ser Arg Glu Glu Ile Gln
          100          105          110
Phe Ile Leu Ser Leu Leu Thr Ile Tyr Ile Ile Leu Leu Trp Gly Asn
          115          120          125
Val Cys Thr Ile Thr Phe Lys Ile Asn Asn Val Ser Lys Leu Ile His
          130          135          140
Val Tyr Ser Ile Ala Leu Trp Met Thr Leu Ile Met Phe Val Gly Gln

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145					150					155					160
Tyr	Met	Ile	Gly	Ile	Asp	Thr	Asp	Met	Leu	Tyr	Val	Lys	Val	Asn	Gly
				165					170					175	
Ile	Ile	Leu	Ile	Gln	Leu	Ser	Ile	Phe	Ser	Ser	Ile	Phe	Leu	Gln	Arg
			180					185					190		
Ile	Leu	His	Lys	Lys	Leu	Ile	Pro	Ser	Tyr	Leu	Leu	Asn	Ile	Val	Leu
		195					200					205			
Gly	Leu	Lys	Ala	Val	Ser	Tyr	Thr	Gly	Ser	Thr	Val	Val	Ile	Ala	Leu
	210					215					220				
Ser	Phe	Ile	Gly	Cys	Tyr	Asn	Lys	Ala	Tyr	Gly	Tyr	Thr	Tyr	Met	Tyr
225					230					235				240	
Lys	Leu	Leu	Phe	Ala	Asp	Ile	Leu	Glu	Leu	Ile	Ser	Leu	Ile	Ala	Leu
			245					250						255	
Tyr	Thr	Leu	Pro	Leu	Gly	Thr	Gln	Ala	Thr	Tyr	Lys	Lys	Leu	Tyr	Leu
		260					265						270		
Gln	Ser	Asp	Glu	Thr	Phe	Thr	Phe	Leu							
		275					280								