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- (54) USING A CYTOKINE SIGNATURE TO DIAGNOSE DISEASE OR INFECTION
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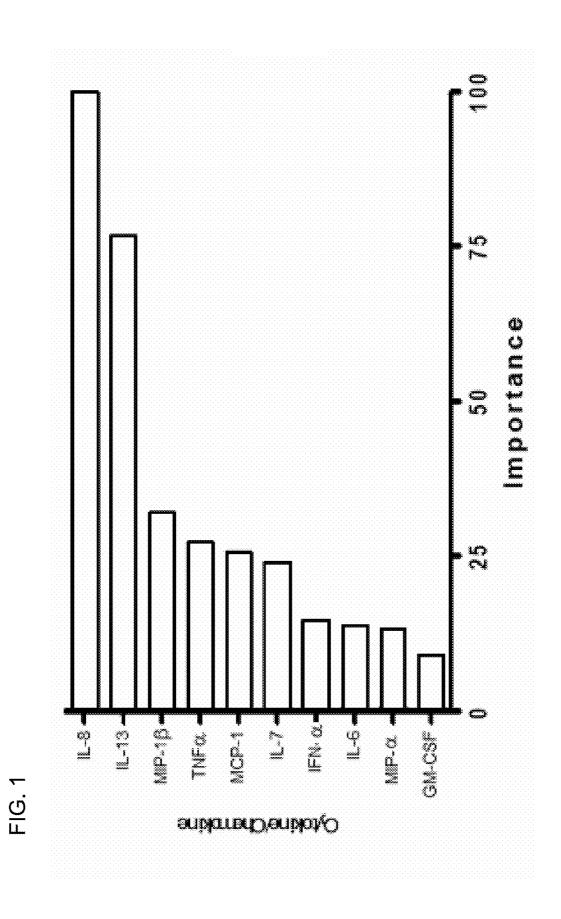
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(57) ABSTRACT

Provided are methods and compositions for detection of levels, activity, or expression of cytokines so as to determine a cytokine signature. A cytokine signature of a subject can be compared to a control or reference value(s) and differences there between used in the diagnosis or monitoring of a neuroimmune disease or a retroviral infection.



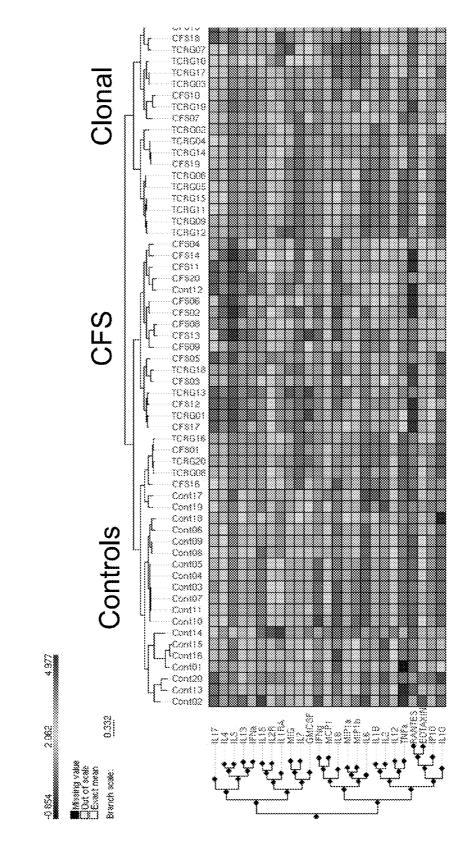
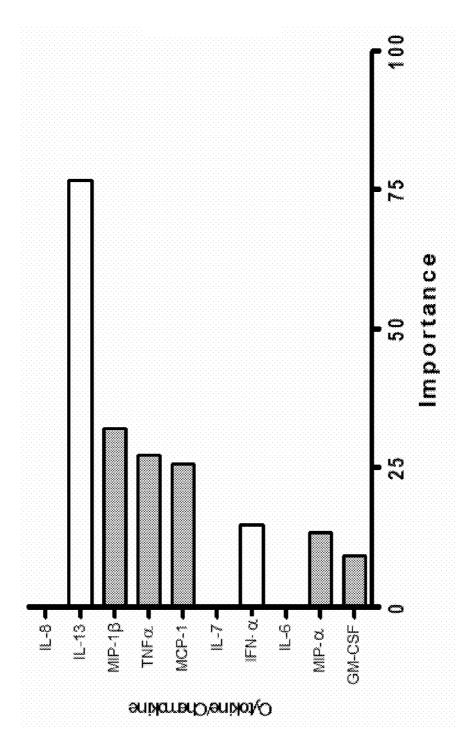
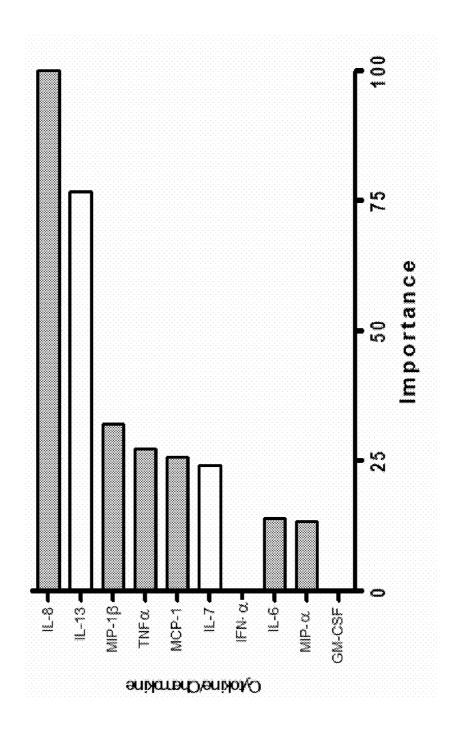


FIG. 2









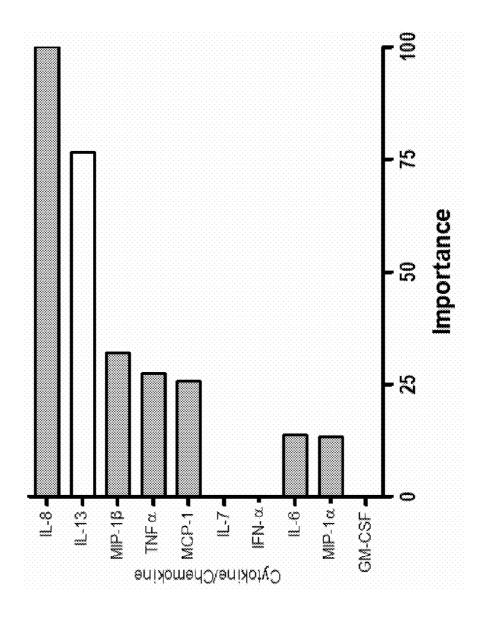


FIG. 5

USING A CYTOKINE SIGNATURE TO DIAGNOSE DISEASE OR INFECTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation-in-Part of PCT International Application No. PCT/2012/023876 filed 3 Feb. 2012, which claims the benefit of U.S. Provisional Application Ser. No. 61/439,328, filed on Feb. 3, 2011, each of which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under grant number R01 AI078234-01A2 awarded by National Institutes of Health. The government has certain rights in the invention.

MATERIAL INCORPORATED-BY-REFERENCE

[0003] The Sequence Listing, which is a part of the present disclosure, includes a computer readable form comprising nucleotide and/or amino acid sequences of the present invention. The subject matter of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0004] The present disclosure generally relates to the differences in cytokine expression seen between healthy individuals and individuals diagnosed with a neuroimmune disease or infected with a retrovirus, including those associated with a retrovirus.

BACKGROUND OF THE INVENTION

[0005] Cytokines are cell-to-cell signals, and include proteins, peptides and glycoproteins. Cytokines are secreted by, inter alia, glial cells in the nervous system, and many immune cells. Cytokines are generally understood to encompass interleukins, interferons (lymphokines) and chemokines. Interleukins (ILs) promote the development and differentiation of T, B and hematopoietic cells in healthy individuals. The functions of at least 35 interleukins are currently known. Interferons (IFNs, or lymphokines) are synthesized and released by lymphocytes in response to the presence of pathogens, and activate MHC and STAT signaling. Chemokines are small cytokines that can stimulate chemotaxis, and are characterized by two or four conserved cysteine residues key to the folding of the peptide. Some chemokines are produced during an immune response to recruit immune cells to the site of infection; other chemokines are homeostatic and control cell migration during tissue growth and/or maintenance.

[0006] Cytokines are recognized by cognate cell-surface receptors. Binding of a cytokine to its receptor triggers intracellular signaling which can ultimately up- or down-regulate genes and alter cell functions. The effect of any given cytokine is dependent on its identity, abundance, and the cell type on which the receptor is located.

[0007] Cytokines are immunomodulating agents, and can be proteins, peptides or glycoproteins. Cytokines are classified as interferons (lymphokines), interleukins and chemokines, based on their presumed or known function; what cells they are secreted by; or which cells they target. There is, however, much cross-classification and overlap in organization within these categories, consistent with the pleiotropic nature of the molecules' functions. Some cytokines are redundant in function with other cytokines, and pleiotropic in their activity. They can be classified into two functional types: (i) type 1 cytokines that upregulate cellular immune responses, and include IFN- γ and TGF- β among others; and (ii) type 2 cytokines which upregulate antibody responses, and include IL-4, IL-10, IL-13, among others.

[0008] Inteferons and lymphokines are secreted by lymphocytes and include, but are not limited to, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon (IFN)- γ . They recruit macrophages and other lymphocytes to sites of infection and prepare the recruited cells to mount an immune response.

[0009] Interleukins are secreted by a wide variety of cells and function to promote the development and differentiation of T, B and hematopoietic cells. Interleukins include, but are not limited to, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, and IL-35.

[0010] Chemokines are a group of smaller cytokines, initially so named because they cause chemotaxis. Some chemokines are considered pro-inflammatory, and recruit cells of the immune system to a site of infection; others are considered homeostatic and control the migration of cells during normal tissue growth and maintenance. Chemokines can be divided into four groups based on the presence and placement of up to six cysteine residues within the peptide.

[0011] The CC chemokines have two adjacent cysteines near their amino terminus. This group includes MCP-1 (or CCL2) and RANTES (or CCL5). The group also includes CCL1 (I-309, TCA-3), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL6 (C10, MRP-2), CCL7 (MARC, MCP-3), CCL8 (MCP-2), CCL9 (same as CCL10; MRP-2, CCF18, MIP-113), CCL11 (Eotaxin), CCL12 (MCP-5), CCL13 (MCP-4, NCC-1, Ckβ10), CCL14 (HCC-1, MCIF, Ckβ1, NCC-2, CCL), CCL15 (Leukotactin-1, MIP-5, HCC-2, NCC-3), CCL16 (LEC, NCC-4, LMC, Ckβ12), CCL17 (TARC, dendrokine, ABCD-2), CCL18 (PARC, DC-CK1, AMAC-1, Ck_β7, MIP-4), CCL19 (ELC, Exodus-3, Ckβ11), CCL20 (LARC, Exodus-1, Ckβ4), CCL21 (SLC, 6Ckine, Exodus-2, Ckβ9, TCA-4), CCL22 (MDC, DC/β-CK), CCL23 (MPIF-1, Ckβ8, MIP-3), CCL24 (Eotaxin-2, MPIF-2, Ck β 6), CCL25 (TECK, Ckβ15), CCL26 (Eotaxin-3, MIP-4a, IMAC, TSC-1), CCL27 (CTACK, ILC, Eskine, PESKY, skinkine), and CCL28 (MEC).

[0012] In the CXC chemokines, the two amino-terminal cysteines are separated by one amino acid. These chemokines are also referred to as α -chemokines; and can be subdivided into glutamic acid-leucine-arginine (ELR) positive or negative, based on the presence or absence of this 3-aa motif before the first cysteine of the CXC motif. The CXC chemokines include, but are not limited to, CXCL1(Gro- α , GRO1, NAP-3, KC), CXCL2 (Gro- β , GRO2, MIP-2 α), CXCL3 (Gro-, GRO3, MIP-2 β), CXCL4 (PF-4), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2, CTAPIII, β -Ta, PEP), CXCL8 (IL-8, NAP-1, MDNCF, GCP-1), CXCL9 (MIG, CRG-10), CXCL10 (IP-10, CRG-2), CXCL11 (I-TAC, β -R1, IP-9), CXCL12 (SDF-1, PBSF), CXCL13 (BCA-1, BLC), CXCL14 (BRAK, bolekine), CXCL15 (Lungkine, WECHE), CXCL16 (SRPSOX), and CXCL17 (DMC, VCC-10).

[0013] The C chemokines (or γ chemokines) have only two cysteines, one of which is near the N-terminus of the peptide, and one of which is near the C-terminus. The two C chemokines are XCL1 (lymphotactin- α , SCM-1a, ATAC) and XCL2 (lymphotactin- β , SCM-1 β). The CX₃C chemokine CX3CL2 (Fractalkine, Neurotactin, ABCD-3) has three amino acids between the two N-terminal cysteine residues.

[0014] The cytokines RANTES, MIP (macrophage inflammatory proteins) 1 α and 1 β (now known as CCL5, CCL3 and CCL4 respectively) suppress HIV-1 (Ciccgu et al., Science 270(5243): 1811-1815, 1995). It has been suggested that increased amounts of these chemokines is associated with more favorable clinical status in AIDS cases (Garzino-Demo et al., PNAS 96(21):11986-11991, 1999).

[0015] It has been reported that initial HIV infection disrupts the normal balance of cytokines by causing the levels of certain cytokines to rise. Cytokines reported to increase during initial HIV infection include IFN_γ, IL-2 and IL-12. As HIV progresses to AIDS, the steady-state levels of IFN_γ, IL-2 and IL-12 are reported to fall. Simultaneously, the levels of another group of cytokines (including IL-4, IL-5, IL-6, IL-10, TNF α) have been reported to increase. According to the Th-1/ Th-2 theory, this change in cytokine expression signature may directly cause many of the symptoms associated with AIDS (Babakhanian, 1995).

[0016] Neuroimmune disease is a category of diseases which have both neurological effects and (auto)immune effects. Neuroimmune diseases can be chronic neuroimmune diseases, or acute neuroimmune diseases. As used herein, neuroimmune disease can include chronic fatigue syndrome, fibromyalgia, myalgic encephalitis, atypical multiple sclerosis, non-epileptic seizures, Gulf War Syndrome or autism.

[0017] Chronic Fatigue Syndrome (CFS) is an example of a neurological disease believed to involve malfunctions in the immune system. CFS is a debilitating disease that affects more than one million people in the US alone. CFS is a disease characterized by severe and debilitating fatigue, sleep abnormalities, impaired memory and concentration, and musculoskeletal pain. In the Western world, the population prevalence is estimated to be of the order of 0.5%-2% (Papanicolaou et al. 2004. Neuroimmunomodulation 11(2):65-74; White. 2007. Popul Health Metr 5(1):6). CFS subjects are known to have a shortened lifespan and are at risk for developing lymphoma. Currently, there is no diagnostic test and no treatment, except for the specific treatment of microbial infections in those cases in which microbial agents can be identified (Devanur and Kerr. 2006. J Clin Virol 37(3):139-150). Although the precise pathogenesis of CFS is unknown, a range of factors have been shown to contribute (Komaroff and Buchwald. 1998. Annu Rev Med 49:1-13; Devanur and Kerr. 2006. supra). Furthermore, a single patient with a bona fide CFS diagnosis can present with variable symptoms over the duration of the illness.

[0018] Several retroviruses such as the MuLVs, primate retroviruses, HIV, HTLV-1 and xenotropic murine leukemia virus-related virus (XMRV) are associated with neurological diseases (C. Power, Trends in Neurosci. 24, 162, 2001; Miller and Meucii 1999 TINS 22(10), 471-479; Power et al. 1994 Journal of Virology 68(7) 4463-4649). Investigation of the molecular mechanism of retroviral induced neurodegeneration in rodent models revealed vascular and inflammatory changes mediated by cytokines and chemokines and these changes were observed prior to any neurological pathology (X. Li, C., Hanson. J. Cmarik, S. Ruscetti J. Virol. 83, 4912,

March, 2009, K. E. Peterson., B Chesebro. Curr. Opin. Microbiol. Immunol. 303, 67 2006). The XMRV genome encodes, in 5'-to-3' order, the 5' long terminal repeat (LTR); a short, apparently non-coding sequence comprising a splice site acceptor ("SA"); the Gag gene; the Pro-Pol gene, comprising a splice donor site ("SD"), the extreme 3'-end of which overlaps with the 5'-end of the Env gene; the Env gene; another short non-coding sequence; the 3'-end LTR; and a poly-A tail (see Urisman et al. 2006 PLoS Pathogens 2(3), e25; Lombardi et al. 2009 Science 326(5952), 585-589).

SUMMARY OF THE INVENTION

[0019] Among the various aspects of the present invention is the provision of a method of predicting symptoms in a subject infected with a retrovirus.

[0020] One aspect provides a method of diagnosing a retroviral infection or a neuroimmune disease in a subject. In some embodiments, the method includes comparing a cytokine expression signature of a subject with a control. In some embodiments, the cytokine expression signature includes an expression level of at least three cytokines or chemokines, which can be selected from IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , or GM-CSF. In some embodiments, the method includes diagnosing the subject with a retroviral infection or a neuroimmune disease where the cytokine expression signature of the subject comprises at least one of the selected cytokines or chemokines at or above a predetermined threshold of expression.

[0021] In some embodiments, the method includes application of an algorithm for determining whether a cytokine signature is indicative of a retroviral infection or a neuroimmune disease in a subject. In some embodiments, the algorithm includes a weighted value for a portion of or all of cytokines or chemokines of the cytokine signature. In some embodiments, the algorithm includes addition of a weighted value to arrive at a sum of weighted values where a cytokine or chemokine of the cytokine expression signature is at or above a predetermined threshold of expression. In some embodiments, application of an algorithm includes diagnosing the subject with a retroviral infection or a neuroimmune disease where the sum of weighted values is at or above a predetermined threshold value.

[0022] Another aspect provides a device for detecting a cytokine expression signature of a subject comprising an array, wherein the array detects the presence or expression level at least three cytokines or chemokines selected from the group consisting of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF.

[0023] Other objects and features will be in part apparent and in part pointed out hereinafter.

DESCRIPTION OF THE DRAWINGS

[0024] Those of skill in the art will understand that the drawings, described below, are for illustrative purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0025] FIG. **1** shows the importance of various cytokines and chemokines in XMRV-related disease as assessed by Random Forests Variables analysis.

[0026] FIG. 2 shows the results of cluster analysis of cytokine/chemokine expression data in XMRV-infected subjects, XMRV-infected subjects with increased $\gamma\delta$ T-cell populations, and healthy controls. **[0027]** FIG. **3** shows the results of Random Forests variable analysis for subject 2623.

[0028] FIG. **4** shows the results of Random Forests variable analysis for subject 1127.

[0029] FIG. **5** shows the results of Random Forests variable analysis for subject 967.

DETAILED DESCRIPTION OF THE INVENTION

[0030] Provided herein is a description of signature changes in cytokine expression that can be reliably associated with a diagnosis of a neuroimmune disease, such as CFS, or with a retroviral infection. The present disclosure is based, at least in part, on the observation that cytokine expression in an individual diagnosed with chronic fatigue syndrome (CFS) is different from cytokine expression in a healthy individual. The present disclosure is based, at least in part, on the correlation of specific changes in cytokine expression with a diagnosis of CFS. The present disclosure is also based, at least in part, on the correlation of specific changes in cytokine expression with a diagnosis of cression with a retroviral infection.

[0031] The inventors have identified a statistically significant dysregulation in the innate immune system in a population of CFS patients when compared to healthy controls. Specifically, it has been observed that, i) plasma levels of interferon alpha (IFN- α) are significantly decreased in CFS patients (p<0.0001), ii) IL-8, IL-6, TNF-α, MIP-1α, MIP-1β, IP-10, and MCP-1 are significantly upregulated in this population; and iii) plasmacytoid dentritic cells (pDCs), when isolated from CFS patients and subjected to the Toll-like receptor (TLR) 7 agonists imiquimod and to a lesser extent, the TLR9 agonist ODN 2213, overproduce the pro-inflammatory cytokines IL-6, TNF-a, MIP-1a, MIP-1β, IP-10, MCP-1, and IFN- α in contrast to pDCs isolated from healthy controls. When taken together, these data implicate the involvement of a dysregulation of plasmacytoid dentritic cells in the pathophysiology of CFS.

[0032] Cytokine Signature

[0033] A cytokine expression signature of a subject, as described herein, can include changes in level, activity, or expression of one or more cytokines for which no or substantially no corresponding changes occur in a control. For example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of a type 1 cytokine or a type 2 cytokine.

[0034] A cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of an inteferon or a lymphokine. For example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon (IFN)- γ . As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-3, IL-4, IL-5, IL-6, IL-7, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, and IL-35.

[0035] A cytokine expression signature of a subject can include changes in level, activity, or expression of one or more chemokines. For example, a cytokine expression signature of a subject can include changes in level, activity, or

expression of one or more of a CC chemokine, a CXC chemokine, a C chemokine (or γ chemokine), RANTES, CCL5, CCL3 and CCL4.

[0036] For example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of CC chemokines selected from MCP-1 (or CCL2), RANTES (or CCL5), CCL1 (I-309, TCA-3), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL6 (C10, MRP-2), CCL7 (MARC, MCP-3), CCL8 (MCP-2), CCL9 (same as CCL10; MRP-2, CCF18), CCL11 (Eotaxin), CCL12 (MCP-5), CCL13 (MCP-4, NCC-1, Ckβ10), CCL14 (HCC-1, MCIF, Ckβ1, NCC-2, CCL), CCL15 (Leukotactin-1, MIP-5, HCC-2, NCC-3), CCL16 (LEC, NCC-4, LMC, Ckβ12), CCL17 (TARC, dendrokine, ABCD-2), CCL18 (PARC, DC-CK1, AMAC-1, Ck_β7, MIP-4), CCL19 (ELC, Exodus-3, Ck_β11), CCL20 (LARC, Exodus-1, Ckβ4), CCL21 (SLC, 6Ckine, Exodus-2, Ck_β9, TCA-4), CCL22 (MDC, DC/β-CK), CCL23 (MPIF-1, Ckβ8, MIP-3), CCL24 (Eotaxin-2, MPIF-2, Ckβ6), CCL25 (TECK, Ckβ15), CCL26 (Eotaxin-3, MIP-4a, IMAC, TSC-1), CCL27 (CTACK, ILC, Eskine, PESKY, skinkine), and CCL28 (MEC).

[0037] As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of CXC chemokines selected from a glutamic acid-leucine-arginine (ELR) positive CXC chemokine or a glutamic acid-leucine-arginine (ELR) negative CXC chemokine. As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more of a CXC chemokine selected from CXCL1(Gro-α, GRO1, NAP-3, KC), CXCL2 (Gro-β, GRO2, MIP-2α), CXCL3 (Gro-, GRO3, MIP-2β), CXCL4 (PF-4), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2, CTAPIII, β-Ta, PEP), CXCL8 (IL-8, NAP-1, MDNCF, GCP-1), CXCL9 (MIG, CRG-10), CXCL10 (IP-10, CRG-2), CXCL11 (I-TAC, β-R1, IP-9), CXCL12 (SDF-1, PBSF), CXCL13 (BCA-1, BLC), CXCL14 (BRAK, bolekine), CXCL15 (Lungkine, WECHE), CXCL16 (SRP-SOX), and CXCL17 (DMC, VCC-10).

[0038] As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more C chemokines selected from XCL1 (lymphotactin- α , SCM-1 α , ATAC), XCL2 (lymphotactin- β , SCM-1 β), and CX3CL2 (Fractalkine, Neurotactin, ABCD-3).

[0039] As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of one or more RANTES, CCL5, CCL3, and CCL4.

[0040] As another example, a cytokine expression signature of a subject can include one or more of those cytokines known to be upregulated by pDCs (e.g., IL-8, IL-6, TNF- α , MIP- α or MIP-1 β). As another example, a cytokine expression signature of a subject can exclude one or more of those cytokines not known to be upregulated by pDCs (e.g., IL-1a, IL-2, IL-3, IL-4, IL-5, IL-13 or IL-15).

[0041] It is understood that a cytokine expression signature, as described herein, can include any combinations of cytokines recited above for which there is a change in expression in a subject as compared to a control. Particular combinations are further discussed below.

[0042] A cytokine expression signature as described herein can include an expression pattern in which one or more cytokines are modulated in a subject as compared to a control. For example, a cytokine expression signature can include an expression pattern in which one or more cytokines are upregulated in a subject as compared to a control. As another example, a cytokine expression signature can include an expression pattern in which one or more cytokines are down regulated in a subject as compared to a control. As another example, a cytokine expression signature can include a cytokine expression pattern in which one or more cytokines are upregulated and one or more other cytokines are down regulated in a subject as compared to a control.

[0043] A cytokine expression signature can include any combination of increase(s) and decrease(s) in the expression levels of any of the cytokines described herein. A cytokine that has an altered expression can include any cytokine identified herein. Alteration in cytokine expression can include both up- or down-regulation of expression. Such alterations can be part of a cytokine expression signature as described herein.

[0044] Upregulated

[0045] A cytokine expression signature can include expression of at least one cytokine upregulated in a subject as compared to a control. For example, a cytokine expression signature can include at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten or more cytokines upregulated in a subject as compared to a control.

[0046] A cytokine (of a cytokine signature) that has a upregulated expression can be selected from IL-8, MIP-1 β , TNF- α , IL-6, IL-2, IP-10, Eotaxin, IL-12, Regulated on Activation, Normal T Expressed and Secreted protein (RANTES), MCP-1 and MIP-1 α . A cytokine signature of a subject can comprise upregulated expression of one or more of cytokines selected from IL-8, MIP-1 β , TNF- α , IL-6, IL-2, IP-10, Eotaxin, IL-12, Regulated on Activation, Normal T Expressed and Secreted protein (RANTES), MCP-1 and MIP-1 α .

[0047] A cytokine signature can include IL-8 expression at least about 10-fold higher in a subject as compared to a control. For example, IL-8 expression can be at least about 20-, at least about 30-, at least about 40-, at least about 50-, at least about 60-, at least about 70-, at least about 80-, or at least about 90-fold higher in a subject as compared to a control. As another example, IL-8 expression can be at least about 100-fold or more higher in a subject as compared to a control.

[0048] A cytokine signature can include MIP-1 β expression at least about 10-fold higher in a subject as compared to a control. For example, MIP-1 β expression can be at least about 20-, at least about 30-, at least about 40-, at least about 50-, at least about 60-, at least about 70-, at least about 80-, or at least about 90-fold higher in a subject as compared to a control. As another example, MIP-1 β expression can be at least about 100-fold or more higher in a subject as compared to a control.

[0049] A cytokine signature can include TNF- α expression at least about 2-fold higher in a subject as compared to a control. For example, TNF- α expression can be at least about 3-, at least about 4-, at least about 5-, at least about 6-, at least about 7-, at least about 8-, or at least about 9-fold higher in a subject as compared to a control. As another example, TNF- α expression can be at least about 10-fold or more higher in a subject as compared to a control.

[0050] A cytokine signature can include IL-6 expression at least about 2-fold higher in a subject as compared to a control. For example, IL-6 expression can be at least about 3-, at least about 4-, at least about 5-, at least about 6-, at least about 7-,

at least about 8-, or at least about 9-fold higher in a subject as compared to a control. As another example, IL-6 expression can be at least about 10-fold or more higher in a subject as compared to a control.

[0051] A cytokine signature can include IL-2 expression at least about 2-fold higher in a subject as compared to a control. For example, IL-2 expression can be at least about 3- or at least about 4-fold higher in a subject as compared to a control. As another example, IL-2 expression can be at least about 5-fold or more higher in a subject as compared to a control.

[0052] A cytokine signature can include IP-10 expression at least about 2-fold higher in a subject as compared to a control. For example, IP-10 expression can be at least about 3-fold higher in a subject as compared to a control. As another example, IP-10 expression can be at least about 4-fold or more higher in a subject as compared to a control.

[0053] A cytokine signature can include Eotaxin expression at least about 2-fold higher in a subject as compared to a control. For example, Eotaxin expression can be at least about 3-fold higher in a subject as compared to a control. As another example, Eotaxin expression can be at least about 4-fold or more higher in a subject as compared to a control.

[0054] A cytokine signature can include IL-12 expression at least about 1.1-fold higher in a subject as compared to a control. For example, IL-12 expression can be at least about 1.2-fold or more higher in a subject as compared to a control.

[0055] A cytokine signature can include RANTES expression at least about 2-fold higher in a subject as compared to a control. For example, RANTES expression can be at least about 3-fold higher in a subject as compared to a control. As another example, RANTES expression can be at least about 4-fold or more higher in a subject as compared to a control.

[0056] A cytokine signature can include MCP-1 expression at least about 1.1-fold higher in a subject as compared to a control. For example, MCP-1 expression can be at least about 1.2-fold or more higher in a subject as compared to a control.

[0057] A cytokine signature can include MIP-1 α expression at least about 2-fold higher in a subject as compared to a control. For example, MIP-1 α expression can be at least about 3-, at least about 4-, at least about 5-, at least about 6-, at least about 7-fold or more higher in a subject as compared to a control.

[0058] Down Regulated

[0059] A cytokine expression signature can include expression of at least one cytokine down regulated in a subject as compared to a control. For example, a cytokine expression signature can include at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten or more cytokines down regulated in a subject as compared to a control.

[0060] A cytokine (of a cytokine signature) that has down regulated expression can be selected from IL-13, IL-5, IL-7, MIG, and IFN- α . A cytokine signature of a subject can comprise down regulated expression of one or more of cytokines selected from IL-13, IL-5, IL-7, MIG, and IFN- α .

[0061] A cytokine signature can include IL-13 expression at least about 2-fold lower in a subject as compared to a control. For example, IL-13 expression can be at least about 3-, at least about 4-, or at least about 5-fold or more lower in a subject as compared to a control.

[0062] A cytokine signature can include IL-5 expression can be at least about 2-fold lower in a subject as compared to

a control. For example, IL-5 expression can be at least about 3- or at least about 4-fold or more lower in a subject as compared to a control.

[0063] A cytokine signature can include IL-7 expression at least about 2-fold lower in a subject as compared to a control. IL-7 expression can be at least about 3-, at least about 4-, or at least about 5-fold or more lower in a subject as compared to a control.

[0064] A cytokine signature can include MIG expression can be at least about 2-fold lower in a subject as compared to a control.

[0065] A cytokine signature can include IFN- α expression at least about 2-fold lower in a subject as compared to a control.

[0066] A cytokine signature can include GM-CSF expression at least about 0.7-fold lower in a subject as compared to a control.

[0067] Combinations

[0068] A cytokine expression signature can include the changes in a cytokine expression described herein. For example, a cytokine expression of one or more cytokines selected from GM-CSF, IL-8, MIP-1 β , TNF- α , IL-6, IL-2, IP-10, Eotaxin, IL-12, Regulated on Activation, Normal T Expressed and Secreted protein (RANTES), MCP-1, MIP-1 α , IL-13, IL-5, IL-7, MIG, and IFN- α , as compared to a control.

[0069] As another example, a cytokine expression signature can include changes in level, activity, or expression of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF, as compared to a control.

[0070] A cytokine expression signature of a subject can include changes in level, activity, or expression of two or more of: (i) IL-8 expression of at least about 10-fold higher in a subject, as compared to a control; (ii) IL-13 expression of at least about 5-fold lower in a subject, as compared to a control; (iii) MIP-1 β expression of at least about 10-fold higher in a subject, as compared to a control; (iv) TNF- α expression of at least about 10- or more-fold higher in a subject, as compared to a control; (v) MCP-1 expression of at least about 1.1-fold higher in a subject, as compared to a control; (vi) IL-7 expression of at least about 5-fold lower in a subject, as compared to a control; (vii) IFN- α expression of at least about 2-fold lower in a subject, as compared to a control; (viii) IL-6 expression of at least about 10- or more-fold higher in a subject, as compared to a control; (ix) MIP-1 α expression of at least about 2-fold higher in a subject, as compared to a control and (x) GM-CSF expression of at least about 0.7-fold higher in a subject, as compared to a control. For example, a cytokine expression signature of a subject can include changes in level, activity, or expression of three or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of four or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of five or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of six or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of seven or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of eight or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of nine or more of (i)-(x). As another example, a cytokine expression signature of a subject can include changes in level, activity, or expression of (i)-(x). The magnitude of change of the level, activity, or expression of cytokines above are exemplary and can include any of the level of change described herein for a particular cytokine.

[0071] Cytokine Detection

[0072] Detection or determination of a cytokine, cytokine activity, expression of a cytokine, or expression levels of a cytokine can be according to conventional methods understood in the art (see e.g., Kotb and Calandra 2010 Cytokines and Chemokines in Infectious Diseases Handbook, Humana Press, 1st ed., ISBN-10 1617372471; Kuchroo et al. 2011 Cytokines and Autoimmune Diseases, Humana Press, 1st ed., ISBN-10 1617372250; House and Descotes 2010 Cytokines in Human Health: Immunotoxicology, Pathology, and Therapeutic Applications, Methods in Pharmacology and Toxicology, Humana Press, 1st ed., ISBN-10 1617375861; DeLey 2010 Cytokine Protocols, Methods in Molecular Biology, Humana Press, 1st ed., ISBN-10 1617372692; Korholz and Kiess 2010 Cytokines and Colony Stimulating Factors, Methods and Protocols, Methods in Molecular Biology, Humana Press, 1st ed., ISBN-10 1617373184). For example, identification of a cytokine can be according to a cell secretion assay (see e.g., Manz et al. 1995 PNAS 92, 1921-1925). As another example, identification of a cytokine can be according to assays described herein.

[0073] Prediction Algorithm

[0074] In some embodiments, a predictive algorithm can provide weighting for presence or magnitude of level, activity, or expression of different combinations of cytokines. An individual cytokine can be assigned a value of relative importance. When that cytokine is present at or above a threshold level (e.g., as described above), the value of relative importance for that cytokine can be added to a total value representing the cytokine signature. Where the total value exceeds a threshold, then a prediction or diagnosis of a neuroimmune disorder (e.g., CFS) or retroviral infection can be made (see e.g., Example 5).

[0075] For example, an individual cytokine at or above a threshold level can be assigned a weighted value such as: IL-8 is 100, IL-13 is 90, MIP-1 β is 80, TNF- α is 70, MCP-1 is 60, IL-7 is 50, IFN- α is 40, IL-6 is 30, MIP-1 α is 20, and GM-CSF is 10. A prediction or diagnosis of a neuroimmune disorder (e.g., CFS) or retroviral infection can be made by any combination of cytokines with a combined value of about 190 or greater, about 200 or greater, about 210 or greater, about 220 or greater, about 230 or greater, about 240 or greater, about 250 or greater, or more.

[0076] For example, an individual cytokine at or above a threshold level can be assigned a weighted value such that IL-8 is 100, IL-13 is 90, MIP-1 β is 80, TNF- α is 70, MCP-1 is 60, IL-7 is 50, IFN- α is 40, IL-6 is 30, MIP-1 α is 20, and GM-CSF is 10, and a prediction or diagnosis of a neuroimmune disorder (e.g., CFS) or retroviral infection can be made by any combination of cytokines or chemokines with a combined value of about 210 or greater.

[0077] Correlation of Cytokine Expression Signature with Neuroimmune Disease

[0078] The present inventors have determined that a cytokine expression signature, as described herein, can be correlated with a diagnosis of a neuroimmune disease. For example, a cytokine expression signature can be correlated with a diagnosis of neuroimmune disease associated with a retroviral infection. As another example, a cytokine expression signature can be correlated with a diagnosis of neuroimmune disease not presently known to be associated with a retroviral infection.

[0079] A cytokine expression signature associated with a neuroimmune disease can include an expression pattern in which one or more cytokines are modulated (e.g., upregulated or down regulated) in a subject having or diagnosed as having the neuroimmune disease.

[0080] A neuroimmune disease that is correlated with a cytokine expression signature can be a chronic neuroimmune disease. A neuroimmune disease correlated with a cytokine expression signature can be, for example, chronic fatigue syndrome, fibromyalgia, myalgic encephalitis, atypical multiple sclerosis, non-epileptic seizures, Gulf War Syndrome or autism.

[0081] A cytokine expression signature associated with a neuroimmune disease can include an expression level of any combination of cytokines as described herein. A cytokine of an expression signature and level, activity, or expression relative to a control can be as discussed herein.

[0082] A cytokine expression signature associated with a neuroimmune disease can be according to any of the cytokine expression signatures discussed herein. For example, a cytokine expression of one or more cytokines selected from GM-CSF, IL-8, MIP-1 β , TNF- α , IL-6, IL-2, IP-10, Eotaxin, IL-12, Regulated on Activation, Normal T Expressed and Secreted protein (RANTES), MCP-1, MIP-1 α , IL-13, IL-5, IL-7, MIG, and IFN- α . As another example, a cytokine expression signature associated with a neuroimmune disease can include changes in level, activity, or expression of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF. Presence or magnitude of upregulated or down regulated level, activity, or expression of a cytokine can be according to the discussion above.

[0083] A control for the purposes of a cytokine expression signature associated with a neuroimmune disease can be, for example, the expression signature of the same or similar group of cytokines in a subject not having or diagnosed as having the neuroimmune disease. As another example, a control for the purposes of a cytokine expression signature associated with a neuroimmune disease can be reference levels of the same or similar group of cytokines. As another example, a control for the purposes of a cytokine expression signature associated with a neuroimmune disease can be reference levels of the same or similar group of cytokines. As another example, a control for the purposes of a cytokine expression signature associated with a neuroimmune disease can be expression levels of the same or similar group of cytokines in the same subject at a point in time in which that subject was healthy or did not have or was not diagnosed as having the neuroimmune disease.

[0084] Correlation of Cytokine Expression Signature with a Retroviral Infection

[0085] The present inventors have discovered that a retroviral infection can be correlated with alterations in cytokine expression. A cytokine expression signature associated with a retroviral infection can include an expression pattern in which one or more cytokines are modulated (e.g., upregulated or down regulated) in a subject infected with a retrovirus relative to a subject who is not infected with the retrovirus.

[0086] A retrovirus as that term is used herein can be, for example, a gamma retrovirus.

[0087] A retrovirus as that term is used herein can be, for example, a MuLVs, primate retrovirus, HIV, HTLV-1 or xeno-

tropic murine leukemia virus-related virus (XMRV) (see Power, Trends in Neurosci. 24, 162, 2001; Miller and Meucii 1999 TINS 22(10), 471-479; Power et al. 1994 Journal of Virology 68(7) 4463-4649)).

[0088] A retrovirus as that term is used herein can be, for example, a retrovirus as described in U.S. Pat. App. Pub. No. 2011/0311484, filed Apr. 6, 2011, incorporated herein by reference in its entirety. A retrovirus as that term is used herein can have a gamma retroviral associated function or activity and be encoded by a sequence at least about 80% sequence identity (e.g., at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% sequence identity) to a sequence according to SEQ ID NO: 1 and, optionally, having one or more nucleotide changes selected from C80T, G90A, A96G, A97G, G111A, A137-157 deletion, T173C, G180A, G183A, C197T, C247T, C257T, C308T, C308G, C319T, C320T, T326C, A329G, C715T, T791G, A804G, T816Del, A856G, A665Del, T691G, G790A (potential hypermethylation site), T791G, T796C, G807Del, A840G, A873G, A875G, C903T, T963G, C5810Del, A6101T, G6154T, G7421A, A7459C, and an insertion at nucleotide position 7322 having a sequence of GAAAAGTCTCTGACCTCGTTGTCTGAG-

GTGGTCCTACAGAACCGGAGGGGAT TAGTCTA (SEQ ID NO: 179); or a functional fragment thereof. For example, an XMRV strain can have at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten, or more, of nucleotide changes described herein. Assays for determining gamma retrovirus functionality can be according to general methods known in the art (see e.g., Kurth 2010 Retroviruses: Molecular Biology, Genomics and Pathogenesis, Caister Academic Press, ISBN-10: 1904455557; Zhu 2010 Human Retrovirus Protocols: Virology and Molecular Biology (Methods in Molecular Biology), 1st Edition, Humana Press, ISBN-10: 1617375993) and those described in U.S. Pat. App. Pub. No. 2011/0311484.

[0089] A retrovirus as that term is used herein can be, for example, a xenotropic murine leukemia virus-related virus (XMRV). An XMRV can be according to a virus described in, for example, Urisman et al. 2006 PLoS Pathogens 2(3), e25; Lombardi et al. 2009 Science 326(5952), 585-589; Silverman et al. WO2006110589; Mikovits et al. US App Pub No. 2010/ 0167268; Mikovits et al. WO2010/148323; Mikovits at al. US App Pub. No. 2011/0117056; and Mikovits et al. US App Pub. No. 2011/0151431, each of which are incorporated herein by reference in their entirety. The XMRV consensus sequence has been described previously (Urisman et al., PLOS Pathogens 2006 2(3):e25), Accession number DQ399707.1, and is referred to herein as VP62, or SEQ ID NO: 1. VP62 was identified from a clone reconstructed from nucleic acids isolated from prostate tumors. Accession number EF185282.1 (SEQ ID NO: 162) is an 8165 nucleotide sequence of VP62, while Accession number DQ399707.1 (SEQ ID NO: 1) is an 8185 nucleotide sequence of VP62. The reference sequence of SEQ ID NO: 1 corresponds to Accession number DQ399707.1.

[0090] A number of clinical observations, previously described in CFS, suggest a defect in the innate immune response. For instance, viral agents such as parvovirus B19, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 6 and 7 (HHV-6 and 7), have been asso-

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ciated with CFS (reviewed by Devanur et al. J Clin Virol, 2006. 37(3): p. 139-50). Most individuals encounter these viruses early in life; however, they are kept in check by the immune system and only reactivate at times of immune suppression. Therefore, the viral reactivation frequently observed in CFS patients suggests suppression of the antiviral immune system. A number of antiviral mechanisms depend on the regulation of type I IFN for proper function. For example, the 2'-5' oligoadenylate synthetase enzymes (OAS), the endoribonuclease L (RNase L) and protein kinase R (PKR) are regulated by type I IFN (Stark et al., Annu Rev Biochem, 1998. 67: p. 227-64); and this pathway has been reported to be dysregulated in CFS patients (see e.g., De Meirleir et al., Am J Med, 2000. 108(2): p. 99-105; De Meirleir et al., Clin Infect Dis, 2002. 34(10): p. 1420-1; author reply 1421-2; Fremont et al., Life Sci, 2006. 78(16): p. 1845-56). A dysregulation in the type I IFN response is consistent with the viral reactivation observed in CFS. Another salient clinical observation consistently described in CFS is the unregulated overproduction of pro-inflammatory cytokines, such as IL-8, IL-6 and TNF- α (Fletcher et al., J Transl Med, 2009. 7: p. 96; Kerr and Tyrell, Curr Pain Headache Rep, 2003. 7(5): p. 333-41; Lombardi et al., In Vivo, 2011. 25(2); Peterson et al., Clin Diagn Lab Immunol, 1994. 1(2): p. 222-6). The over expression of these cytokines may be responsible for many of the symptoms associated with CFS. [0091] A cytokine expression signature that is associated with infection with a retroviral infection can include an expression level of a cytokine as described herein. A cytokine of an expression signature and expression levels relative to a control can be as discussed above.

[0092] A cytokine expression signature correlated with a retroviral infection in a subject can be according to any of the cytokine expression signatures discussed above. For example, a cytokine expression signature can include changes in level, activity, or expression of one or more cytokines selected from GM-CSF, IL-8, MIP-1 β , TNF- α , IL-6, IL-2, IP-10, Eotaxin, IL-12, Regulated on Activation, Normal T Expressed and Secreted protein (RANTES), MCP-1, MIP-1 α , IL-13, IL-5, IL-7, MIG, and IFN- α . As another example, a cytokine expression signature associated with infection with XMRV can include changes in level, activity, or expression of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF. Levels of upregulated or down regulated expression for any of these cytokines can be according to the discussion above.

[0093] A control for the purposes of a cytokine expression signature associated with a retroviral infection can be, for example, the expression signature of the same or similar group of cytokines in a subject not infected with the retrovirus. As another example, a control for the purposes of a cytokine expression signature associated with a retroviral infection can be reference levels of the same or similar group of cytokines. As another example, a control for the purposes of a cytokine expression signature associated with a retroviral infection can be reference levels of the same or similar group of cytokine expression signature associated with a retroviral infection can be expression levels of the same or similar group of cytokines in the same subject at a point in time in which that subject was healthy or was not infected with the retrovirus.

[0094] An amount of retrovirus present in a subject can be associated with a degree of change of one or more cytokines of a cytokine signature. For example, an amount of a retrovirus present in a subject can be correlated to an index number describing the modulated cytokine signature. An amount of a retrovirus present in a subject can be determined according to

methods known in the art, such as determination of viral titre. For example, an retrovirus viral titre of a subject or a sample of a subject can be associated with a degree of change in a cytokine signature, or one or more components thereof, of the subject or the sample of the subject. For example, increasing viral titre can be associated with an increasing change in cytokine expression from a subject who is negative for a retrovirus. As another example, increasing viral titre can correlate to a change in a cytokine expression; so that, at a relatively low retrovirus titre, a first cytokine expression signature is observed; and at a relatively higher retrovirus titre, a second cytokine expression signature is observed.

[0095] Mechanism

[0096] While under no obligation to do so, and without limiting the present invention in any way, mechanisms underlying a correlation of altered cytokine expression with retroviral infection or symptoms of neuroimmune disease are provided herein.

[0097] Single stranded RNA and CpG DNA initiate the synthesis of type I IFN through the activation TLR 7/8 and 9 respectively, where TNF receptor associated factor 6 (TRAF6) plays a pivotal role in the activation of pro-inflammatory cytokine production. A TRAF6 initiated cascade leads to phosphorylation and nuclear translocation of IRF7 and 8, consequently, triggering transcription of multiple proinflammatory cytokines and IFN-a. To prevent over-expression of these cytokines, Fas-associated Death Domain (FADD) interacts with the tripartite motif-containing protein 21 (TRIM21) promoting TRIM21 ubiquitin ligase activity and subsequently down-regulating cytokine production. Thus, TRIMM21 provides a negative feedback loop to prevent over-production of inflammatory cytokines. Findings described herein support that dysregulation of TRIM21 can lead to the over production of pro-inflammatory cytokines and the hyper-reactivity of IFN- α expression in CFS patients. [0098] Viral reactivation is a common occurrence in CFS; but a mechanism to account for this condition has not been reported. As pDCs are thought to be primarily involved in responses to viral infection, the inventors propose that a pDC dysregulation may be a contributing factor to viral reactivation. Plasmacytoid dendritic cells are the primary producers of IFN- α and also produce pro-inflammatory cytokines that are consistent with previous observations in CFS. Observations reported herein are consistent with a dysregulation in the negative feedback loop for IFN-a control. CFS patients display a number of immune abnormalities, mostly involving the innate immune system; but some employ the humorial immune system as well. Plasmacytoid dendritic cells are professional antigen-presenting cells but they also produce cytokines, which activate T-cells, B-cells and NK cells. Therefore, pDCs link innate and adaptive immunity, which is a requisite to explain the pathology of CFS.

[0099] Furthermore, an interrelated dysregulation may occur in the pathways mediating type I IFN and pro-inflammatory cytokine production in pDCs of CFS. Dysregulation of pDCs may account for the aberrant IFN and pro-inflammatory cytokine production as well as the other abnormalities observed in the innate immune system of CFS patients. As shown herein, CFS patients have decreased plasma levels of INF-a. Because pDC are major producers of INF-a, it is expected that pathogenesis of CFS may be explained by dysfunction of these cells. Indeed, data demonstrated that while producing limited amount of INF-a in vivo, pDC from CFS are releasing 20 folds more INF-a when stimulated with TLR

ligands in vitro as compared to healthy donors. Although the pattern of pro-inflammatory cytokine produced by stimulated pDC was similar between patients and controls, actual production was 3-20 folds higher in the CFS patients. This dysregulation is also consistent with other chronic immune diseases such as Sjogren's syndrome and systemic lupus erythematosus.

[0100] Recently, a novel intracellular antiviral function has been reported for TRIM21, involving intracellular antibodymediated proteolysis (Mallery et al., Proc Natl Acad Sci USA. 107(46): p. 19985-90). A dysregulation of the biochemical pathway involving TRIM21, FADD or TRAF6 in pDCs suggests the origin of inflammatory cytokines in addition to the dysregulation of IFN. Plasmacytoid dendritic cells are found primarily in the gut, the spleen and the lymph nodes (Dzionek et al., Hum Immunol, 2002. 63(12): p. 1133-48). Thus the inventors propose that pDC involvement of CFS is consistent with the lymphadenopathy, splenomegaly and gastrointestinal abnormalities commonly reported in CFS patients (see Carruthers et al., Journal of Chronic Fatigue Syndrome, 2003. 11(1): p. 7115).

[0101] The tripartite motif (TRIM) family member, TRIM21, is an E3 ubiquitin ligase that is known to ubiquitinate the IFN regulatory factors IRF3, IRF7 and IRF8 through a cooperative interaction with the Fas-associated death domain (FADD). The interaction between TRIM21 and FADD enhances TRIM21 ubiquitin ligase activity to downregulate type I IFN by promoting the degradation of IRF7. But TRIM21 transcription is enhanced by type I IFN, suggesting TRIM21 plays an important role in a type I IFN negative feedback loop. TRIM21 also plays an important role in the regulation of NF-kb-dependent pro-inflammatory cytokine production through the negative regulation of NFkb. Therefore, TRIM21 functions in both innate and acquired immunity through its E3 ligase activity. Recent reports suggest that it has a more direct intracellular antiviral capability. It was reported that the antiviral capacity of TRIM21 is through its Fc binding domain (Mallery et al., Proc Natl Acad Sci USA. 107(46): p. 19985-90). TRIM21 binds, with high affinity, to the Fc domain of immunoglobin, which are attached to the incoming virus, and target it to the proteasome via its E3 ubiquitin ligase activity. Rapid proteasomal degradation of virions in the cytosol occurs before translation of virally encoded genes can commence. Therefore, a dysregulation of TRIM21 could result in reduced antiviral clearance, as is often observed in CFS patients. Murine TRIM21 knockout mice appear phenotypically normal if left undisturbed, however; when challenged with TLR agonists they produce abnormally high levels of pro-inflammatory cytokines compared to wild-type mice (Espinosa et al., J Exp Med, 2009. 206(8): p. 1661-71). TRIM21 was originally identified as an autoantigen in Sjogren's syndrome and systemic lupus erythematosus. Both diseases have many overlapping symptoms to that of CFS such as chronic fatigue, inflammation, exercise intolerance, and muscle and joint pain and like CFS, diseases also occur to greater extent in women. Moreover, preliminary research suggests that the cancer drug Rituxan (rituximatab), which lowers the level of B cells, may be an effective treatment for a subgroup of CFS patients (Fluge and Mella, BMC Neurol, 2009. 9: p. 28) suggestive of an autoimmune condition similar to Sjogren's syndrome and systemic lupus. A defect in the TRIM21 pathway is consistent with an autoimmune condition characterized by the excessive production of pro-inflammatory cytokines, and the hyper-reactivity of IFN- α as is often observed in CFS patients.

[0102] Plasmacytoid dendritic cells are the primary producers of type I IFN; they are responsible for over 95% of type I IFN produced by leukocytes. Although they have the ability to produce all type I IFNs, the primary product of plasmacytoid dendritic cells is IFN- α . Large quantities of IFN are produced by pDCs in response to viral infection through the initiation of pattern recognition receptors known as Toll-like receptors (TLR). Type I IFN producing TLRs of pDCs are located in endosomal compartments and are activated by ssRNA (TLR7/8) and by CpG dsDNA (TLR9). IFN then proceeds to act locally and globally, through the activation of the interferon-alpha/beta receptors, IFNAR1 and IFNAR2. The binding of IFN to its receptor results in subunit dimerization followed by activation of their associated Janus protein kinases, which in turn phosphorylate several proteins, including STAT1 and STAT2.

[0103] A number of clinical observations are consistent with a pDC involvement in CFS. First, pDC are found primarily in the gut, the spleen and the lymph nodes. Therefore, a pDC involvement of CFS is consistent with the lymphadenopathy, splenomegaly and gastrointestinal abnormalities commonly reported in CFS patients. Second, the most prevalent inflammatory cytokines identified herein, IL-8, IL-6, TNF- α , MIP- α and MIP-1 β are produced by pDCs; however, cytokines not produced by pDCs such as IL-1a, IL-2, IL-3, IL-4, IL-5, IL-13 and IL-15 are seldom upregulated in CFS patients. Finally, pDCs are responsible for 95% of all IFN- α production. Therefore, a dysregulation of IFN- α is most likely to occur in pDCs. These clinical and biochemical observations support that a TRIM21 dsyregulation occurs in the pDCs of CFS patients.

[0104] Production of type I interferon is involved with the innate antiviral response in CFS patients. During infection IFN- α promotes the production of IL-15, which performs a critical role in the development, maintenance and function of NK cells and activation of T cells. IFN- α also stimulates NK cell activity via the upregulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Additionally, the three principal components of the RNase L antiviral pathway (OAS, RNase L and PKR) are transcriptionally upregulated by type I IFN. CFS literature is replete with references to NK cell and RNase L dysfunction. Dysregulation of type I IFN may contribute to the innate immune abnormalities associated with CFS.

[0105] Thus, initial low levels of INF-a combined with high levels of pro-inflammatory cytokines produced by pDC may set the stage for chronic inflammation, interferon hyper-reactivity and susceptibility to viral infection commonly observed in CFS patients.

[0106] Identified herein are various cytokine expression signatures that are reliably and reproducibly associated with CFS symptoms in subjects infected with a retorvirus. These cytokine expression signatures are different from that in healthy subjects who are not infected with a retrovirus, or who do not display CFS symptoms, as described herein. It is presently thought that infection with a retrovirus can induce changes in cytokine expression patterns. Significant changes in cytokine expression can cause inflammation within a subject's body. When cytokine expression in an infected individual becomes significantly different from that in an uninfected individual, it is thought that the associated inflammation can cause symptoms of neuroimmune diseases.

In some instances, the symptoms can be one or more symptoms of CFS. In other instances, the inflammatory responses can cause neuroimmune diseases other than CFS, such as fibromyalgia, myalgic encephalitis, atypical multiple sclerosis, autism, non-epileptic seizures, or Gulf War Syndrome.

[0107] Physical symptoms of CFS can include, but are not limited to, those described in Carruthers et al. 2003 J Chronic Fatigue Syndrome 11, 1-12. More specifically, physical symptoms can include post-exertional malaise or fatigue, sleep dysfunction, and pain; have two or more neurlogical/ cognitive manifestations and one or more symptoms from two or the categories of autonomic, neuroendocrine and immune manifestations. Autonomic manifestations can include orthostatic intolerance-neurally mediated hypotension (NMH); postural orthostatic tachycardia syndrome (POTS); delayed postural hypotension; light-headedness, extreme pallor; nausea and irritable syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; or exertional dyspnea. Neuroendocrine manifestations can include loss of thermostatic stability-subnormal body temperature and marked diurnal fluctuation; sweating episodes; recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change-anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress. Immune manifestations can include tender lymphnodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, or medications or chemicals. In order to meet the criteria for CFS, these symptoms will have persisted for at least six months and usually have a distinct onset, although onset may be gradual.

[0108] The above proposed mechanism may explain why some subjects (such as subject 2623, infra) can be diagnosed as infected with a retrovirus but do not appear to display any, some, or all symptoms of a neuroimmune disease. In such a subject, a cytokine expression signature may not be significantly different enough from the cytokine expression pattern in an uninfected individual. Therefore, no or substantially no chronic inflammation occurs, and there are no or substantially no apparent symptoms of neuroimmune disease.

[0109] The above-proposed mechanism may also accommodate the changes in symptoms sometimes seen in a subject with chronic neuroimmune diseases. It is reasonable to assume that, over time, fluctuation of specific inflammatory cytokine expression levels can occur. Such fluctuation in expression of a cytokine could reasonably lead to a fluctuation in one or more symptoms of a neuroimmune disease.

[0110] Diagnosis

[0111] A cytokine expression signature, as described herein, can be used to diagnose a retroviral infection, conditions associated with a retroviral infection, or a neuroimmune disease. For example, a cytokine expression signature, as described herein, can be used to diagnose a retroviral infection in a subject. As another example, a cytokine expression signature, as described herein, can be used to diagnose a neuroimmune disease in a subject.

[0112] A cytokine expression signature used to diagnose a retroviral infection, conditions associated with a retroviral infection, or a neuroimmune disease can include level, activity, or expression of a cytokine as described herein. A cytokine of an expression signature and level, activity, or expression relative to a control can be as discussed above.

[0113] A method of diagnosis can include determination of level, activity, or expression of one or more cytokines of a

cytokine expression signature in a subject or a sample of a subject. The cytokine level, activity, or expression signature profile (e.g., the expression pattern of cytokines of the signature) can be correlated with the presence of a retrovirus in the subject or the sample of the subject. Correlation of the cytokine expression signature and presence of a retrovirus can serve as, or contribute to, the diagnosis of a retrovirul infection in the subject. Similarly, the cytokine level, activity, or expression signature profile (e.g., the expression pattern of cytokines of the signature) of a subject or a sample of the subject can be correlated with a neuroimmune disease in the subject. Determination in a subject or a sample of a subject of a cytokine level, activity, or expression signature correlated to a neuroimmune disease can serve as, or contribute to, the diagnosis of the neuroimmune disease in the subject.

[0114] Sample and Subject

[0115] Methods for the identification of a cytokine level, activity, or expression signature described herein are generally performed on a subject or on a sample from a subject. A sample can contain or be suspected of containing a retrovirus. [0116] A sample can be a biological sample from a subject. A sample can be a biological sample from a subject. A sample can be a blood sample, a serum sample, a plasma sample, a cerebrospinal fluid sample, or a solid tissue sample. For example, the sample can be a blood sample, such as a peripheral blood sample. As another example, a sample can be a solid tissue sample. As another example, a sample can be a solid tissue sample. As another example, a sample can include cells of a subject. For example, a sample can include cells such as fibroblasts, endothelial cells, peripheral blood mononuclear cells, hematopoietic cells, or a combination thereof.

[0117] The subject can be a subject having, diagnosed with, suspected of having, or at risk for developing a retroviral infection. A subject considered at risk of developing a retroviral infection can be, for example and without limitation, an individual with a familial history of the retrovirus, an individual contacted with a biological sample suspected of comprising the retrovirus, or an individual residing in a region comprising a cluster of individuals with the retroviral infection.

[0118] The subject can be a subject having, diagnosed with, suspected of having, or at risk for developing a neuroimmune disease or a lymphoma. For example, a subject can have, be diagnosed with, be suspected of having, or be at risk for developing a retroviral-related neuroimmune disease or a retroviral-related lymphoma. For example, a subject can be tested for the presence of an retrovirus where the subject exhibits one or more sign or a symptom associated with a neuroimmune disease or a lymphoma. As another example, a subject can have been diagnosed with a neuroimmune disease or lymphoma, or diagnosed with a retroviral-related neuroimmune disease or retroviral-related neuroimmune disease or symptom associated neuroimmune disease or lymphoma, or diagnosed with a retroviral-related neuroimmune disease or retroviral-related lymphoma.

[0119] A subject considered at risk of developing a neuroimmune disease or lymphoma can be, for example and without limitation, an individual with a familial history of a neuroimmune disease or lymphoma or an individual residing in a region comprising a cluster of individuals with a neuroimmune disease or lymphoma. For example, a subject can be considered at risk of developing CFS, if, without limitation, the individual has a familial history of CFS, or the individual resides in a region comprising a cluster of individual with comparison of the individual resides in a region comprising a cluster of individuals with CFS.

[0120] In some cases, subjects infected with a retrovirus can exhibit no or substantially no persistent symptoms; i.e., they are apparently healthy. In other cases, subjects infected

with a retrovirus are diagnosed with CFS. In other cases, subjects infected with a retrovirus are diagnosed with one or more cancer. In other cases, subjects infected with a retrovirus exhibit altered immune responses. In some cases, subjects infected with a retrovirus exhibit digestive-tract symptoms. Some subjects infected with a retrovirus develop multiple clinical symptoms, for example both CFS and cancer.

[0121] For example, a subject can be one which fulfills the 1994 CDC Fukuda Criteria for CFS (Fukuda et al., Ann Intern Med 1994; 121: 953-9); the 2003 Canadian Consensus Criteria (CCC) for ME/CFS (Carruthers et al, J Chronic Fatigue Syndrome 2003; 11:1-12; Jason et al., J Chronic Fatigue S 2004; 12:37-52), or both the Fukuda and CCC criteria. The CCC requires post-exertional malaise, which many clinicians believe is the sine qua non of ME/CFS. In contrast, the Fukuda and 1991 Oxford Criteria do not require exercise intolerance for a diagnosis of ME/CFS. The CCC further requires that subjects exhibit post-exertional fatigue, unrefreshing sleep, neurological/cognitive manifestations and pain, rather than these being optional symptoms.

[0122] The subject can be an animal subject, preferably a mammal, more preferably horses, cows, dogs, cats, sheep, pigs, mice, rats, monkeys, guinea pigs, and chickens, and most preferably a human.

[0123] As another example, the subject can be an animal, such as a laboratory animal that can serve as a model system for investigating a neuroimmune disease or lymphoma (see e.g., Chen, R. et al., Neurochemical Research 33: 1759-1767, 2008; Kumar, A., et al., Fundam. Clin. Pharmacol. 23(1): 89-95, February 2009; Gupta, A., et al, Immunobiology 214: 33-39, 2009; Singh, A., et al., Indian J. Exp. Biol. 40: 1240-1244, 2002; Ford, R. J., et al. Blood 109: 4899-4906, 2007; Smith, M. R., et al., Leukemia 20: 891-893, 2006; Bryant, J., et al., Lab. Invest. 80: 557-573, 2000; M'kacher, R., et al., Cancer Genet Cytogenet. 143: 32-38, 2003).

[0124] Device

[0125] Also provided is a device for use in detecting a cytokine expression signature described herein. Such a device can detect one of more cytokines or cytokine levels described herein. A device as described herein can be contacted with a biological sample so as to detect presence or level of one or more cytokines described herein.

[0126] Devices for detection of cytokines are understood in the art (see e.g., Khan et al. 2004 Cytometyery Part B: Clinical Cytometry 61B(A), 35-39; Li and Reichert 2003 Langmuir 19(5), 1557-1566; Huang et al. 2001 Analytical Biochemistry 294(1), 55-62; Haab 2005 Molecular and Cellular Proteomics 4, 377-383; Luchansky and Bailey 2010 Anal Chem 82(5), 1975-1981; Elshal and McCoy 2006 Methods 38(4), 317-323; Cytokine Antibody Array, Isogen Life Science, Netherlands; BioPlex Cytokine Assay, Bio-Rad; xMAP, Luminex Corp. Austin, Tex.; Human Cytokine Array Kit, R&D Systems, Minneapolis, Minn.). One of ordinary skill in the art can adapt conventional cytokine-detection devices for specificity with respect to one or more cytokines described herein. A device can incorporate a predictive algorithm described herein. A device can include an indicator for when a combination of cytokines of an specified expression signature described herein is present in a sample. A device can include an indicator for when a combination of levels of cytokines of an specified expression signature described herein is present in a sample.

[0127] A device can include an array (e.g., a microarray) for detection of one of more cytokines or cytokine levels

described herein. A device can include a cytokine array membrane created by spotting capture antibodies onto the membrane. For example, a device can provide high-throughput simultaneous screening of multiple cytokine expression based on a protein array system. For example, a device can include an antibody-based array for detection of one of more cytokines or cytokine levels described herein. For example, a device can include an silicon photonic microring resonator for real-time detection of one or more cytokines described herein on account of their spectral sensitivity toward surface binding events between a target and antibody-modified microrings (see generally, Luchansky and Bailey 2010 Anal Chem 82(5), 1975-1981). For example, a device can include a multiplex bead array cytokine assay (see generally, Elshal and McCoy 2006 Methods 38(4), 317-323). For example, a device can include a cytokine detection protein array that combines cDNA microarray technology and sandwich fluoroimmunoassay, where a protein array can be printed by spotting one or more cytokines described herein onto planar substrates (see generally Li and Reichert 2003 Langmuir 19(5), 1557-1566).

[0128] Therapeutic Methods

[0129] Also provided is a process of treating a retroviral infection or a neuroimmune disease in a subject. As described herein, a cytokine expression signature of a subject or a sample of a subject can be correlated to a retroviral infection, thus providing or contributing to a diagnosis of a retroviral infection in the subject. As described herein, a cytokine expression signature of a subject or a sample of a subject can be correlated to a neuroimmune disease, thus providing or contributing to a diagnosis of the neuroimmune disease in the subject. Upon detection or determination of a cytokine expression signature described herein, a subject can be diagnosed with a retroviral infection or a neuroimmune disease and thereafter administered appropriate therapeutic treatment.

[0130] Protocols or agents for treatment of a neuroimmune disease can be according to a conventional therapeutic treatment known in the art.

[0131] The neuroimmune disease being diagnosed or treated can be CFS. Treating CFS can comprise administration of a therapeutically effective amount of an agent that restores cytokine expression to that of a healthy individual, which restores cytokine expression to levels similar to those in a healthy individual, which restores cytokine signaling to that of a healthy individual, or which restores cytokine signaling to levels similar to those in a healthy individual. Treating CFS can suppress or prevent CFS symptoms.

[0132] Furthermore, the present disclosure provides methods of treating symptoms of a retroviral infection, or directly treating a retroviral infection, in a subject. Protocols or agents for treatment of a retroviral infection can be according to a conventional therapeutic treatment known in the art. Therapeutic agents for treatment of a retroviral infection include, but are not limited to, a retroviral integrase inhibitor (e.g., raltegravir, Merck & Co., brand name Isentress; L-000870812, Merck & Co.) and a nucleoside reverse transcriptase inhibitor (e.g., tenofovir disoproxil fumarate, Gilead Sciences, brand name Viread; zidovudine, Glaxo-SmithKline, azidothymidine (AZT)) (see Singh et al. 2010 PLoS ONE 5(4): e9948).

[0133] Treating symptoms of a retroviral infection, or directly treating a retroviral infection, can comprise administration of a therapeutically effective amount of an agent that

restores cytokine expression to that of a healthy individual, which restores cytokine expression to levels similar to those in a healthy individual, which restores cytokine signaling to that of a healthy individual, or which restores cytokine signaling to levels similar to those in a healthy individual. Treating symptoms of a retroviral infection, or directly treating a retroviral infection, can suppress or prevent retroviral infection symptoms.

[0134] In some embodiments, a therapeutic agent can be a cytokine antagonist. The cytokine antagonist can be an anti-cytokine antibody, such as an anti-IFN α antibody or an anti-IFN α antibody (see, eg, Jkurkovich et al., Medical Hypotheses 59(6): 770-780, 2002, Anticytokine therapy—new approach to the treatment of autoimmune and cytokine-disturbance diseases). The cytokine antagonist can be an agent possessing anti-TNF properties, such as infliximab or etanercept. The cytokine antagonist can possess anti-interleukin-1 (IL-1) or anti-interleukin-6 (IL-6) properties. The cytokine antagonist can be a glucocorticoid.

[0135] Methods described herein are generally performed on a subject in need thereof. A subject in need of the therapeutic methods described herein can be diagnosed with a neuroimmune disease, such as CFS, or at risk thereof. A subject in need of the therapeutic methods described herein can be infected with a retrovirus, diagnosed with a retroviral infection, or exhibiting one or more symptoms of a retroviral infection. A determination of the need for treatment will typically be assessed by a history and physical exam consistent with the disease or condition at issue. Diagnosis of the various conditions treatable by the methods described herein is within the skill of the art. The subject can be an animal subject, preferably a mammal, more preferably horses, cows, dogs, cats, sheep, pigs, mice, rats, monkeys, guinea pigs, and chickens, and most preferably a human.

[0136] An effective amount of an agent described herein is generally that which can restore cytokine expression to that of a healthy individual, which restores cytokine expression to levels similar to those in a healthy individual, which restores cytokine signaling to that of a healthy individual, or which restores cytokine signaling to levels similar to those in a healthy individual. An effective amount of an agent can suppress or prevent some, substantially all, or all symptoms of a neuroimmune disease, such as CFS. Alternatively, an effective amount of an agent can suppress cyfes cyfes and the constraint of the cyfes of the cyfes. Symptoms related to CFS can include those used to diagnose CFS as described herein.

[0137] When used in the treatments described herein, a therapeutically effective amount of an agent can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt form and with or without a pharmaceutically acceptable excipient. For example, the compounds of the invention can be administered, at a reasonable benefit/risk ratio applicable to any medical treatment, in a sufficient amount to suppress or prevent a retroviral infection, a neuroimmune disease, such as CFS, or altered cytokine expression that is associated with a retroviral infection or a neuroimmune disease, such as CFS.

[0138] The amount of a composition described herein that can be combined with a pharmaceutically acceptable carrier to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be appreciated by those skilled in the art that the unit content of agent contained in an individual dose of each dosage form need not in itself constitute a therapeutically effective amount, as the necessary therapeutically effective amount could be reached by administration of a number of individual doses.

[0139] Toxicity and therapeutic efficacy of compositions described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} , (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index that can be expressed as the ratio LD_{50}/ED_{50} , where large therapeutic indices are preferred.

[0140] The specific therapeutically effective dose level for any particular subject will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the composition employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts (see e.g., Koda-Kimble et al. (2004) Applied Therapeutics: The Clinical Use of Drugs, Lippincott Williams & Wilkins, ISBN 0781748453; Winter (2003) Basic Clinical Pharmacokinetics, 4th ed., Lippincott Williams & Wilkins, ISBN 0781741475; Sharqel (2004) Applied Biopharmaceutics & Pharmacokinetics, McGraw-Hill/Appleton & Lange, ISBN 0071375503). For example, it is well within the skill of the art to start doses of the composition at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose may be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by an attending physician within the scope of sound medical judgment.

[0141] Administration of an agent can occur as a single event or over a time course of treatment. For example, an agent can be administered daily, weekly, bi-weekly, or monthly. For treatment of acute conditions, the time course of treatment will usually be at least several days. Certain conditions could extend treatment from several days to several weeks. For example, treatment could extend over one week, two weeks, or three weeks. For more chronic conditions, treatment could extend from several weeks to several months or even a year or more.

[0142] Treatment in accord with the methods described herein can be performed prior to, concurrent with, or after conventional treatment modalities for a retroviral infection or a neuroimmune disease, such as CFS.

[0143] An agent can be administered simultaneously or sequentially with another agent, such as an antibiotic, an antiinflammatory, or another agent. For example, an agent can be administered simultaneously with another agent, such as an antibiotic or an antiinflammatory. Simultaneous administration can occur through administration of separate compositions, each containing one or more of agent described herein, an antibiotic, an antiinflammatory, or another agent. Simultaneous administration can occur through administration for agent.

tion of one composition containing two or more of an agent described herein, an antibiotic, an antiinflammatory, or another agent. An agent can be administered sequentially with an antibiotic, an antiinflammatory, or another agent. For example, an agent can be administered before or after administration of an antibiotic, an antiinflammatory, or another agent.

[0144] Compositions or agents described herein can be administered in a variety of means known to the art. For example, administration can be parenteral, pulmonary, oral, topical, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, ophthalmic, buccal, or rectal administration. As another example, administration can include, for example, methods involving oral ingestion, direct injection (e.g., systemic or stereotactic), implantation of cells engineered to secrete the factor of interest, drugreleasing biomaterials, polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, implantable matrix devices, mini-osmotic pumps, implantable pumps, injectable gels and hydrogels, liposomes, micelles (e.g., up to 30 µm), nanospheres (e.g., less than 1 um), microspheres (e.g., 1-100 um), reservoir devices, a combination of any of the above, or other suitable delivery vehicles to provide the desired release profile in varying proportions. Other methods of controlled-release delivery of agents will be known to the skilled artisan and are within the scope of the invention.

[0145] General

[0146] Compositions and methods described herein utilizing molecular biology protocols can be according to a variety of standard techniques known to the art (see, e.g., Sambrook and Russel (2006) Condensed Protocols from Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, ISBN-10: 0879697717; Ausubel et al. (2002) Short Protocols in Molecular Biology, 5th ed., Current Protocols, ISBN-10: 0471250929; Sambrook and Russel (2001) Molecular Cloning: A Laboratory Manual, 3d ed., Cold Spring Harbor Laboratory Press, ISBN-10: 0879695773; Elhai, J. and Wolk, C. P. 1988. Methods in Enzymology 167, 747-754; Studier (2005) Protein Expr Purif. 41(1), 207-234; Gellissen, ed. (2005) Production of Recombinant Proteins: Novel Microbial and Eukaryotic Expression Systems, Wiley-VCH, ISBN-10: 3527310363; Baneyx (2004) Protein Expression Technologies, Taylor & Francis, ISBN-10: 0954523253).

[0147] Definitions and methods described herein are provided to better define the present disclosure and to guide those of ordinary skill in the art in the practice of the present disclosure. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[0148] In some embodiments, numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth, used to describe and claim certain embodiments of the present disclosure are to be understood as being modified in some instances by the term "about." In some embodiments, the term "about" is used to indicate that a value includes the standard deviation of the mean for the device or method being employed to determine the value. In some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the present disclosure are approximations, the numerical values set forth in the specific examples are reported as precisely as practicable. The numerical values presented in some embodiments of the present disclosure may contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein.

[0149] In some embodiments, the terms "a" and "an" and "the" and similar references used in the context of describing a particular embodiment (especially in the context of certain of the following claims) can be construed to cover both the singular and the plural, unless specifically noted otherwise. In some embodiments, the term "or" as used herein, including the claims, is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive.

[0150] The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and can also cover other unlisted steps. Similarly, any composition or device that "comprises," "has" or possessing only those one or more features is not limited to possessing only those one or more features and can cover other unlisted features.

[0151] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the present disclosure and does not pose a limitation on the scope of the present disclosure otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the present disclosure.

[0152] Groupings of alternative elements or embodiments of the present disclosure disclosed herein are not to be construed as limitations. Each group member can be referred to and claimed individually or in any combination with other members of the group or other elements found herein. One or more members of a group can be included in, or deleted from, a group for reasons of convenience or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0153] Citation of a reference herein shall not be construed as an admission that such is prior art to the present disclosure. **[0154]** Having described the present disclosure in detail, it will be apparent that modifications, variations, and equivalent embodiments are possible without departing the scope of the present disclosure defined in the appended claims. Furthermore, it should be appreciated that all examples in the present disclosure are provided as non-limiting examples.

EXAMPLES

[0155] The following non-limiting examples are provided to further illustrate the present disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the present disclosure, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the present disclosure.

Example 1

[0156] This example describes methods that can be used to obtain nucleic acid samples from subjects.

[0157] DNA and RNA isolation. Whole blood can be drawn from subjects by venipuncture using standardized phlebotomy procedures into 8-mL greencapped Vacutainers containing the anti-coagulant sodium heparin (Becton Dickinson). Plasma can be collected by centrifugation, aspirated and stored at -80° C. for later use. The plasma can be replaced with PBS and the blood resuspended and further diluted with an equal volume of PBS. PBMCs can be isolated by layering the diluted blood onto Ficoll-Paque PLUS (GE Healthcare), centrifuging for 22 min at 800 g, aspirating the PBMC layer and washing it once in PBS. The PBMCs (approximately 2×10^7 cells) can be centrifuged at 500 g for 7 min and either stored as frozen unactivated cells in 90% FBS and 10% DMSO at -80° C. for further culture and analysis or resuspended in TRIzol (Invitrogen) and stored at -80° C. for DNA and RNA extraction and analysis. DNA can be isolated from TRIzol according the to manufacturer's protocol and also can be isolated from frozen PBMC pellets using the QIAamp DNA Mini purification kit (QIAGEN) according to the manufacturer's protocol and the final DNA can be resuspended in RNase/DNase free water and quantified using the Quant-iTTM Pico Green dsDNA Kit (Invitrogen). RNA can be isolated from TRIzol according to the manufacturer's protocol and quantified using the Quant-iT Ribo Green RNA kit (Invitrogen). cDNA can be made from RNA using the iScript Select cDNA synthesis kit (Bio-Rad) according to the manufacturer's protocol.

Example 2

[0158] This example describes methods of amplifying, and determining the nucleic acid sequence of, XMRV polynucleotides.

[0159] PCR. Nested PCR can be performed with separate reagents in a separate laboratory room designated to be free of high copy amplicon or plasmid DNA. Negative controls in the absence of added DNA can be included in every experiment. Identification of XMRV gag and env genes can be performed by PCR in separate reactions. Reactions can be performed as follows: 100 to 250 ng DNA, 2 μ L of 25 mM MgC12, 25 μ L of HotStart-IT FideliTaq Master Mix (USB Corporation), 0.75 μ L of each of 20 μ M forward and reverse oligonucleotide primers in reaction volumes of 50 μ L. For identification of gag, 419F (5'-ATCAGTTAACCTACCCGAGTCGGAC-3') (SEQ ID NO: 5) and 1154R (5'-GCCGCTCTTCTTCATTGTTCTC-3') (SEQ ID NO: 6) can be used as forward and reverse primers. For env, 5922F (5'-GCTAATGCTACCTC-CCTCGG-3') (SEQ ID NO: 7) and 6273R (5'-GGAGC-

CCACTGAGGAATCAAAACAGG-3') (SEQ ID NO: 8) can be used. For both gag and env PCR, 94° C. for 4 min initial denaturation can be performed for every reaction followed by 94° C. for 30 seconds, 57° C. for 30 seconds and 72° C. for 1 minute. The cycle can be repeated 45 times followed by final extension at 72° C. for 2 minutes. Six microliters of each reaction product can be loaded onto 2% agarose gels in TBE buffer with 1 kb+DNA ladder (Invitrogen) as markers. PCR products can be purified using Wizard SV Gel and PCR Clean-Up kit (Promega) and sequenced. PCR amplification for sequencing full-length XMRV genomes can be performed on DNA amplified by nested or semi-nested PCR from overlapping regions from PBMC DNA. For 5' end amplification of R-U5 region, 4F (5'-CCAGTCATCCGATAGACT-GAGTCGC-3') (SEQ ID NO: 9) and 1154R can be used for first round and 4F and 770R (5'-TACCATCCTGAGGC-CATCCTACATTG-3') (SEQ ID NO: 10) can be used for second round. For regions including gag-pro and partial pol, 350F(5'-GAGTTCGTATTCCCGGCCGCAGC-3') (SEQ ID NO: 11) and 5135R (5'-CCTGCGGCATTCCAAATCTCG-3') (SEQ ID NO: 12) can be used for first round followed by second round with 419F and 4789R (5'-GGGTGAGTCTGT-GTAGGGAGTCTAA-3') (SEQ ID NO: 13). For regions including partial pol and env region, 4166F (5'-CAAGAAG-GACAACGGAGAGCTGGAG-3') (SEQ ID NO: 14) and 7622R (5'-GGCCTGCACTACCGAAAT TCTGTC-3') (SEQ ID NO: 15) can be used for first round followed by 4672F (5'-GAGCCACCTACAATCAGACAAAAGGAT-3') (SEQ ID NO: 16) and 7590R (5'-CTGGACCAAGCGGT-TGAGAATACAG-3') (SEQ ID NO: 17) for second round. For the 3' end including the U3-R region, 7472F (5'-TCAG-GACAAGGGTGGTTTGAG-3') (SEQ ID NO: 18) and 8182R (5'-CAAACAGCAAAAGGCTTTATTGG-3') (SEQ ID NO: 19) can be used for first round followed by 7472F and 8147R (5'-CCGGGCGACTCAGTCTATC-3') (SEQ ID NO: 20) for second round. The reaction mixtures and conditions can be as described above except for the following: For larger fragments, extension can be done at 68° C. for 10 min instead of 72° C. All second round PCR products can be column purified as mentioned above and overlapping sequences can be determined with internal primers. Nested RT-PCR for gag sequences can be done as described with modifications. GAG-O-R primer can be used for 1st strand synthesis; cycle conditions can be 52° C. annealing, for 35 cycles. For second round PCR, annealing can be at 54° C. for 35 cycles.

[0160] Once nucleic acids have been amplified by PCR, standard sequencing techniques can be used to determine the nucleic acid sequence thereof. Standard in silico translation techniques can be used to determine amino acid sequences from nucleic acid sequences.

Example 3

[0161] Cytokine analysis can be made by any quantitative method including but not limited to microplate assays such as Enzyme-linked immunosorbent assay (ELISA); multiplexing assay using antibody-conjugated microspheres, such as the Luminex xMAP Bead-based assay or Bender MedSystems bead-based system; systems involving the amplification of cytokine mRNA of the direct measurement of intracellular cytokines using flow cytometry or any other method that can quantitatively measure cytokines.

Example 4

[0162] This example describes biomarkers associated with neuroimmune diseases, and specifically, with CFS. The methods in this example are as described in Examples 1-3, unless otherwise specified.

[0163] Cytokine and chemokine profiles are altered by infection. The inventors therefore examined the levels of 26 cytokines and chemokines from 156 XMRV-infected individuals and 140 healthy controls in an attempt to identify any hallmarks of XMRV infection. XMRV status was determined both by PCR-based and serological experiments, which detected XMRV env nucleic acid and protein, respectively.

[0164] Table 2 shows that a number of cytokines and chemokines are differentially expressed in XMRV-infected individuals. Notably, inflammatory chemokines such as IL-8 and MIP-1 α and MIP-1 β are upregulated in XMRV-infected subjects.

TABLE 2

Cytokines and chemokines up-regulated in XMRV-infected subjects						
	XMRV positive		XMRV	XMRV negative		
	Mean	S.E.	Mean	S.E.		
IL-8	1067	(267)	11.1	(1.3)	< 0.0001	
MIP-1β	1840	(580)	157	(40)	< 0.0001	
TNF-α	109	(48)	12.8	(4.6)	< 0.0001	
IL-6	271	(78)	29	(12)	< 0.0001	
IL-2	99	(59)	29	(11)	< 0.0001	
IP-10	84	(15)	32.6	(3.0)	< 0.0001	
Eotaxin	258	(18)	87.5	(5.9)	< 0.0001	
IL-12	272	(18)	210	(34)	0.0002	
Rantes	26191	(3554)	8458	(529)	0.0041	
MCP-1	468	(42)	421	(41)	0.0003	
MIP-1a	673	(360)	91	(28)	0.006	

[0165] Table 3 shows that a number of cytokines were down regulated in XMRV-infected subjects when compared to healthy controls. Notably, IL-13, involved in anti-inflammatory responses, is down regulated in XMRV-positive subjects. IFN- α is also down regulated, as is IL-7, which is a key regulator of interferon signaling.

TABLE 3

Cytokines and chemokines down-regulated in XMRV-infected subjects						
	XMRV	positive	XMRV	negative		
	Mean	S.E.	Mean	S.E.		
IL-13	24.4	(2.4)	89.5	(6.9)	< 0.0001	
IL-5	7.11	(0.64)	22.2	(5.3)	< 0.0001	
IL-7	21.1	(4.8)	82	(7.3)	< 0.0001	
MIG	43.7	(7.3)	83	(13)	< 0.0001	
IFN-α	29.5	(3.0)	60.6	(4.4)	< 0.0001	

[0166] Table 4 lists cytokines and chemokines that are differentially expressed in XMRV-infected subjects relative to healthy controls, and describes their functions.

TABLE 4

Cytokine/ Chemokine	P value Function In Inflammation
	Upregulated in XMRV-infected subjects
IL-6	< 0.0001 Stimulates chronic inflammation
MIP-1a	0.0062 Elevated in neurodegenerative disease
IL-8	<0.0001 RNase L and CMV activated
MIP-1β	<0.0001 Elevated in Neurodegenerative disease
TNF-α	<0.0001 Stimulates chronic inflammation
MCP-1	0.003 Elevated in chronic inflammatory diseases
	Down regulated in XMRV-infected subjects
IL-13	< 0.0001 Inhibits inflammatory cytokine production
IL-7	<0.0001 Stimulates proliferation of B and T lymphocytes and NK cells
IFN-α	<0.0001 Stimulates macrophages and NK cells to elicit an anti-viral response
GM-CSF	<0.0001 Stimulates proliferation of B and T lymphocytes and NK cells

Example 5

[0167] This example describes a method of predicting a subject's XMRV status. Unless otherwise described, methods are as described in Examples 1-4.

[0168] Using data described above, the present inventors have developed an algorithm that predicts XMRV infection status from chemokine and cytokine expression information, with about 95% accuracy (Table 5). The inventors used the data described, including the pre-determined XMRV status, above as a training set for a Random Forest algorithm. The prediction algorithm was constructed using a standard Random Forest learning algorithm.

TABLE 5

Accuracy	of Random Fo	est algorithm in pred	licting XMR	V status
Actual Class	Total Cases	Percent Correct	Control N = 137	Positive N = 159
Control Positive	140 156	92.857 95.513	130 7	10 149

[0169] The Random Forest prediction algorithm identified the cytokines and chemokines listed in Table 4, above, as most critical in identifying XMRV status of an individual. FIG. **1** shows the relative importance of each.

[0170] When individual cytokines and chemokines are assigned a value of importance such that IL-8 is 100, IL-13 is 90, MIP-1 β is 80, TNF- α is 70, MCP-1 is 60, IL-7 is 50, IFN- α is 40, IL-6 is 30, MIP-1 α is 20, and GM-CSF is 10 then the prediction of CFS can be made by any combination of cytokines, cytokines and chemokines or chemokines with a combined value of about 210 or greater.

Example 6

[0171] This example describes a method of identifying XMRV-infected subjects. Unless otherwise described, methods are as described in Examples 1-5.

[0172] For some individuals in the dataset used in these experiments, data was available which indicated the presence of $\gamma\delta$ T-cells. $\gamma\delta$ T-cells are cells that play an active role in the

regulation and resolution of pathogen-induced immune responses. They accumulate at sites of inflammation caused by infections; and also in auto-immune diseases. γδ T-cells are also known to up-regulate MIP1- α , MIP1- β , and TNF- α . Clinically, the presence of yo T-cells indicates chronic infection or cancer.

[0173] Data was collected from subjects who had been diagnosed with CFS who were subsequently diagnosed with cancer. Many of the CFS patients were also yo T-cell positive patients; and all CFS patients subsequently tested were found to have XMRV. These results are summarized in Table 6.

TABLE 6

	$\gamma\delta$ T-cells can be detected in CFS subjects with cancer						
ID#	XMRV status	γδ T-cell status	Type of Cancer				
1103	positive	positive	MCL				
1109	positive	negative	Thymoma				
1125	positive	positive + IGH	MCL				
1186	positive	positive	Lymphoma				
1199	positive	positive	Lymphoma				
1150	positive	positive	Lymphoma				
1320	positive	Not tested	Thymoma				
1321	Not tested	Not tested	MCL				
1174	positive	positive	Thymoma				
1205	positive	Not tested	lymphoma				
1172	positive	positive	MCL				
1127	positive	positive	CLL				
1322	Not tested	Not tested	MCL				
1181	positive	Not tested	CLL				
1188	positive	positive	CLL				
1189	positive	positive	MCL				

subjects labeled as "Not Tested" were deceased by the time subsequent data collection for XMRV/T-cell status occurred MCL = mantle cell lymphoma;

CLL = chronic lymphocytic leukemia

Example 7

[0174] This example describes the phenotype of XMRVinfected subjects. Unless otherwise described, methods are as in Examples 1-6.

[0175] Clustering analysis was applied to the cytokine/ chemokine dataset as described above. Cluster analysis clearly identified three groups that include healthy controls; CFS patients that have elevated $\gamma\delta$ T-cell populations, and CFS patients who do not have elevated yô T-cell populations (see e.g., FIG. 2). The $\gamma\delta$ T-cell positive group has a prominent inflammatory response, as indicated by the high expression of pro-inflammatory cytokines and chemokines. Without being limited by theory, the present inventors hypothesize that this inflammation contributes to or causes the CFS symptoms associated with XMRV pathology. The inventors also hypothesize that inflammation may be a marker of disease progression.

Example 8

[0176] This example describes the cytokine signature and disease state of an XMRV-positive subject. Methods are as in examples 1-7, unless otherwise specified.

[0177] Subject 2623 is a 52-year-old female. She is positive for XMRV as determined by PCR and seroconversion tests, but does not display symptoms of chronic immune disease. FIG. 3 shows the expression levels of the cytokines and chemokines that were identified by the Random Forests analysis (supra) as a signature of XMRV infection. The cytokines and chemokines that were in the normal range have been removed from this dataset (eg, IL-8, IL-7 and IL-6). Of the remaining cytokines and chemokines, IL-13 and IFN- α show decreased expression relative to that in an uninfected subject; whereas MIP1 α , MIP1 β , TNFa and GM-CSF show increased expression relative to that in an uninfected subject. Not shown is subject 2623's increased IL-12 expression; IL-2 expression was identified by the cluster analysis (supra) to be important in staging disease progression.

Example 9

[0178] This example describes the cytokine signature and disease state of an XMRV-positive subject. Methods are as in examples 1-8, unless otherwise specified.

[0179] Subject 1127 is a 63-year-old female. She is positive for XMRV and has been diagnosed with CFS. She also has clonal populations of $\gamma\delta$ -T cells, and eventually developed CLL. FIG. 4 shows the expression levels of the cytokines and chemokines that were identified by the Random Forests analysis (supra) as a signature of XMRV infection. The cytokines and chemokines that were in the normal range have been removed from this dataset (eg, IFN-a, GM-CSF).

Example 10

[0180] This example describes the cytokine signature and disease state of an XMRV-positive subject. Methods are as in examples 1-9, unless otherwise specified.

[0181] Subject 967 is a 31-year-old female. She is positive for XMRV and has chronic immune disease. She does not have clonal populations of $\gamma\delta$ -T cells. FIG. 5 shows the expression levels of the cytokines and chemokines that were identified by the Random Forests analysis (supra) as a signature of XMRV infection. She has elevated IL-8, MIP-1 α , MIP-1β, TNFα, IL-6 and GM-CSF. Not shown is subject 967's elevated RANTES levels; RANTES is not included as part of the diagnostic signature but is consistent with the findings of the cluster analysis.

Example 11

[0182] This example describes cytokine and chemokine dysregulation in CFS patients. Methods are as in examples 1-10, unless otherwise specified.

[0183] CFS patients that meet both the CDC and Canadian Consensus Criteria. Patients were not selected on the basis of absence or presence of a known retroviral infection. Detection of cytokines was according to Multiplex Bean Immunoassays by patient and control.

[0184] Results showed an upregulation of the pro-inflammatory cytokines IL-6, IL-8, MIP-1 α , MIP-1 β and TNF- α in the plasma of CFS patients (Table 7).

TABLE 7

	Patient Mean N = 164 (pg/mL)	Patient Median N = 164 (pg/mL)	Control Mean N = 139 (pg/mL)	Control Median N = 139 (pg/mL)
	τ	Jp-Regula	ted	
IL-8 IL-6 IL-1β MIP-1β MIP-1α	$\begin{array}{c} (8290 \pm 1011) \\ (2623 \pm 515) \\ (219.3 \pm 29.2) \\ (3701 \pm 797) \\ (1813 \pm 334) \end{array}$	3574 30 80.4 281 97	$\begin{array}{c} (13.1 \pm 1.6) \\ (28.4 \pm 10.7) \\ (88.9 \pm 20.5) \\ (157.3 \pm 40.3) \\ (90.6 \pm 19.2) \end{array}$	8.3 4.0 55.8 85.0 63.9

TABLE 7-continued

	Patient Mean N = 164 (pg/mL)	Patient Median N = 164 (pg/mL)	Control Mean N = 139 (pg/mL)	Control Median N = 139 (pg/mL)
EOTAXIN	(205.4 ± 15.1)	141.0	(102.5 ± 8.5)	84.1
TNF-α	(158.1 ± 38)	19.9	(13.2 ± 4.25)	6.3
MCP-1	(788.8 ± 51.3)	593.1	(423.8 ± 40.5)	291.1
IP-10	(110.0 ± 20.8)	34.3	(35.6 ± 3.71)	23.2
IFN-γ	(20.0 ± 1.23)	15.6	(13.9 ± 0.866)	11.8
IL-12	(215.4 ± 14.0)	160	(212.8 ± 31.1)	131.8
IL-2	(30.6 ± 9.2)	13.2	(28.5 ± 10.2)	11.8
	Ľ	own-regu	lated	
IL-13	(38.27 ± 3.2)	25.08	(84.8 ± 6.5)	77.5
IL-13 IL-7	(58.27 ± 5.2) (57.2 ± 15)	23.08	(34.8 ± 0.3) (76.9 ± 6.8)	68.4
IL-7 IFN-α	· · · · · · · · · · · · · · · · · · ·	22.8	(70.9 ± 0.8) (58.3 ± 4.1)	48.7
	(48.1 ± 5.7)		· · · · ·	
MIG	(54.7 ± 10.4)	30.9	(78.5 ± 11.6)	53.2

All mean values are significant at the 95% C.I. by the log transformed Student t-Test.

[0185] CFS patients often report gastrointestinal issues similar to that of Crohn's disease and ulcerative colitis. In this study, pDCs from Crohn's patients, ulcerative colitis patients, and healthy controls were isolated and cultured in the presence or absence of the TLR agonist's imiquimod and ODN 2218.

[0186] Results showed that pro-inflammatory cytokine production of pDCs was significantly greater in the two patient groups than in the control group. Additionally, the upregulated cytokines observed, were similar to that observed in the plasma of CFS patients. These similarities suggest that CFS patients may also have dysfunction of pDCs.

[0187] To explore this possibility, pDCs were isolated from two healthy controls and one classic CFS patient who reported a viral flu-like onset of CFS and who has consistently displayed elevated plasma levels of pro-inflammatory cytokines. The isolated pDCs were cultured in the presence and absence of imiquimod and ODN for 22 hours. Levels of multiple cytokines were evaluated in culture media by multiplex analysis. Cytokine levels were determined in supernatants of pDC collected from CFS patients and healthy controls. pDC fraction of PBMC was isolated using CD304 positive selection (Miltenyi). TLR7 and 9 agonists were used to stimulate pDC for 22 hours. At the end of stimulation, supernatants were analyzed by Luminex multiplex assay.

[0188] Results showed little or no difference was observed for IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-7, IL-13, IL-17, IFN-7 GM-CSF, MIG, IP-10 and RANTES. IL-8 was elevated in all samples, including the non-stimulated pDCs, suggesting that activation occurred during the pDC purification process. But similar to the observed results in Crohn's disease and ulcerative colitis, a dramatic upregulation of the cytokines IL-6, MIP-1 α , MIP-1 β and TNF- α was observed in the pDCs isolated from the CFS patient but not in the control samples (data not shown). The stimulated pDC cytokine production was similar between the healthy controls; however, on average, the CFS patient's pDCs produced 3 times the inflammatory cytokines as the healthy controls. Strikingly, the IFN-a production of activated pDCs of the CFS patient was approximately 20 times that of the healthy controls in spite of having relatively normal plasma IFN- α levels (data not shown). Both control subjects had plasma cytokine levels within normal ranges, and the CFS subject had elevated plasma levels of pro-inflammatory cytokines, consistent with previous results (Data not show).

[0189] These data support that pDCs of CFS patients are more responsive to TLR agonists, with the greatest difference observed in the production IFN- α .

Example 12

[0190] It is thought that an interrelated dysregulation occurs in the pathways mediating type I IFN and pro-inflammatory cytokine production in pDCs of CFS. Dysregulation of pDCs may account for the aberrant IFN and pro-inflammatory cytokine production as well as the other abnormalities observed in the innate immune system of CFS patients.

[0191] Previous data indicate that CFS patients have decreased plasma levels of INF-a. Because pDC are major producers of INF-a, it is expected that pathogenesis of CFS may be explained by dysfunction of these cells. Indeed, data demonstrated that while producing limited amount of INF-a in vivo, pDC from CFS are releasing 20 folds more INF-a when stimulated with TLR ligands in vitro as compared to healthy donors. Although the pattern of pro-inflammatory cytokine produced by stimulated pDC was similar between patients and controls, actual production was 3-20 folds higher in the CFS patients.

[0192] An ex vivo cell model system is used to characterize the mechanism of dysregulation of IFN and pro-inflammatory cytokines associated with CFS

[0193] IRF7, TRAF6, TRIM21 and FADD are evaluated at the level of transcription, translation and protein turnover (half-life) in pDCs cells of CFS patients and healthy controls in the presence and absence of TLR agonists. Sequencing and quantitative PCR, western blot analysis, ELISA of cell culture media; and IHC staining at multiple time points are used in the presence and absence of TLR agonists imiquimod and ODN 2213, using magnetically purified pDCs from CFS patients and healthy controls.

[0194] The ubiquidation, phosphorylation and nuclear translocation of IRF7, TRAF6, TRIM21 and FADD are characterized in pDCs of CFS patients and healthy controls in the presence and absence of TLR agonists.

[0195] Ten CFS patients that meet both the CDC and Canadian Consensus Criteria and 10 healthy controls are used in these experiments. Leukocytes are separated from whole blood by density gradient using Ficoll-Paque. Subject pDCs are purified by negative selection, in order to prevent any unforeseen effects by antibody binding, using the antibodies CD3, CD7, CD16, CD19, CD56, CD123, and CD235a (Miltenyi Biotec). The isolated pDCs are CD303 (BDCA-2)+, (BDCA-4/Neuropilin-1)⁺, CD123⁺, CD4⁺, CD304 CD45RA⁺, CD141 (BDCA-3)^{dim} and CD1c (BDCA-1)⁻, CD2⁻, which lack expression of lineage markers (CD3, CD14, CD16, CD19, CD20, CD56), and express neither myeloid markers such as CD13 and CD33, nor Fc receptors such as CD32, CD64, or FcaRI (Dzionek et al., Hum Immunol, 2002. 63(12): p. 1133-48). Cell line purity is evaluated by flow cytometry with the surface makers CD303 and CD123. Isolated pDCs are cultured on RPMI complete media supplemented with IL-3 (Jones et al., Nat Med, 2008. 14(4): p. 429-36) in the presence or absence of imiquimod and ODN 2213. The same experiment is made using pDC depleted lymphocytes as a control. Primary cells are cultured and analyzed for cytokine production at four separate time points, T=0 hrs, 6 hrs, 22 hrs and 4 days. Culture media is collected at each time point and flash frozen for cytokine analysis using Luminex multi-plex bead system. All measurements are made in triplicate for each time point then averaged.

[0196] Transcription analysis is made on the time point that produce optimal cytokine production by collecting cells on TRIzol for mRNA according to the manufacture's instructions; cDNA synthesis and Q-PCR is performed using the Superscript III Platinum CellsDirect Two-step qRT-PCR Kit. Transcriptome analysis is made using an Illumina HISeq 1000 with 50 pb single end reads and confirmed by RT-PCR. Proteomic analysis is then made by conducting a contig blast and a human reference guided alignment. Nuclear translocation is investigated by IHC using anti-TRIM21, FADD, IRF7 and IRF8 antibodies. Protein turnover is measured by western blot analysis on cells treated with GolgiStop to prevent cytokine secretion (BD PharMigen) and compared relative to control values and reported as a percentage change. Glyceraldehyde-3-phosphate dehydrogenase is used as a housekeeping gene control as well as a control for all experiments. Characterization of ubiquidation and phosphorylation of IRF7, TRAF6, TRIM21 and TRAFF is made by western blot using anti-ubiquitin and anit-phos[ho antibodies, which are commercially available. Nuclear localization is made by IHC of fixed pDC cells with anti-IRF7, TRAF6, TRIM21 and TRAF6 antibodies.

[0197] To determine differences between patient and controls, common nonparametric data analysis is used. Numerical data is analyzed with the computer program Prism and Flow cytometry analysis is made using the computer program FloJo. Densitometry analysis of western blots is made using program Image Quant (GE Health Sciences). DNASTAR software is used for denovo assembly and transcript identification of data is produced by next generation transcriptome sequencing.

[0198] It is expected to identify the point of dysregulation of cytokine production in the pDCs of CFS patients. If a decrease in transcription is observed, this would indicate that the disruption is occurring between the TLR and the initiation of transcription by the transcription complex. If normal transcription is observed but translation is not or is reduced compared to controls this would indicate the protein translation machinery is involved. In the event that a dysregulation is not observed at the level of TRIM21, FADD, IRF7 or IRF8, a transcriptome wide comparison is conducted between the pDCs of patients and controls to identify any differences that may account for the cytokine dysregulation not explained either by the TRIM21 pathway or dysregulation of pDCs.

[0199] Taken together, initial low levels of INF-a combined with high levels of pro-inflammatory cytokines produced by pDC may set the stage for chronic inflammation, interferon hyper-reactivity and susceptibility to viral infection commonly observed in CFS patients.

SEQUENCE LISTING

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115 120 125 Yr Pro Ala Leu Thr Pro Ser Ser Ly No Pro Hy Pro Gla Val Leu Pro Asp Ser Gly Pro Lu Hy Pro Pro Hy Pro Gla Asp Val Leu Pro	Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro 100 105 110	
130 135 140 Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Thr Glu Asp Pro Pro Tyr Gly Ala Gln Pro Ser Gly Ala Pro Ser Thr Ser Ser Ser Ser Thr Ser Ser Ser Thr Ser Ser Ser Thr Ser Ser Thr Ser Ser Thr Ser Ser Thr Ser	Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu 115 120 125	
145 150 155 160 Pro Pro Pro Tyr Gly Ala Gln Pro Ser Fro Pro Tyr Gly Ala Gln Pro Ser Fro Pro Tyr Gly Ala Gln Pro Ser Fro Pro Pro Tyr Gly Ala Glu Ser Fro Pro Ser Fro Pro Ser Fro Pro Ser Pro Met Glu Glu Ala Ala Th Th Ser Glu Ala Ala Th Th Ser Glu Ala As Th Ser Fro Pro Ser Fro Met Val Ser Arg Leu Arg As Pro	Tyr Pro Ala Leu Thr Pro Ser Ile Lys Ser Lys Pro Pro Lys Pro Gln 130 135 140	
165 170 175 Glu Glu Ala Ala Ala Thr Ser Glu Re <t< td=""><td>Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp 145 150 155 160</td><td></td></t<>	Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp 145 150 155 160	
IR0 IR0 IR0 VAI See See See See See See See See See VI See VI See See See See See See See See See VI See See See See See See See See See VI See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See See	Pro Pro Tyr Gly Ala Gln Pro Ser Ser Ala Arg Glu Asn Asn 165 170 175	
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225 230 235 240 Pro Ser Phe Ser Glu Asp Pro Gly Lys Leu Thr Ala Leu Ile Glu Ser 245 250 111 Glu Ser 255 Val Leu Ile Thr His Gln Pro Thr Trp Asp Asp Cys Gln Gln Leu Leu 260 265 260 270 Gly Thr Leu Leu Thr Gly Glu Glu Lys 280 210 Arg Val Leu Leu 285 240	Thr Ser Gln Ala Phe Pro Leu Arg Met Gly Gly Asp Gly Gln Leu Gln 210 215 220	
245 250 255 Val Leu Ile Thr His Gln Pro Thr Trp Asp Asp Cys Gln Gln Leu Leu 260 265 270 Gly Thr Leu Leu Thr Gly Glu Glu Lys Gln Arg Val Leu Leu Glu Ala 275 280 285	Tyr Trp Pro Phe Ser Ser Asp Leu Tyr Asn Trp Lys Asn Asn Asn 225 230 235 240	
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Lys	Gly	Ile 355	Thr	Gln	Gly	Pro	Asn 360	Glu	Ser	Pro	Ser	Ala 365	Phe	Leu	Glu
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Pro	Asp	Ile	Gly	Arg 405	ГЛЗ	Leu	Glu	Arg	Leu 410	Glu	Asp	Leu	Lys	Ser 415	ГЛа
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Glu	Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
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Asp 465	Arg	Arg	Arg	His	Arg 470	Glu	Met	Ser	Lys	Leu 475	Leu	Ala	Thr	Val	Val 480
Ile	Gly	Gln	Arg	Gln 485	Asp	Arg	Gln	Gly	Gly 490	Glu	Arg	Arg	Arg	Pro 495	Gln
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-	-	515		-	-		520	-		-	-	525	Arg		
	530					535	_		-	-	540	-	Gln		
545					550					555			Pro		560
			-	565	-				570				Gln	575	
-			580	-	-			585			-		Thr 590	-	-
		595					600					605	Ala		
	610					615					620		Tyr		
625	-	-	_		630		-		-	635			His		640
_		-		645			-		650	-			Leu	655	
			660			-		665	-			-	Thr 670	Ū	-
		675					680					685	Phe		
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Thr	Pro	Leu 755	Leu	Pro	Val	ГЛа	Lys 760	Pro	Gly	Thr	Asn	n Asp 765	-	Arg	Pro
Val	Gln 770	Asp	Leu	Arg	Glu	Val 775	Asn	Гуз	Arg	Val	Glu 780	_) Ile	His	Pro
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Gln	Trp	Tyr	Thr	Val 805	Leu	Asp	Leu	Lys	Asp 810	Ala	Phe	e Ph∈	e Cys	Leu 815	Arg
Leu	His	Pro	Thr 820	Ser	Gln	Pro	Leu	Phe 825	Ala	Phe	Glu	ı Trp	Arg 830	-	Pro
Glu	Met	Gly 835	Ile	Ser	Gly	Gln	Leu 840	Thr	Trp	Thr	Arg	j Leu 845		Gln	Gly
Phe	Lys 850	Asn	Ser	Pro	Thr	Leu 855	Phe	Asp	Glu	Ala	Leu 860		Arg	Asp	Leu
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Aap	Asp	Leu	Leu	Leu 885	Ala	Ala	Thr	Ser	Glu 890	Gln	Asp	о Сує	Gln	Arg 895	Gly
Thr	Arg	Ala	Leu 900	Leu	Gln	Thr	Leu	Gly 905	Asn	Leu	Gly	r Tyr	Arg 910		. Ser
Ala	Lys	Lys 915	Ala	Gln	Ile	Сүз	Gln 920	Lys	Gln	Val	Lys	925		Gly	Tyr
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Val 945	Met	Gly	Gln	Pro	Thr 950	Pro	Lys	Thr	Pro	Arg 955	Gln	ı Lev	ı Arg	Glu	. Phe 960
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Trp	Gly	Pro 995	Asp	Gln	Gln	Lys	Ala 100	-	r Gl	n Glu	u Il	-	rs G 005	ln A	la Leu
Leu	Thr 1010		a Pro	o Ala	a Lei	1 Gly 10	-	eu P:	ro A	sp L		'hr .020	Lya	Pro	Phe
Glu	Leu 1025		e Va	l Asj	p Glı	1 Ly: 10		ln G	ly T	yr A		уя .035	Gly	Val	Leu
Thr	Gln 1040		s Le	u Gl	y Pro	5 Trj 104		rg A	rg P	ro V		la .050	Tyr	Leu	Ser
Lys	Lys 1059		ı Asj	p Pro	o Val	1 Al. 10		la G	ly T	rp P:		ro .065	Сув	Leu	Arg
Met	Val 1070		a Ala	a Ile	e Ala	a Va 10		eu Tl	hr L	ys A:		la .080	Gly	Lys	Leu
Thr	Met 1085		y Glı	n Pro	o Lei	1 Va 10		le L	eu A	la P:		lis .095	Ala	Val	Glu
Ala	Leu 1100		l Ly:	s Glı	n Pro	o Pro 110		ab y:	rg T	rp L		er .110	Asn	Ala	Arg

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Phe	Gly 1130	Pro	Val	Val	Ala	Leu 1135		Pro	Ala	Thr	Leu 1140	Leu	Pro	Leu
Pro	Glu 1145		Glu	Ala	Pro	His 1150		Сүз	Leu	Glu	Ile 1155		Ala	Glu
Thr	His 1160	Gly	Thr	Arg	Pro	Asp 1165		Thr	Asp	Gln	Pro 1170	Ile	Pro	Asp
Ala	Asp 1175		Thr	Trp	Tyr	Thr 1180		Gly	Ser	Ser	Phe 1185	Leu	Gln	Glu
Gly	Gln 1190	Arg	Arg	Ala	Gly	Ala 1195		Val	Thr	Thr	Glu 1200		Glu	Val
Ile	Trp 1205		Arg	Ala	Leu	Pro 1210		Gly	Thr	Ser	Ala 1215		Arg	Ala
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Lys	Leu 1235		Val	Tyr	Thr	Asp 1240		Arg	Tyr	Ala	Phe 1245	Ala	Thr	Ala
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Gly	His 1295	Gln	Lys	Gly	Asn	Ser 1300		Glu	Ala	Arg	Gly 1305	Asn	Arg	Met
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Lys	Asn 1670		Glu	ı Pro	Arg	Trp 167		ys (Gly	Pro	Tyr	Thr 168		al	Leu	Leu	
Thr	Thr 1685		Thr	Ala	Leu	Lys 169		al A	Asp	Gly	Ile	Ser 169		a	Trp	Ile	
His	Ala 1700		His	8 Val	Lys	Ala 170		la 1	Thr	Thr	Pro	Pro 171		a	Gly	Thr	
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Gly	Asp		Gln 20	Arg	Ile 2	Ala	Ser	Ası 25	n Gl	ln S	er V	al A		7al 80	Lys	s Lys	
Arg	Arg	Trp 35	Val	Thr	Phe		Ser 40	Ala	a Gl	Lu T	rp P	ro T 4		he	Asr	ı Val	
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Lys 65	Ser	Arg	Val		Cys : 70	Pro	Gly	Pro	o Hi	is G 7		is P	ro A	/ab	Glr	n Val 80	
Pro	Tyr	Ile	Val	Thr 85	Trp (Glu .	Ala	Leı	u Al 90		yr A	ap P	ro I	ro	Pro 95	Trp	
Val	Lys	Pro	Phe	Val	Ser 3	Pro	Lys	Pro	o Pi	ro P	ro L	eu P	ro 7	hr	Ala	a Pro	

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			100					105					110		
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Tyr	Pro 130	Ala	Leu	Thr	Pro	Ser 135	Ile	Lys	Ser	Lys	Pro 140	Pro	Lys	Pro	Gln
Val 145	Leu	Pro	Asp	Ser	Gly 150	Gly	Pro	Leu	Ile	Asp 155	Leu	Leu	Thr	Glu	Asp 160
Pro	Pro	Pro	Tyr	Gly 165	Ala	Gln	Pro	Ser	Ser 170	Ser	Ala	Arg	Glu	Asn 175	Asn
Glu	Glu	Glu	Ala 180	Ala	Thr	Thr	Ser	Glu 185	Val	Ser	Pro	Pro	Ser 190	Pro	Met
Val	Ser	Arg 195	Leu	Arg	Gly	Arg	Arg 200	Asp	Pro	Pro	Ala	Ala 205	Asp	Ser	Thr
Thr	Ser 210	Gln	Ala	Phe	Pro	Leu 215	Arg	Met	Gly	Gly	Asp 220	Gly	Gln	Leu	Gln
Tyr 225	Trp	Pro	Phe	Ser	Ser 230	Ser	Asp	Leu	Tyr	Asn 235	Trp	Lys	Asn	Asn	Asn 240
Pro	Ser	Phe	Ser	Glu 245	Asp	Pro	Gly	Lys	Leu 250	Thr	Ala	Leu	Ile	Glu 255	Ser
Val	Leu	Ile	Thr 260	His	Gln	Pro	Thr	Trp 265	Asp	Asp	СЛа	Gln	Gln 270	Leu	Leu
_		275			Gly		280	-		-		285			
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	-		-	405	ГЛЗ			-	410		-		-	415	-
			420		Val			425					430		
		435			Arg		440	-		-	-	445			
Lys	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
Asp 465	Arg	Arg	Arg	His	Arg 470	Glu	Met	Ser	Lys	Leu 475	Leu	Ala	Thr	Val	Val 480
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Val	Gln	Arg 35	Asp	Ser	Pro	His	Gln 40	Val	Phe	Asn	Val	Thr 45	Trp	Lys	Ile	
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Thr 65	Met	Thr	Asp	Thr	Phe 70	Pro	Lys	Leu	Tyr	Phe 75	Asp	Leu	Сув	Asp	Leu 80	
Val	Gly	Asp	Asn	Trp 85	Asp	Asp	Pro	Glu	Pro 90	Asp	Ile	Gly	Asp	Gly 95	Суз	
Arg	Ser	Pro	Gly 100	Gly	Arg	Lys	Arg	Thr 105	Arg	Leu	Tyr	Asp	Phe 110	Tyr	Val	
Суз	Pro	Gly 115	His	Thr	Val	Leu	Thr 120	Gly	Суз	Gly	Gly	Pro 125	Arg	Glu	Gly	
Tyr	Cys 130	Gly	Lys	Trp	Gly	Cys 135	Glu	Thr	Thr	Gly	Gln 140	Ala	Tyr	Trp	Lys	
Pro 145	Ser	Ser	Ser	Trp	Asp 150	Leu	Ile	Ser	Leu	Lys 155	Arg	Gly	Asn	Thr	Pro 160	
Lys	Gly	Gln	Gly	Pro 165	Сүз	Phe	Asp	Ser	Ser 170	Val	Gly	Ser	Gly	Ser 175	Ile	
Gln	Gly	Ala	Thr 180	Pro	Gly	Gly	Arg	Cys 185	Asn	Pro	Leu	Val	Leu 190	Glu	Phe	
Thr	Asp	Ala 195	Gly	Lys	Arg	Ala	Ser 200	Trp	Asp	Ala	Pro	Lys 205	Thr	Trp	Gly	
Leu	Arg 210	Leu	Tyr	Arg	Ser	Thr 215	Gly	Ala	Asp	Pro	Val 220	Thr	Leu	Phe	Ser	
Leu 225	Thr	Arg	Gln	Val	Leu 230	Asn	Val	Gly	Pro	Arg 235	Val	Pro	Ile	Gly	Pro 240	
Asn	Pro	Val	Ile	Thr 245	Glu	Gln	Leu	Pro	Pro 250	Ser	Gln	Pro	Val	Gln 255	Ile	
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Gln A	Ala 370	Leu	Cys	Asn	Thr	Thr 375	Gln	Lys	Thr	Ser	Asp 380	Gly	Ser	Tyr	Tyr		
Leu 2 385	Ala	Ser	Pro	Ala	Gly 390	Thr	Ile	Trp	Ala	Сув 395	Ser	Thr	Gly	Leu	Thr 400		
Pro (Суз	Leu	Ser	Thr 405	Thr	Val	Leu	Asn	Leu 410	Thr	Thr	Asp	Tyr	Cys 415	Val		
Leu V	Val	Glu	Leu 420	Trp	Pro	Lys	Val	Thr 425	Tyr	His	Ser	Pro	Asn 430	Tyr	Val		
Tyr (Gly	Gln 435	Phe	Glu	Lys	Lys	Thr 440	Lys	Tyr	Гуз	Arg	Glu 445	Pro	Val	Ser		
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370 375 380 110 110 380 110 110 380 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 110 110 390 1100 1100
385 390 395 400 Pro Cys Leu Ser Thr Thr Val Leu Asn Leu Thr Thr Asp Tyr Cys Val Leu Val Glu Leu Trp Pro Lys Val Thr Tyr Tyr Cys Val Leu Val Glu Leu Trp Pro Lys Val Thr Tyr His Ser Pro Asp Tyr Val Tyr Gly Gln Phe Gly Lys Lys Thr Lys Tyr Lys Arg Glu Pro Val Ser Leu Thr Leu Leu Leu Leu Gly Gly Gly Thr Met Gly Gly Ile Ala Ala Gly Val Gly Thr Gly Gly Gly Ile Ala Leu Ala Leu Ala Leu Ala Leu Ala Leu Ala <t< td=""></t<>
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485490495Ser Val Ser Ala Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val 500Ser Leu Glu Thr Ser Leu Ser Glu Val Val 505Val Ser Glu Val Val 510Leu Gln Asn Arg Arg Gly Leu Asp Leu Leu Phe 515Leu Lys Glu Gly Gly 520Ser Leu Phe 520Leu Lys Glu Gly Gly 525Leu Cys Ala Ala Leu Lys Lys Glu Cys Cys Phe 530Ala Asp His Thr 540Gly Val Val Arg Asp Ser Met Ala Lys Leu Arg Glu Arg Leu Asn Gln
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530 535 540 Gly Val Val Arg Asp Ser Met Ala Lys Leu Arg Glu Arg Leu Asn Gln
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Arg Gln Lys Leu Phe Glu Ser Gly Gln Gly Trp Phe Glu Gly Leu Phe Asn Arg Ser Pro Trp Phe Thr Thr Leu Ile Ser Thr Ile Met Gly Pro Leu Ile Val Leu Leu Leu Leu Leu Phe Gly Pro Cys Ile Leu Asn Arg Leu Val Gln Phe Val Lys Asp Arg Ile Ser Val Val Gln Ala Leu Val Leu Thr Gln Gln Tyr His Gln Leu Lys Ser Ile Asp Pro Glu Glu Val Glu Ser Arg Glu <210> SEQ ID NO 34 <211> LENGTH: 1733 <212> TYPE: PRT <213> ORGANISM: Xenotropic MuLV-related Virus VP35 <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (537)..(537) <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid <400> SEOUENCE: 34 Met Gly Gln Thr Val Thr Thr Pro Leu Ser Leu Thr Leu Gln His Trp Gly Asp Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro Ala Leu Thr Leu Ser Ile Lys Ser Lys Pro Pro Lys Pro Gln Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp Pro Pro Pro Tyr Gly Val Gln Pro Ser Ser Ala Arg Glu Asn Asn Glu Glu Glu Ala Ala Thr Thr Ser Glu Val Ser Pro Pro Ser Pro Met Val Ser Arg Leu Arg Gly Arg Arg Asp Pro Pro Ala Ala Asp Ser Thr Thr Ser Gln Ala Phe Pro Leu Arg Met Gly Gly Asp Gly Gln Leu Gln Tyr Trp Pro Phe Ser Ser Asp Leu Tyr Asn Trp Lys Asn Asn Asn Pro Ser Phe Ser Glu Asp Pro Gly Lys Leu Thr Ala Leu Ile Glu Ser

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Gly	Lys 290	Ala	Val	Arg	Gly	Asn 295	Asp	Gly	Arg	Pro	Thr 300	Gln	Leu	Pro	Asn
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Thr	Thr	Glu	Gly	Arg 325	Asn	His	Leu	Val	Leu 330	Tyr	Arg	Gln	Leu	Leu 335	Leu
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Arg	Leu 370	Lys	Glu	Ala	Tyr	Arg 375	Arg	Tyr	Thr	Pro	Tyr 380	Asp	Pro	Glu	Asp
Pro 385	Gly	Gln	Glu	Thr	Asn 390	Val	Ser	Met	Ser	Phe 395	Ile	Trp	Gln	Ser	Ala 400
Pro	Asp	Ile	Gly	Arg 405	Lys	Leu	Glu	Arg	Leu 410	Glu	Asp	Leu	Lys	Ser 415	Lys
Thr	Leu	Gly	Asp 420	Leu	Val	Arg	Glu	Ala 425	Glu	Гла	Ile	Phe	Asn 430	Гла	Arg
Glu	Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
Lys	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
Asp 465	Arg	Arg	Arg	His	Arg 470	Glu	Met	Ser	Lys	Leu 475	Leu	Ala	Thr	Val	Val 480
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Leu	Asp	Lys	Asp 500	Gln	Сүз	Ala	Tyr	Суз 505	Lys	Glu	Lys	Gly	His 510	Trp	Ala
Lys	Asp	Cys 515	Pro	Lys	Гла	Pro	Arg 520	Gly	Pro	Arg	Gly	Pro 525	Arg	Pro	Gln
Thr	Ser 530	Leu	Leu	Thr	Leu	Gly 535	Asp	Xaa	Gly	Gly	Gln 540	Gly	Gln	Glu	Pro
Pro 545	Pro	Glu	Pro	Arg	Ile 550	Thr	Leu	ГЛа	Val	Gly 555	Gly	Gln	Pro	Val	Thr 560
Phe	Leu	Val	Asp	Thr 565	Gly	Ala	Gln	His	Ser 570	Val	Leu	Thr	Gln	Asn 575	Pro
Gly	Pro	Leu	Ser 580	Asp	Гла	Ser	Ala	Trp 585	Val	Gln	Gly	Ala	Thr 590	Gly	Gly
Lys	Arg	Tyr 595	Arg	Trp	Thr	Thr	Asp 600	Arg	Lys	Val	His	Leu 605	Ala	Thr	Gly
Lys	Val 610	Thr	His	Ser	Phe	Leu 615	His	Val	Pro	Asp	Сув 620	Pro	Tyr	Pro	Leu
Leu 625	Gly	Arg	Asp	Leu	Leu 630	Thr	Lys	Leu	Lys	Ala 635	Gln	Ile	His	Phe	Glu 640
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Glu	Pro	Asp 675	Val	Pro	Leu	Gly	Ser 680	Thr	Trp	Leu	Ser	Asp 685	Phe	Pro	Gln
Ala	Trp 690	Ala	Glu	Thr	Gly	Gly 695	Met	Gly	Leu	Ala	Val 700	Arg	Gln	Ala	Pro
Leu 705	Ile	Ile	Pro	Leu	Lys 710	Ala	Thr	Ser	Thr	Pro 715	Val	Ser	Ile	Lys	Gln 720
Tyr	Pro	Met	Ser	Gln 725	Glu	Ala	Arg	Leu	Gly 730	Ile	ГЛа	Pro	His	Ile 735	Gln
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Thr	Pro	Leu 755	Leu	Pro	Val	Lys	Lys 760	Pro	Gly	Thr	Asn	Asp 765	Tyr	Arg	Pro
Val	Gln 770	Aap	Leu	Arg	Glu	Val 775	Asn	Lys	Arg	Val	Glu 780	Asp	Ile	His	Pro
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Gln	Trp	Tyr	Thr	Val 805	Leu	Asp	Leu	Lys	Asp 810	Ala	Phe	Phe	Сув	Leu 815	Arg
Leu	His	Pro	Thr 820	Ser	Gln	Pro	Leu	Phe 825	Ala	Phe	Glu	Trp	Arg 830	Asp	Pro
Glu	Met	Gly 835	Ile	Ser	Gly	Gln	Leu 840	Thr	Trp	Thr	Arg	Leu 845	Pro	Gln	Gly
Phe	Lys 850	Asn	Ser	Pro	Thr	Leu 855	Phe	Asp	Glu	Ala	Leu 860	His	Arg	Asp	Leu
Ala 865	Aab	Phe	Arg	Ile	Gln 870	His	Pro	Asp	Leu	Ile 875	Leu	Leu	Gln	Tyr	Val 880
Asp	Aab	Leu	Leu	Leu 885	Ala	Ala	Thr	Ser	Glu 890	Gln	Asp	Сүз	Gln	Arg 895	Gly
Thr	Arg	Ala	Leu 900	Leu	Gln	Thr	Leu	Gly 905	Asn	Leu	Gly	Tyr	Arg 910	Ala	Ser
Ala	Lys	Lys 915	Ala	Gln	Ile	Суз	Gln 920	Lys	Gln	Val	Lys	Tyr 925	Leu	Gly	Tyr
Leu	Leu 930	Lys	Glu	Gly	Gln	Arg 935	Trp	Leu	Thr	Glu	Ala 940	Arg	Lys	Glu	Thr
Val 945	Met	Gly				Pro			Pro					Glu	
Leu	Gly	Thr	Ala	Gly 965	Phe	Cys	Arg	Leu	Trp 970	Ile	Pro	Gly	Phe	Ala 975	Glu
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Trp	Gly	Pro 995	Asp	Gln	Gln	Lys	Ala 1000	-	r Glı	n Glu	ı Ile	∋ Ly: 100		ln A	la Leu
Leu	Thr 1010		a Pro	> Ala	a Lei	1 Gly 101		eu Pi	ro As	зр Le		nr 1 020	'ya I	Pro I	?he
Glu	Leu 1025		e Val	l Asp	Glu	1 Ly: 103		ln G	Ly Ty	vr Al		үв (035	Gly N	/al I	leu
Thr	Gln 1040		s Leu	ı Gly	/ Pro	5 Tr <u>1</u> 104		rg Ai	rg Pi	co Vá		la 5 050	fyr I	Leu f	Ser
Lys	Lys 1055		ı Asp) Pro	Va:	L Ala 100		La GI	Ly Ti	rp Pi		ro (065	Cys I	Leu A	Arg

Met	Val 1070	Ala	Ala	Ile	Ala	Val 1075	Leu	Thr	Lys	Asp	Ala 1080	Gly	Lys	Leu
Thr	Met 1085	Gly	Gln	Pro	Leu	Val 1090	Ile	Leu	Ala	Pro	His 1095	Ala	Val	Glu
Ala	Leu 1100	Val	Lys	Gln	Pro	Pro 1105	Asp	Arg	Trp	Leu	Ser 1110	Asn	Ala	Arg
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Phe	Gly 1130	Pro	Val	Val	Ala	Leu 1135		Pro	Ala	Thr	Leu 1140	Leu	Pro	Leu
Pro	Glu 1145	Lys	Glu	Ala	Pro	His 1150	Asp	Cys	Leu	Glu	Ile 1155	Leu	Ala	Glu
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Ala	Asp 1175	Tyr	Thr	Trp	Tyr	Thr 1180	Asp	Gly	Ser	Ser	Phe 1185	Leu	Gln	Glu
Gly	Gln 1190	Arg	Arg	Ala	Gly	Ala 1195	Ala	Val	Thr	Thr	Glu 1200	Thr	Glu	Val
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Glu	Leu 1220	Ile	Ala	Leu	Thr	Gln 1225	Ala	Leu	Lys	Met	Ala 1230	Glu	Gly	Lys
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Gly	His 1295	Gln	Lys	Gly	Asn	Ser 1300	Ala	Glu	Ala	Arg	Gly 1305	Asn	Arg	Met
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His	Phe 1340	His	Tyr	Thr	Glu	Thr 1345	Asp	Leu	Lys	Arg	Leu 1350	Arg	Glu	Leu
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Lys	Pro 1370	Val	Met	Pro	Asp	Gln 1375	Ser	Val	Phe	Glu	Leu 1380	Leu	Asp	Ser
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Leu	Asp 1400	Arg	Glu	Glu	Ser	Pro 1405	Tyr	Tyr	Met	Leu	Asn 1410	Arg	Asp	Arg
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Asn	Ala 1430	Ser	Lys	Ala	Lys	Ile 1435	Gly	Ala	Gly	Val	Arg 1440	Val	Arg	Gly
His	Arg	Pro	Gly	Thr	His	Trp	Glu	Val	Asp	Phe	Thr	Glu	Val	Гла

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Tyr	Arg 1580	Ala	Arg	Asn	Thr	Pro 1585		Pro	His	Gly	Leu 1590	Thr	Pro	Tyr
Glu	Ile 1595	Leu	Tyr	Gly	Ala	Pro 1600		Pro	Leu	Val	Asn 1605	Phe	His	Asp
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Gly	Asp '		Gln 2 20	Arg :	Ile 2	Ala S	er A 2		ln S	er V	al As _l	9 Va 30	l Ly:	s Lys
Arg		Irp ' 35	Val	Thr 1	Phe (er A 0	la G	lu T	rp P:	ro Th: 45	r Phe	e Asr	n Val
Gly	Trp 1	Pro (Gln 2	Asp (Gly ?	Thr B	he A	sn L	eu G	ly V	al Ile	e Se:	r Glr	n Val

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Pro	Tyr	Ile	Val	Thr 85	Trp	Glu	Ala	Leu	Ala 90	Tyr	Asp	Pro	Pro	Pro 95	Trp
Val	Lys	Pro	Phe 100	Val	Ser	Pro	Lys	Pro 105	Pro	Pro	Leu	Pro	Thr 110	Ala	Pro
Val	Leu	Pro 115	Pro	Gly	Pro	Ser	Ala 120	Gln	Pro	Pro	Ser	Arg 125	Ser	Ala	Leu
Tyr	Pro 130	Ala	Leu	Thr	Leu	Ser 135	Ile	Lys	Ser	ГÀа	Pro 140	Pro	Lys	Pro	Gln
Val 145	Leu	Pro	Asp	Ser	Gly 150	Gly	Pro	Leu	Ile	Asp 155	Leu	Leu	Thr	Glu	Asp 160
Pro	Pro	Pro	Tyr	Gly 165	Val	Gln	Pro	Ser	Ser 170	Ser	Ala	Arg	Glu	Asn 175	Asn
Glu	Glu	Glu	Ala 180	Ala	Thr	Thr	Ser	Glu 185	Val	Ser	Pro	Pro	Ser 190	Pro	Met
Val	Ser	Arg 195	Leu	Arg	Gly	Arg	Arg 200	Asp	Pro	Pro	Ala	Ala 205	Asp	Ser	Thr
Thr	Ser 210	Gln	Ala	Phe	Pro	Leu 215	Arg	Met	Gly	Gly	Asp 220	Gly	Gln	Leu	Gln
Tyr 225	Trp	Pro	Phe	Ser	Ser 230	Ser	Asp	Leu	Tyr	Asn 235	Trp	Lys	Asn	Asn	Asn 240
Pro	Ser	Phe	Ser	Glu 245	Asp	Pro	Gly	Lys	Leu 250	Thr	Ala	Leu	Ile	Glu 255	Ser
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Gly	Thr	Leu 275	Leu	Thr	Gly	Glu	Glu 280	Lys	Gln	Arg	Val	Leu 285	Leu	Glu	Ala
Gly	Lys 290	Ala	Val	Arg	Gly	Asn 295	Asp	Gly	Arg	Pro	Thr 300	Gln	Leu	Pro	Asn
Glu 305	Val	Asn	Ala	Ala	Phe 310	Pro	Leu	Glu	Arg	Pro 315	Asp	Trp	Asp	Tyr	Thr 320
Thr	Thr	Glu	Gly	Arg 325	Asn	His	Leu	Val	Leu 330	Tyr	Arg	Gln	Leu	Leu 335	Leu
Ala	Gly	Leu	Gln 340	Asn	Ala	Gly	Arg	Ser 345	Pro	Thr	Asn	Leu	Ala 350	Lys	Val
Lys	Gly	Ile 355	Thr	Gln	Gly	Pro	Asn 360	Glu	Ser	Pro	Ser	Ala 365	Phe	Leu	Glu
Arg	Leu 370	Lys	Glu	Ala	Tyr	Arg 375	Arg	Tyr	Thr	Pro	Tyr 380	Asp	Pro	Glu	Asp
Pro 385	Gly	Gln	Glu	Thr	Asn 390	Val	Ser	Met	Ser	Phe 395	Ile	Trp	Gln	Ser	Ala 400
Pro	Asb	Ile	Gly	Arg 405	Гла	Leu	Glu	Arg	Leu 410	Glu	Asp	Leu	Lys	Ser 415	Lys
Thr	Leu	Gly	Asp 420	Leu	Val	Arg	Glu	Ala 425	Glu	Гла	Ile	Phe	Asn 430	Гла	Arg
Glu	Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
Lys	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg

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Asp Arg Arg Arg His Arg Glu Met Ser Lys Leu Leu Ala Thr Val Val Ile Gly Gln Arg Gln Asp Arg Gln Gly Gly Glu Arg Arg Arg Pro Gln Leu Asp Lys Asp Gln Cys Ala Tyr Cys Lys Glu Lys Gly His Trp Ala Lys Asp Cys Pro Lys Lys Pro Arg Gly Pro Arg Gly Pro Arg Pro Gln 515 520 525 Thr Ser Leu Leu Thr Leu Gly Asp <210> SEQ ID NO 36 <211> LENGTH: 645 <212> TYPE: PRT <213> ORGANISM: Xenotropic MuLV-related Virus VP42 <400> SEOUENCE: 36 Met Glu Ser Pro Ala Phe Ser Lys Pro Leu Lys Asp Lys Ile Asn Pro Trp Gly Pro Leu Ile Ile Met Gly Ile Leu Val Arg Ala Gly Ala Ser Val Gln Arg Asp Ser Pro His Gln Val Phe Asn Val Thr Trp Lys Ile Thr Asn Leu Met Thr Gly Gln Thr Ala Asn Ala Thr Ser Leu Leu Gly Thr Met Thr Asp Thr Phe Pro Lys Leu Tyr Phe Asp Leu Cys Asp Leu Val Gly Asp Asn Trp Asp Asp Pro Glu Pro Asp Ile Gly Asp Gly Cys Arg Ser Pro Gly Gly Arg Lys Arg Thr Arg Leu Tyr Asp Phe Tyr Val Cys Pro Gly His Thr Val Leu Thr Gly Cys Gly Gly Pro Arg Glu Gly Tyr Cys Gly Lys Trp Gly Cys Glu Thr Thr Gly Gln Ala Tyr Trp Lys Pro Ser Ser Ser Trp Asp Leu Ile Ser Leu Lys Arg Gly Asn Thr Pro Lys Gly Gln Gly Pro Cys Phe Asp Ser Ser Val Gly Ser Gly Ser Ile Gln Gly Ala Thr Pro Gly Gly Arg Cys Asn Pro Leu Val Leu Glu Phe Thr Asp Ala Gly Lys Arg Ala Ser Trp Asp Ala Pro Lys Thr Trp Gly Leu Arg Leu Tyr Arg Ser Thr Gly Ala Asp Pro Val Thr Leu Phe Ser Leu Thr Arg Gln Val Leu Asn Val Gly Pro Arg Val Pro Ile Gly Pro Asn Pro Val Ile Thr Glu Gln Leu Pro Pro Ser Gln Pro Val Gln Ile Met Leu Pro Arg Pro Pro Arg Pro Pro Pro Ser Gly Ala Ala Ser Met Val Pro Gly Ala Pro Pro Pro Ser Gln Gln Pro Gly Thr Gly Asp Arg

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Leu	Leu 290	Asn	Leu	Val	Glu	Gly 295	Ala	Tyr	Gln	Ala	Leu 300	Asn	Leu	Thr	Ser
Pro 305	Asp	Lys	Thr	Gln	Glu 310	Суз	Trp	Leu	Суз	Leu 315	Val	Ser	Gly	Pro	Pro 320
Tyr	Tyr	Glu	Gly	Val 325	Ala	Val	Leu	Gly	Thr 330	Tyr	Ser	Asn	His	Thr 335	Ser
Ala	Pro	Ala	Asn 340	-	Ser	Val	Thr	Ser 345	Gln	His	Lys	Leu	Thr 350	Leu	Ser
Glu	Val	Thr 355	Gly	Gln	Gly	Leu	Суз 360	Ile	Gly	Ala	Val	Pro 365	Lys	Thr	His
Gln	Ala 370	Leu	Суз	Asn	Thr	Thr 375	Gln	LÀa	Thr	Ser	Aap 380	Gly	Ser	Tyr	Tyr
Leu 385	Ala	Ser	Pro	Ala	Gly 390	Thr	Ile	Trp	Ala	Суз 395	Ser	Thr	Gly	Leu	Thr 400
Pro	Cys	Leu	Ser	Thr 405	Thr	Val	Leu	Asn	Leu 410	Thr	Thr	Asp	Tyr	Cys 415	Val
Leu	Val	Glu	Leu 420	Trp	Pro	Гла	Val	Thr 425	Tyr	His	Ser	Pro	Asn 430	Tyr	Val
Tyr	Gly	Gln 435	Phe	Glu	ГЛа	Гла	Thr 440	Гла	Tyr	Lys	Arg	Glu 445	Pro	Val	Ser
Leu	Thr 450	Leu	Ala	Leu	Leu	Leu 455	Gly	Gly	Leu	Thr	Met 460	Gly	Gly	Ile	Ala
Ala 465	Gly	Val	Gly	Thr	Gly 470	Thr	Thr	Ala	Leu	Val 475	Ala	Thr	Lys	Gln	Phe 480
Glu	Gln	Leu	Gln	Ala 485	Ala	Ile	His	Thr	Asp 490	Leu	Gly	Ala	Leu	Glu 495	Lys
Ser	Val	Ser	Ala 500	Leu	Glu	Lys	Ser	Leu 505	Thr	Ser	Leu	Ser	Glu 510	Val	Val
Leu	Gln	Asn 515	Arg	Arg	Gly	Leu	Asp 520	Leu	Leu	Phe	Leu	Lys 525	Glu	Gly	Gly
Leu	Cys 530	Ala	Ala	Leu	Lys	Glu 535	Glu	Суз	Суз	Phe	Tyr 540	Ala	Asp	His	Thr
Gly 545	Val	Val	Arg	Asp	Ser 550	Met	Ala	Lys	Leu	Arg 555	Glu	Arg	Leu	Asn	Gln 560
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Leu	Ile	Val 595	Leu	Leu	Leu	Ile	Leu 600	Leu	Phe	Gly	Pro	Суя 605	Ile	Leu	Asn
Arg	Leu 610	Val	Gln	Phe	Val	Lys 615	Asp	Arg	Ile	Ser	Val 620	Val	Gln	Ala	Leu
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Val	Glu	Ser	Arg	Glu 645											
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					c_fea 7)										

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

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435 440 445 Lye Glu Glu Arg
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4465 470 475 480 Ile Gly Gln Arg Gln Arg Gln Arg Gln
485 490 490 495 Leu Asp Lys Asp Gln Cys Ala Tyr Cys Lys Gly Fib Tyr Ala Lys Asp Cys Pro Lys Gly Fro Arg Gly Fro Arg Gly Fro Arg Gly
LysAspCysProLysLysProArgGlyProArgGlyProArgGlyProArgGlyProArgGlyProArgGlyProArgGlyGlnGluGlnGluGlnGluProGlnGluProGlnGluProValGlnGluProValThrSanGluProArgThLeuGlyAlaGluGluProValThrSanGluProValThrSanSanGluGluProValThrSanSanSanGluGluProValThrSanSanSanGluProValThrSanSa
515 520 525 Fir Sis Sis 520 525 Fir Ser Leu Thr Leu Gly Asp Xaa Gly Gly Gln Gly Glu Pro Pro Glu Pro Arg Ile Thr Leu Lys Val Gly Gln Gly Gln Pro Val Thr S45 Pro Glu Asp Thr Gly Ala Gln His Ser Val Gly Gln Asp Val Ser Val Gln Glu Asp Pro Ser Asp Lys Val Gln Glu Asp Pro Ser Asp Pro Ser Asp Pro Ser Asp Pro Ser Pro Glu Asp Gly Asp Pro Pro Ser Pro S
530 535 540 Pro Glu Pro Arg Ile The Leu Lys Val Gly Gln Pro Val Thr S55 Pro Glu Arg Thr Gly Ala Gly Ala Gly S55 Gly Gln Pro Val Ann S56 Pro Leu Val Asp Thr Gly Ala Gln His Ser Val Gln Gly Ala Thr Ser Val Gln Gly Ala Thr Ser Ala Thr Ser Val Gln Gly Ala Thr Gly Ser Ala Thr Ser Pro Leu Ser Pro Leu Ser Pro Leu Ser Ser Pro Leu Ser Ser Pro Leu Ala Thr Ser Ser Ser Ser Ser Ser Ser
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565 570 577 Gly Pro Leu Ser Asp Lys Ser Ala Trp Sad Gly Ala The Sad Gly Sad Gly Ala The Sad Sad Sad Sad Gly Ala The Sad Sad Sad Sad Gly Ala The Sad
580 580 585 590 590 Lys Arg Tyr Arg Tyr Arg Tyr Thr Thr Asp GU Val His Leu Ala Thr Gly Lys Val Thr His Ser Phe Leu His Val Pro Asp Cys Pro Tyr Pro Leu Leu Gly Arg Asp Leu Leu His Val Pro Asp Cys Pro Tyr Pro Leu Leu Gly Arg Asp Leu Leu His Val Gly Asp Cys Pro Tyr Pro Leu Gly Arg Gly Val Gly Pro Met Gly Gly Gly Gly Asp Glu Gly Asp Gly G
595 600 605 605 Lys Val Thr His Ser Phe Leu His Val Pro Asp Cys Pro Tyr Pro Leu Leu Gly Arg Asp Leu Leu Thr Lys Leu Tyr Pro Leu Glu Gas Glu Gas Glu His Pro Asp Cys Pro Tyr Pro Leu Gas Gly Arg Asp Leu Thr Lys Leu Thr Math Glu Gly Pro Met Gly Gln Pro Leu Glu
610 615 620 Leu Gly Arg Asp Leu Thr Lys Alu S I His Phe Glu Gly Ser Gly Ala Gln Val Gly Pro Met Gly Gln Pro Leu Gly Gln Gln <t< td=""></t<>
625 630 635 640 Gly Ser Gly Ala Gln Val Gln Val Gly Val Gly Pro $\stackrel{655}{650}$ Gly Gln Pro Leu Gln $\stackrel{655}{655}$ 640 Glu Thr Leu Asn Ile Glu Asp Glu Tyr Arg Leu His Glu Thr Ser Lys $\stackrel{655}{665}$ 660 7 Glu Pro $\stackrel{655}{650}$ Val $\stackrel{655}{650}$ 7 7 7 Glu Thr Leu Asn Ile Glu Gly Ser Thr Trp Leu Ser $\stackrel{655}{685}$ 7 7 7 Glu Pro $\stackrel{655}{675}$ Val $\stackrel{615}{695}$ 7 7 7 7 Glu Pro $\stackrel{655}{675}$ Val $\stackrel{615}{695}$ 7 7 7 7 7 Glu Pro $\stackrel{655}{675}$ Val $\stackrel{616}{655}$ 7 7 7 7 7 7 Glu Pro $\stackrel{655}{675}$ Val $\stackrel{610}{665}$ 610 1
645 650 655 Leu Thr Leu Asn Ile Glu Asp Glu Tyr Arg Leu His Glu Thr Ser Lys Glu Asp Val Pro Leu Glu Asp Glu Tyr Arg Leu His Glu Thr Ser Lys Glu Arg Pro Asp Val Pro Leu Gly Ser Thr Trp Leu Ser Asp Pro Gln Gln Ala Trp Ala Glu Thr Gly Gly Leu Ala Yal Arg Gln Ala Pro
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Thr Val Pro Asn Pro Tyr Asn Leu Leu Ser Gly Leu Pro Pro Ser His
785 790 795 800

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Gln	Trp	Tyr	Thr	Val 805	Leu	Asp	Leu	Lys	Asp 810		Phe	Phe	e Cys	Leu 815	Arg	
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Glu	Met	Gly 835	Ile	Ser	Gly	Gln	Leu 840	Thr	Trp	Thr	Arg	Leu 845		Gln	Gly	
Phe	Lys 850	Asn	Ser	Pro	Thr	Leu 855	Phe	Asp	Glu	Ala	Leu 860		Arg	Asp	Leu	
Ala 865	Asp	Phe	Arg	Ile	Gln 870	His	Pro	Asp	Leu	Ile 875		Leu	Gln	Tyr	Val 880	
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Val 945	Met	Gly	Gln	Pro	Thr 950	Pro	Гла	Thr	Pro	Arg 955		ı Leu	. Arg	Glu	. Phe 960	
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Met	Ala	Ala	Pro 980	Leu	Tyr	Pro	Leu	Thr 985	Lys	Thr	Gly	Thr	Leu 990		Asn	
Trp	Gly	Pro 995	Asp	Gln	Gln	Lys	Ala 100	-	r Gl:	n Gl	u Il	-	່ອ ເວີ	ln A	la Le	≥u
Leu	Thr 1010		a Pro	o Ala	a Leu	ı Gly 101		eu Pi	ro A	ap L		'hr .020	Lys	Pro	Phe	
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Thr	Gln 1040	-	s Leu	ı Gly	7 Pro	5 Trp 104		rg A:	rg P	ro V		la 050	Tyr	Leu	Ser	
Lys	Lys 1055		ı Asp	p Pro	o Val	L Ala 106		la G	ly T	rp P		ro .065	Сүз	Leu	Arg	
Met	Val 1070		a Alá	a Ile	e Ala	a Val 107		eu Tl	hr L	ys A	_	la .080	Gly	Lys	Leu	
Thr	Met 1085	-	7 Glr	n Pro) Lei	ı Val 109		le L	eu A	la P		(is .095	Ala	Val	Glu	
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Met	Thr 1115		з Туз	r Glr	n Ala	a Met 112		eu L	eu A	ap T		sp 125	Arg	Val	Gln	
Phe	Gly 1130		o Val	L Val	L Ala	a Leu 113		∍n P:	ro A	la T		eu 140	Leu	Pro	Leu	
Pro	Glu 1145	-	s Glu	ı Ala	a Pro) His 115		ap C	ys L	eu G		le 155	Leu	Ala	Glu	
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Ala	Asp 1175		r Thi	r Tr <u>p</u>	у Туз	: Thi 118		∃p G	ly G	ly S		he 185	Leu	Gln	Glu	
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-	С	O	n	C.	1	n	u	е	а

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Ala	Asp 1310	Gln	Ala	Ala	Arg	Glu 1315	Ala	Ala	Met	Lys	Ala 1320	Val	Leu	Glu
Thr	Ser 1325	Thr	Leu	Leu	Ile	Glu 1330	Asp	Ser	Thr	Pro	Tyr 1335	Thr	Pro	Pro
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Lys	Pro 1370	Val	Met	Pro	Asp	Gln 1375	Ser	Val	Phe	Glu	Leu 1380	Leu	Asp	Ser
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Leu	Asp 1400	Arg	Glu	Glu	Ser	Pro 1405		Tyr	Met	Leu	Asn 1410	Arg	Asp	Arg
Thr	Ile 1415	Gln	Tyr	Val	Thr	Glu 1420	Thr	Cys	Thr	Ala	Cys 1425	Ala	Gln	Val
Asn	Ala 1430	Ser	Lys	Ala	Lys	Ile 1435	Gly	Ala	Gly	Val	Arg 1440	Val	Arg	Gly
His	Arg 1445	Pro	Gly	Thr	His	Trp 1450	Glu	Val	Asp	Phe	Thr 1455	Glu	Val	Lys
Pro	Gly 1460	Leu	Tyr	Gly	Tyr	Lys 1465	Tyr	Leu	Leu	Val	Phe 1470	Val	Asp	Thr
Phe	Ser 1475	Gly	Trp	Val	Glu	Ala 1480	Phe	Pro	Thr	Lys	Arg 1485	Glu	Thr	Ala
Lya	Val 1490	Val	Ser	Lys	Lys	Leu 1495	Leu	Glu	Asp	Ile	Phe 1500	Pro	Arg	Phe
Gly	Met 1505	Pro	Gln	Val	Leu	Gly 1510	Ser	Asp	Asn	Gly	Pro 1515	Ala	Phe	Ala
Ser	Gln 1520	Val	Ser	Gln	Ser	Val 1525	Ala	Asp	Leu	Leu	Gly 1530	Ile	Asp	Trp
Lys	Leu 1535	His	Сүз	Ala	Tyr	Arg 1540	Pro	Gln	Ser	Ser	Gly 1545	Gln	Val	Glu
Arg	Met 1550	Asn	Arg	Thr	Ile	Lys 1555	Glu	Thr	Leu	Thr	Lys 1560	Leu	Thr	Leu
Ala	Ser 1565	Gly	Thr	Arg	Asp	Trp 1570	Val	Leu	Leu	Leu	Pro 1575	Leu	Ala	Leu
Tyr	Arg	Ala	Arg	Asn	Thr	Pro	Gly	Pro	His	Gly	Leu	Thr	Pro	Tyr

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Pro	Glu 1610		Ser	Lys	s Leu	ι Thi 161		sn Se	er P:	ro S	Ser	Leu 1620		Ala	His	
Leu	Gln 1625		Leu	. Glr	n Ala	1 Val 163		ln G	ln G	lu V	Val	Trp 1635	-	Pro	Leu	
Ala	Ala 1640		Tyr	Glr	n Asp) Glr 164		eu A	ap G	ln F	ro	Val 1650		Pro	His	
Pro	Phe 1655		Val	Glγ	/ Asp) Ala 166		al T:	rp V.	al A	Arg	Arg 1665		Gln	Thr	
rÀa	Asn 1670		. Glu	Pro	> Arg	167 167		ys G	Ly P:	ro I	'yr	Thr 1680		Leu	Leu	
Thr	Thr 1685		Thr	Ala	a Lev	ι Lys 169		al As	ap G	ly I	le	Ser 1695	Ala	Trp	Ile	
His	Ala 1700		His	Va]	L Lya	8 Ala 170		la Tì	nr Tl	hr F	ro	Pro 1710		Gly	Thr	
Ala	Trp 1715		Val	Glr	n Arg	j Sei 172		ln A:	an Pi	ro L	Jeu	Lys 1725	Ile	Arg	Leu	
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Tyr 225	Trp	Pro	Phe	Ser	Ser 230	Ser	Asp	Leu	Tyr	Asn 235	Trp	Lys	Asn	Asn	Asn 240
Pro	Ser	Phe	Ser	Glu 245	Asp	Pro	Gly	Lys	Leu 250	Thr	Ala	Leu	Ile	Glu 255	Ser
Val	Leu	Ile	Thr 260	His	Gln	Pro	Thr	Trp 265	Asp	Asp	Суз	Gln	Gln 270	Leu	Leu
Gly	Thr	Leu 275	Leu	Thr	Gly	Glu	Glu 280	Lys	Gln	Arg	Val	Leu 285	Leu	Glu	Ala
Arg	Lys 290	Ala	Val	Arg	Gly	Asn 295	Asp	Gly	Arg	Pro	Thr 300	Gln	Leu	Pro	Asn
Glu 305	Val	Asn	Ala	Ala	Phe 310	Pro	Leu	Glu	Arg	Pro 315	Asp	Trp	Gly	Tyr	Thr 320
Thr	Thr	Glu	Gly	Arg 325	Asn	His	Leu	Val	Leu 330	Tyr	Arg	Gln	Leu	Leu 335	Leu
Ala	Gly	Leu	Gln 340	Asn	Ala	Gly	Arg	Ser 345	Pro	Thr	Asn	Leu	Ala 350	Lys	Val
Lys	Gly	Ile 355	Thr	Gln	Gly	Pro	Asn 360	Glu	Ser	Pro	Ser	Ala 365	Phe	Leu	Glu
Arg	Leu 370	Lys	Glu	Ala	Tyr	Arg 375	Arg	Tyr	Thr	Pro	Tyr 380	Asp	Pro	Glu	Asp
Pro 385	Gly	Gln	Glu	Thr	Asn 390	Val	Ser	Met	Ser	Phe 395	Ile	Trp	Gln	Ser	Ala 400
Pro	Asp	Ile	Gly	Arg 405	Гла	Leu	Glu	Arg	Leu 410	Glu	Asp	Leu	Lys	Ser 415	Lys
Thr	Leu	Gly	Asp 420	Leu	Val	Arg	Glu	Ala 425	Glu	Гла	Ile	Phe	Asn 430	Гла	Arg
Glu	Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
ГЛа	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
Asp 465	Arg	Arg	Arg	His	Arg 470	Glu	Met	Ser	Lys	Leu 475	Leu	Ala	Thr	Val	Val 480
Ile	Gly	Gln	Arg	Gln 485	Asp	Arg	Gln	Gly	Gly 490	Glu	Arg	Arg	Arg	Pro 495	Gln
Leu	Asp	Lys	Asp 500	Gln	Суз	Ala	Tyr	Cys 505	Lys	Glu	ГЛа	Gly	His 510	Trp	Ala
Lys	Asp	Cys 515	Pro	ГЛЗ	ГЛа	Pro	Arg 520	Gly	Pro	Arg	Gly	Pro 525	Arg	Pro	Gln
Thr	Ser 530	Leu	Leu	Thr	Leu	Gly 535	Asp								
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			NCE :												
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Trp	Gly	Pro	Leu	Ile	Ile	Met	Gly	Ile	Leu	Val	Arg	Ala	Gly	Ala	Ser

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												0011	0 1 11		
			20					25					30		
Val	Gln	Arg 35	Asp	Ser	Pro	His	Gln 40	Val	Phe	Asn	Val	Thr 45	Trp	Lys	Ile
Thr	Asn 50	Leu	Met	Thr	Gly	Gln 55	Thr	Ala	Asn	Ala	Thr 60	Ser	Leu	Leu	Gly
Thr 65	Met	Thr	Asp	Thr	Phe 70	Pro	ГЛа	Leu	Tyr	Phe 75	Asp	Leu	Сүз	Asp	Leu 80
Val	Gly	Aab	Asn	Trp 85	Asp	Asp	Pro	Glu	Pro 90	Asp	Ile	Gly	Asp	Gly 95	Суз
Arg	Ser	Pro	Gly 100	Gly	Arg	ГЛа	Arg	Thr 105	Arg	Leu	Tyr	Asp	Phe 110	Tyr	Val
Суа	Pro	Gly 115	His	Thr	Val	Leu	Thr 120	Gly	Суз	Gly	Gly	Pro 125	Arg	Glu	Gly
Tyr	Cys 130	Gly	Lys	Trp	Gly	Суз 135	Glu	Thr	Thr	Gly	Gln 140	Ala	Tyr	Trp	Lys
Pro 145	Ser	Ser	Ser	Trp	Asp 150	Leu	Ile	Ser	Leu	Lys 155	Arg	Gly	Asn	Thr	Pro 160
Lys	Gly	Gln	Gly	Pro 165	Сүз	Phe	Asp	Ser	Ser 170	Val	Gly	Ser	Gly	Ser 175	Ile
Gln	Gly	Ala	Thr 180	Pro	Gly	Gly	Arg	Cys 185	Asn	Pro	Leu	Val	Leu 190	Glu	Phe
Thr	Asp	Ala 195	Gly	LYa	Arg	Ala	Ser 200	Trp	Aab	Ala	Pro	Lys 205	Thr	Trp	Gly
Leu	Arg 210	Leu	Tyr	Arg	Ser	Thr 215	Gly	Ala	Asp	Pro	Val 220	Thr	Leu	Phe	Ser
Leu 225	Thr	Arg	Gln	Val	Leu 230	Asn	Val	Gly	Pro	Arg 235	Val	Pro	Ile	Gly	Pro 240
Asn	Pro	Val	Ile	Thr 245	Glu	Gln	Leu	Pro	Pro 250	Ser	Gln	Pro	Val	Gln 255	Ile
Met	Leu	Pro	Arg 260	Thr	Pro	Arg	Pro	Pro 265	Pro	Ser	Gly	Ala	Ala 270	Ser	Met
Val	Pro	Gly 275	Ala	Pro	Pro	Pro	Ser 280	Gln	Gln	Pro	Gly	Thr 285	Gly	Asp	Arg
Leu	Leu 290	Asn	Leu	Val	Glu	Gly 295	Ala	Tyr	Leu	Ala	Leu 300	Asn	Leu	Thr	Ser
Pro 305	Asp	Lys	Thr	Gln	Glu 310	Сүз	Trp	Leu	Суз	Leu 315	Val	Ser	Gly	Pro	Pro 320
Tyr	Tyr	Glu	Gly	Val 325	Ala	Val	Leu	Gly	Thr 330	Tyr	Ser	Asn	His	Thr 335	Ser
Ala	Pro	Ala	Asn 340	Сүз	Ser	Val	Thr	Ser 345	Gln	His	Lys	Leu	Thr 350	Leu	Ser
Glu	Val	Thr 355	Gly	Gln	Gly	Leu	Сув 360	Ile	Gly	Ala	Val	Pro 365	ГЛа	Thr	His
Gln	Ala 370	Leu	Сүз	Asn	Thr	Thr 375	Gln	ГÀа	Thr	Ser	Asp 380	Gly	Ser	Tyr	Tyr
Leu 385	Ala	Ser	Pro	Ala	Gly 390	Thr	Ile	Trp	Ala	Сув 395	Ser	Thr	Gly	Leu	Thr 400
Pro	Сув	Leu	Ser	Thr 405	Thr	Val	Leu	Asn	Leu 410	Thr	Thr	Asp	Tyr	Суз 415	Val
Leu	Val	Glu	Leu 420	Trp	Pro	ГЛЗ	Val	Thr 425	Tyr	His	Ser	Pro	Asn 430	Tyr	Val

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565 570 575 Asn Arg Ser Pro Trp Phe Thr Thr Leu Ile Ser Thr Ile Met Gly Pro	
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Leu Ile Val Leu Leu Leu Leu Phe Gly Pro Cys Ile Leu Asn 595 600 605	
Arg Leu Val Gln Phe Val Lys Asp Arg Ile Ser Val Val Gln Ala Leu 610 615 620	
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Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val 50 55 60	
Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val 65 70 75 80	
Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp 85 90 95	
Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro 100 105 110	

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Pro	Pro	Pro	Tyr	Gly 165	Ala	Gln	Pro	Ser	Ser 170	Ser	Ala	Arg	Glu	Asn 175	Asn
Glu	Glu	Glu	Ala 180	Ala	Thr	Thr	Ser	Glu 185	Val	Ser	Pro	Pro	Ser 190	Pro	Met
Val	Ser	Arg 195	Leu	Arg	Gly	Arg	Arg 200	Asp	Pro	Pro	Ala	Ala 205	Asp	Ser	Thr
Thr	Ser 210	Gln	Ala	Phe	Pro	Leu 215	Arg	Met	Gly	Gly	Asp 220	Gly	Gln	Leu	Gln
Tyr 225	Trp	Pro	Phe	Ser	Ser 230	Ser	Asp	Leu	Tyr	Asn 235	Trp	Lys	Asn	Asn	Asn 240
Pro	Ser	Phe	Ser	Glu 245	Asp	Pro	Gly	ГÀа	Leu 250	Thr	Ala	Leu	Ile	Glu 255	Ser
Val	Leu	Ile	Thr 260	His	Gln	Pro	Thr	Trp 265	Asp	Asp	Сүз	Gln	Gln 270	Leu	Leu
Gly	Thr	Leu 275	Leu	Thr	Gly	Glu	Glu 280	Lys	Gln	Arg	Val	Leu 285	Leu	Glu	Ala
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Lys	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
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Trp	Gly	Pro 995	Asp	Gln	Gln		la 000	Tyr	Gln	Glu		ys (205	Gln j	Ala Leu
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Met	Val 1070		a Ala	a Il∈	e Ala	Val 1075		Thr	Lys	Asn	Ala 1080		Lys	Leu
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Ala	Leu 1100		L Lys	s Glr	n Pro	Pro 1105		Arg	Trp	Leu	Ser 1110		Ala	Arg
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Phe	Gly 1130		> Val	. Val	. Ala	Leu 1135		Pro	Ala	Thr	Leu 1140		Pro	Leu
Pro	Glu 1145		g Glu	ı Ala	Pro	His 1150		Суз	Leu	Glu	Ile 1155		Ala	Glu
Thr	His 1160		7 Thr	Arg	Pro	Asp 1165		Thr	Asp	Gln	Pro 1170		Pro	Asp
Ala	Asp 1175		r Thr	Trp) Tyr	Thr 1180		Gly	Ser	Ser	Phe 1185	Leu	Gln	Glu
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Lys	Leu 1235		n Val	. Tyr	Thr	Asp 1240		Arg	Tyr	Ala	Phe 1245	Ala	Thr	Ala
His	Val 1250		a Gly	/ Glu	l Ile	Tyr 1255		Arg	Arg	Gly	Leu 1260	Leu	Thr	Ser
Glu	Gly 1265		g Glu	l Il∈	e Lys	Asn 1270		Asn	Glu	Ile	Leu 1275	Ala	Leu	Leu
Lys	Ala 1280		ı Phe	e Leu	l Pro	Lys 1285	-	Leu	Ser	Ile	Ile 1290	His	СЛа	Pro
Gly	His 1295		n Lys	g Gly	' Asn	Ser 1300		Glu	Ala	Arg	Gly 1305	Asn	Arg	Met
Ala	Asp 1310		n Ala	ı Ala	. Arg	Glu 1315		Ala	Met	Lys	Ala 1320		Leu	Glu
Thr	Ser 1325		: Leu	ı Leu	l Ile	Glu 1330		Ser	Thr	Pro	Tyr 1335	Thr	Pro	Pro

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Leu	His 1385	Arg	Leu	Thr	His	Leu 1390		Pro	Gln	Lys	Met 1395	Lys	Ala	Leu
Leu	Asp 1400	Arg	Glu	Glu	Ser	Pro 1405		Tyr	Met	Leu	Asn 1410	Arg	Asp	Arg
Thr	Ile 1415	Gln	Tyr	Val	Thr	Glu 1420		Cys	Thr	Ala	Cys 1425	Ala	Gln	Val
Asn	Ala 1430	Ser	Lys	Ala	Lys	Ile 1435	Gly	Ala	Gly	Val	Arg 1440	Val	Arg	Gly
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Phe	Ser 1475	Gly	Trp	Val	Glu	Ala 1480	Phe	Pro	Thr	Lys	Arg 1485	Glu	Thr	Ala
Lys	Val 1490	Val	Ser	Lys	Lys	Leu 1495	Leu	Glu	Asp	Ile	Phe 1500	Pro	Arg	Phe
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Val	Ser	Arg 195	Leu	Arg	Gly	Arg	Arg 200	Asp	Pro	Pro	Ala	Ala 205	Asp	Ser	Thr	
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Arg	Lys 290	Ala	Val	Arg	Gly	Asn 295	Aab	Gly	Arg	Pro	Thr 300	Gln	Leu	Pro	Asn	
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Thr	Thr	Glu	Gly	Arg 325	Asn	His	Leu	Val	Leu 330	Tyr	Arg	Gln	Leu	Leu 335	Leu	
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Gl	ı Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
Ly	9 Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
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Ly	a yab	Cys 515	Pro	Lys	LÀa	Pro	Arg 520	Gly	Pro	Arg	Gly	Pro 525	Arg	Pro	Gln
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Ala	Pro	Ala	Asn 340	Cys	Ser	Val	Thr	Ser 345	Gln	His	Lys	Leu	Thr 350	Leu	Ser
Glu	Val	Thr 355	Gly	Gln	Gly	Leu	Сув 360	Ile	Gly	Ala	Val	Pro 365	Lys	Thr	His
Gln	Ala 370	Leu	Сүз	Asn	Thr	Thr 375	Gln	Lys	Thr	Ser	Asp 380	Gly	Ser	Tyr	Tyr
Leu 385	Ala	Ser	Pro	Ala	Gly 390	Thr	Ile	Trp	Ala	Сув 395	Ser	Thr	Gly	Leu	Thr 400
Pro	Cys	Leu	Ser	Thr 405	Thr	Val	Leu	Asn	Leu 410	Thr	Thr	Asp	Tyr	Cys 415	Val
Leu	Val	Glu	Leu 420	Trp	Pro	Lys	Val	Thr 425	Tyr	His	Ser	Pro	Asn 430	Tyr	Val
Tyr	Gly	Gln 435	Phe	Glu	Lys	Lys	Thr 440	Lys	Tyr	Гла	Arg	Glu 445	Pro	Val	Ser
Leu	Thr 450	Leu	Ala	Leu	Leu	Leu 455	Gly	Gly	Leu	Thr	Met 460	Gly	Gly	Ile	Ala
Ala 465	Gly	Val	Gly	Thr	Gly 470	Thr	Thr	Ala	Leu	Val 475	Ala	Thr	Гла	Gln	Phe 480
Glu	Gln	Leu	Gln	Ala 485	Ala	Ile	His	Thr	Asp 490	Leu	Gly	Ala	Leu	Glu 495	Lys
Ser	Val	Ser	Ala 500	Leu	Glu	Lys	Ser	Leu 505	Thr	Ser	Leu	Ser	Glu 510	Val	Val
Leu	Gln	Asn 515	Arg	Arg	Gly	Leu	Asp 520	Leu	Leu	Phe	Leu	Lys 525	Glu	Gly	Gly
Leu	Сув 530	Ala	Ala	Leu	ГЛа	Glu 535	Glu	Сув	Сув	Phe	Tyr 540	Ala	Asp	His	Thr
Gly 545	Val	Val	Arg	Asp	Ser 550	Met	Ala	ГÀа	Leu	Arg 555	Glu	Arg	Leu	Asn	Gln 560
Arg	Gln	Lys	Leu	Phe 565	Glu	Ser	Arg	Gln	Gly 570	Trp	Phe	Glu	Gly	Leu 575	Phe

Asn Arg Ser Pro Trp Phe Thr Thr Leu Ile Ser Thr Ile Met Gly Pro Leu Ile Val Leu Leu Leu Leu Leu Phe Gly Pro Cys Ile Leu Asn Arg Leu Val Gln Phe Val Lys Asp Arg Ile Ser Val Val Gln Ala Leu Val Leu Thr Gln Gln Tyr His Gln Leu Lys Ser Ile Asp Pro Glu Glu 625 630 Val Glu Ser Arg Glu <210> SEQ ID NO 43 <211> LENGTH: 1733 <212> TYPE: PRT <213> ORGANISM: Xenotropic MuLV-related Virus VP62 <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (537)..(537) $<\!223\!>$ OTHER INFORMATION: Xaa can be any naturally occurring amino acid <400> SEOUENCE: 43 Met Gly Gln Thr Val Thr Thr Pro Leu Ser Leu Thr Leu Gln His Trp Gly Asp Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro Ala Leu Thr Pro Ser Ile Lys Ser Lys Pro Pro Lys Pro Gln 130 135 Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp Pro Pro Pro Tyr Gly Ala Gln Pro Ser Ser Ser Ala Arg Glu Asn Asn Glu Glu Glu Ala Ala Thr Thr Ser Glu Val Ser Pro Pro Ser Pro Met Val Ser Arg Leu Arg Gly Arg Arg Asp Pro Pro Ala Ala Asp Ser Thr Thr Ser Gln Ala Phe Pro Leu Arg Met Gly Gly Asp Gly Gln Leu Gln Tyr Trp Pro Phe Ser Ser Ser Asp Leu Tyr Asn Trp Lys Asn Asn Asn Pro Ser Phe Ser Glu Asp Pro Gly Lys Leu Thr Ala Leu Ile Glu Ser Val Leu Ile Thr His Gln Pro Thr Trp Asp Asp Cys Gln Gln Leu Leu

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Glγ	7 Thr	Leu 275	Leu	Thr	Gly	Glu	Glu 280	Lys	Gln	Arg	Val	Leu 285	Leu	Glu	Ala
Arg	1 Lys 290	Ala	Val	Arg	Gly	Asn 295	Asp	Gly	Arg	Pro	Thr 300	Gln	Leu	Pro	Asn
Glu 305	ı Val	Asn	Ala	Ala	Phe 310	Pro	Leu	Glu	Arg	Pro 315	Asp	Trp	Asp	Tyr	Thr 320
Thi	Thr	Glu	Gly	Arg 325	Asn	His	Leu	Val	Leu 330	Tyr	Arg	Gln	Leu	Leu 335	Leu
Ala	u Gly	Leu	Gln 340	Asn	Ala	Gly	Arg	Ser 345	Pro	Thr	Asn	Leu	Ala 350	Lys	Val
Lys	g Gly	Ile 355	Thr	Gln	Gly	Pro	Asn 360	Glu	Ser	Pro	Ser	Ala 365	Phe	Leu	Glu
Arg	j Leu 370	Lys	Glu	Ala	Tyr	Arg 375	Arg	Tyr	Thr	Pro	Tyr 380	Asp	Pro	Glu	Asp
Pro 385	Gly	Gln	Glu	Thr	Asn 390	Val	Ser	Met	Ser	Phe 395	Ile	Trp	Gln	Ser	Ala 400
Pro	Asp	Ile	Gly	Arg 405	ГЛа	Leu	Glu	Arg	Leu 410	Glu	Asp	Leu	Lys	Ser 415	Lys
Thi	: Leu	Gly	Asp 420	Leu	Val	Arg	Glu	Ala 425	Glu	ГÀа	Ile	Phe	Asn 430	Lys	Arg
Glu	ı Thr	Pro 435	Glu	Glu	Arg	Glu	Glu 440	Arg	Ile	Arg	Arg	Glu 445	Ile	Glu	Glu
Lys	Glu 450	Glu	Arg	Arg	Arg	Ala 455	Glu	Asp	Glu	Gln	Arg 460	Glu	Arg	Glu	Arg
Asp 465	Arg	Arg	Arg	His	Arg 470	Glu	Met	Ser	Lys	Leu 475	Leu	Ala	Thr	Val	Val 480
Ile	e Gly	Gln	Arg	Gln 485	Asp	Arg	Gln	Gly	Gly 490	Glu	Arg	Arg	Arg	Pro 495	Gln
Leu	ı Asp	Lys	Asp 500	Gln	Суз	Ala	Tyr	Cys 505	Lys	Glu	Lys	Gly	His 510	Trp	Ala
Lys	Asp	Cys 515	Pro	Lys	Lys	Pro	Arg 520	Gly	Pro	Arg	Gly	Pro 525	Arg	Pro	Gln
Thi	Ser 530	Leu	Leu	Thr	Leu	Gly 535	Asp	Xaa	Gly	Gly	Gln 540	Gly	Gln	Glu	Pro
Pro 545	Pro	Glu	Pro	Arg	Ile 550	Thr	Leu	Lys	Val	Gly 555	Gly	Gln	Pro	Val	Thr 560
Phe	e Leu	Val	Asp	Thr 565	Gly	Ala	Gln	His	Ser 570	Val	Leu	Thr	Gln	Asn 575	Pro
Glγ	/ Pro	Leu	Ser 580	Asp	Lys	Ser	Ala	Trp 585	Val	Gln	Gly	Ala	Thr 590	Gly	Gly
Lys	Arg	Tyr 595	Arg	Trp	Thr	Thr	Asp 600	Arg	Lys	Val	His	Leu 605	Ala	Thr	Gly
Lys	8 Val 610	Thr	His	Ser	Phe	Leu 615	His	Val	Pro	Asp	Cys 620	Pro	Tyr	Pro	Leu
Leu 625	ı Gly	Arg	Asp	Leu	Leu 630	Thr	Lys	Leu	Lys	Ala 635	Gln	Ile	His	Phe	Glu 640
Glγ	/ Ser	Gly	Ala	Gln 645	Val	Val	Gly	Pro	Met 650	Gly	Gln	Pro	Leu	Gln 655	Val
Leu	ı Thr	Leu	Asn 660	Ile	Glu	Asp	Glu	Tyr 665	Arg	Leu	His	Glu	Thr 670	Ser	Lys
Glu	ı Pro	Asp	Val	Pro	Leu	Gly	Ser	Thr	Trp	Leu	Ser	Asp	Phe	Pro	Gln

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		675					680					685			
Ala	Trp 690	Ala	Glu	Thr	Gly	Gly 695	Met	Gly	Leu	Ala	Val 700	Arg	Gln	Ala	Pro
Leu 705	Ile	Ile	Pro	Leu	Lys 710	Ala	Thr	Ser	Thr	Pro 715	Val	Ser	Ile	Lys	Gln 720
Tyr	Pro	Met	Ser	Gln 725	Glu	Ala	Arg	Leu	Gly 730	Ile	ГЛа	Pro	His	Ile 735	Gln
Arg	Leu	Leu	Asp 740	Gln	Gly	Ile	Leu	Val 745	Pro	Сүз	Gln	Ser	Pro 750	Trp	Asn
Thr	Pro	Leu 755	Leu	Pro	Val	Lys	Lys 760	Pro	Gly	Thr	Asn	Asp 765	Tyr	Arg	Pro
Val	Gln 770	Asp	Leu	Arg	Glu	Val 775	Asn	Lys	Arg	Val	Glu 780	Asp	Ile	His	Pro
Thr 785	Val	Pro	Asn	Pro	Tyr 790	Asn	Leu	Leu	Ser	Gly 795	Leu	Pro	Pro	Ser	His 800
Gln	Trp	Tyr	Thr	Val 805	Leu	Asp	Leu	Lys	Asp 810	Ala	Phe	Phe	Сув	Leu 815	Arg
Leu	His	Pro	Thr 820	Ser	Gln	Pro	Leu	Phe 825	Ala	Phe	Glu	Trp	Arg 830	Asp	Pro
Glu	Met	Gly 835	Ile	Ser	Gly	Gln	Leu 840	Thr	Trp	Thr	Arg	Leu 845	Pro	Gln	Gly
Phe	Lys 850	Asn	Ser	Pro	Thr	Leu 855	Phe	Asp	Glu	Ala	Leu 860	His	Arg	Asp	Leu
Ala 865	Asp	Phe	Arg	Ile	Gln 870	His	Pro	Asp	Leu	Ile 875	Leu	Leu	Gln	Tyr	Val 880
Asp	Asp	Leu	Leu	Leu 885	Ala	Ala	Thr	Ser	Glu 890	Gln	Asp	Суз	Gln	Arg 895	Gly
Thr	Arg	Ala	Leu 900	Leu	Gln	Thr	Leu	Gly 905	Asn	Leu	Gly	Tyr	Arg 910	Ala	Ser
Ala	Lys	Lys 915	Ala	Gln	Ile	Сүз	Gln 920	Lys	Gln	Val	Lys	Tyr 925	Leu	Gly	Tyr
Leu	Leu 930	Lys	Glu	Gly	Gln	Arg 935	Trp	Leu	Thr	Glu	Ala 940	Arg	Lys	Glu	Thr
Val 945	Met	Gly	Gln	Pro	Thr 950	Pro	Lys	Thr	Pro	Arg 955	Gln	Leu	Arg	Glu	Phe 960
Leu	Gly	Thr	Ala	Gly 965	Phe	Сүз	Arg	Leu	Trp 970	Ile	Pro	Gly	Phe	Ala 975	Glu
Met	Ala	Ala	Pro 980	Leu	Tyr	Pro	Leu	Thr 985	Lys	Thr	Gly	Thr	Leu 990	Phe	Asn
Trp	Gly	Pro 995	Asp	Gln	Gln	Lys	Ala 1000		r Glı	n Glu	ı Ile	e Ly: 100		ln A	la Leu
Leu	Thr 1010		a Pro	o Ala	a Leu	1 Gl 103		eu Pi	ro As	зр Le		hr 1 020	Lys I	Pro I	Phe
Glu	Leu 1025		∋ Val	l Asj	ọ Glư	1 Ly: 103		ln G	ly Ty	yr Ai		ys (035	Gly V	/al I	Leu
Thr	Gln 1040		s Leu	ı Gly	y Pro	5 Trj 104		rg Ai	rg Pi	ro Va		la ' 050	Fyr I	Seu S	Ser
Lys	Lys 1055		ı Ası	o Pro	o Val	l Ala 100		la Gi	ly Ti	rp P:		ro (065	Cys I	leu A	Arg
Met	Val 1070		a Ala	a Ile	e Ala	a Va: 10'		∋u Tł	nr Ly	ys Ai	-	la (080	Gly I	'ya I	Leu

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													10.00	-
Thr	Met 1085	-	Gln	Pro	Leu	Val 1090	Ile	Leu	Ala	Pro	His 1095	Ala	Val	Glu
Ala	Leu 1100		Гла	Gln	Pro	Pro 1105	Asp	Arg	Trp	Leu	Ser 1110	Asn	Ala	Arg
Met	Thr 1115	His	Tyr	Gln	Ala	Met 1120	Leu	Leu	Asp	Thr	Asp 1125	Arg	Val	Gln
Phe	Gly 1130	Pro	Val	Val	Ala	Leu 1135	Asn	Pro	Ala	Thr	Leu 1140	Leu	Pro	Leu
Pro	Glu 1145	-	Glu	Ala	Pro	His 1150	Asp	Суз	Leu	Glu	Ile 1155	Leu	Ala	Glu
Thr	His 1160		Thr	Arg	Pro	Asp 1165	Leu	Thr	Asp	Gln	Pro 1170	Ile	Pro	Asp
Ala	Asp 1175	Tyr	Thr	Trp	Tyr	Thr 1180	Asp	Gly	Ser	Ser	Phe 1185	Leu	Gln	Glu
Gly	Gln 1190	-	Arg	Ala	Gly	Ala 1195	Ala	Val	Thr	Thr	Glu 1200	Thr	Glu	Val
Ile	Trp 1205	Ala	Arg	Ala	Leu	Pro 1210	Ala	Gly	Thr	Ser	Ala 1215	Gln	Arg	Ala
Glu	Leu 1220	Ile	Ala	Leu	Thr	Gln 1225	Ala	Leu	Lys	Met	Ala 1230	Glu	Gly	Lys
Lys	Leu 1235	Asn	Val	Tyr	Thr	Asp 1240	Ser	Arg	Tyr	Ala	Phe 1245	Ala	Thr	Ala
His	Val 1250	His	Gly	Glu	Ile	Tyr 1255	Arg	Arg	Arg	Gly	Leu 1260	Leu	Thr	Ser
Glu	Gly 1265	Arg	Glu	Ile	Lys	Asn 1270	Lys	Asn	Glu	Ile	Leu 1275	Ala	Leu	Leu
Lys	Ala 1280	Leu	Phe	Leu	Pro	Lys 1285	Arg	Leu	Ser	Ile	Ile 1290	His	Суз	Pro
Gly	His 1295	Gln	Lys	Gly	Asn	Ser 1300	Ala	Glu	Ala	Arg	Gly 1305	Asn	Arg	Met
Ala	Asp 1310	Gln	Ala	Ala	Arg	Glu 1315	Ala	Ala	Met	Lys	Ala 1320	Val	Leu	Glu
Thr	Ser 1325	Thr	Leu	Leu	Ile	Glu 1330	Asp	Ser	Thr	Pro	Tyr 1335	Thr	Pro	Pro
His	Phe 1340	His	Tyr	Thr	Glu	Thr 1345	Asp	Leu	Lys	Arg	Leu 1350	Arg	Glu	Leu
Gly	Ala 1355	Thr	Tyr	Asn	Gln	Thr 1360	Lys	Gly	Tyr	Trp	Val 1365	Leu	Gln	Gly
Lys	Pro 1370		Met	Pro	Aab	Gln 1375	Ser	Val	Phe	Glu	Leu 1380	Leu	Asp	Ser
Leu	His 1385		Leu	Thr	His	Leu 1390	Ser	Pro	Gln	Lys	Met 1395	-	Ala	Leu
Leu	Asp 1400		Glu	Glu	Ser	Pro 1405	Tyr	Tyr	Met	Leu	Asn 1410	Arg	Asp	Arg
Thr	Ile 1415	Gln	Tyr	Val	Thr	Glu 1420	Thr	Сув	Thr	Ala	Cys 1425	Ala	Gln	Val
Asn	Ala 1430	Ser	ГЛа	Ala	Lys	Ile 1435	Gly	Ala	Gly	Val	Arg 1440	Val	Arg	Gly
His	Arg 1445	Pro	Gly	Thr	His	Trp 1450	Glu	Val	Asp	Phe	Thr 1455	Glu	Val	Lys
Pro	Gly 1460	Leu	Tyr	Gly	Tyr	Lys 1465	Tyr	Leu	Leu	Val	Phe 1470	Val	Asp	Thr

Phe Ser Gly Trp	Val Glu Ala		Lys Arg Glu Thr Ala
1475	1480		1485
Lys Val Val Ser	Lys Lys Leu		Ile Phe Pro Arg Phe
1490	1495		1500
Gly Met Pro Gln	. Val Leu Gly		Gly Pro Ala Phe Ala
1505	1510		1515
Ser Gln Val Ser	Gln Ser Val		Leu Gly Ile Asp Trp
1520	1525		1530
Lys Leu His Cys	Ala Tyr Arg		Ser Gly Gln Val Glu
1535	1540		1545
Arg Met Asn Arg	Thr Ile Lys		Ihr Lys Leu Thr Leu
1550	1555		1560
Ala Ser Gly Thr	Arg Asp Trp		Leu Pro Leu Ala Leu
1565	1570		1575
Tyr Arg Ala Arg	Asn Thr Pro		Gly Leu Thr Pro Tyr
1580	1585		1590
Glu Ile Leu Tyr	Gly Ala Pro		Val Asn Phe His Asp
1595	1600		1605
Pro Glu Met Ser	Lys Leu Thr		Ser Leu Gln Ala His
1610	1615		1620
Leu Gln Ala Leu	Gln Ala Val		Val Trp Lys Pro Leu
1625	1630		1635
Ala Ala Ala Tyr	Gln Asp Gln	-	Pro Val Ile Pro His
1640	1645		1650
Pro Phe Arg Val	Gly Asp Ala	-	Arg Arg His Gln Thr
1655	1660		1665
Lys Asn Leu Glu	Pro Arg Trp		Fyr Thr Val Leu Leu
1670	1675		1680
Thr Thr Pro Thr	Ala Leu Lys		Ile Ser Ala Trp Ile
1685	1690		1695
His Ala Ala His	Val Lys Ala		Pro Pro Ala Gly Thr
1700	1705		1710
Ala Trp Lys Val	Gln Arg Ser		Leu Lys Ile Arg Leu
1715	1720		1725
Thr Arg Gly Ala 1730	Pro		
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-	Val Thr Thr P	ro Leu Ser Le	ı Thr Leu Gln His Trp
	5	10	15
Gly Asp Val Gln .	Arg Ile Ala S	er Asn Gln Se:	r Val Asp Val Lys Lys
20		25	30
Arg Arg Trp Val	Thr Phe Cys S	-	o Pro Thr Phe Asn Val
35	4		45
Gly Trp Pro Gln .	Asp Gly Thr P	he Asn Leu Gly	y Val Ile Ser Gln Val
50	55		60
Lys Ser Arg Val	Phe Cys Pro G	ly Pro His Gly	y His Pro Asp Gln Val
65	70	75	80

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	- $ -$	11C	TTT	.uc	-0

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

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Leu Asp Lys Asp Gln Cys Ala Tyr Cys Lys Glu Lys Gly His Trp Ala Lys Asp Cys Pro Lys Lys Pro Arg Gly Pro Arg Gly Pro Arg Pro Gln Thr Ser Leu Leu Thr Leu Gly Asp <210> SEQ ID NO 45 <211> LENGTH: 645 <212> TYPE: PRT <213> ORGANISM: Xenotropic MuLV-related Virus VP62 <400> SEOUENCE: 45 Met Glu Ser Pro Ala Phe Ser Lys Pro Leu Lys Asp Lys Ile Asn Pro Trp Gly Pro Leu Ile Ile Met Gly Ile Leu Val Arg Ala Gly Ala Ser Val Gln Arg Asp Ser Pro His Gln Val Phe Asn Val Thr Trp Lys Ile Thr Asn Leu Met Thr Gly Gln Thr Ala Asn Ala Thr Ser Leu Leu Gly Thr Met Thr Asp Thr Phe Pro Lys Leu Tyr Phe Asp Leu Cys Asp Leu Val Gly Asp Asn Trp Asp Asp Pro Glu Pro Asp Ile Gly Asp Gly Cys Arg Ser Pro Gly Gly Arg Lys Arg Thr Arg Leu Tyr Asp Phe Tyr Val Cys Pro Gly His Thr Val Leu Thr Gly Cys Gly Gly Pro Arg Glu Gly Tyr Cys Gly Lys Trp Gly Cys Glu Thr Thr Gly Gln Ala Tyr Trp Lys $% \left({{\left[{{{\rm{Cys}}} \right]}_{\rm{T}}}} \right)$ Pro Ser Ser Ser Trp Asp Leu Ile Ser Leu Lys Arg Gly Asn Thr Pro Lys Gly Gln Gly Pro Cys Phe Asp Ser Ser Val Gly Ser Gly Ser Ile 165 170 175 Gln Gly Ala Thr Pro Gly Gly Arg Cys Asn Pro Leu Val Leu Glu Phe Thr Asp Ala Gly Lys Arg Ala Ser Trp Asp Ala Pro Lys Thr Trp Gly Leu Arg Leu Tyr Arg Ser Thr Gly Ala Asp Pro Val Thr Leu Phe Ser Leu Thr Arg Gln Val Leu Asn Val Gly Pro Arg Val Pro Ile Gly Pro Asn Pro Val Ile Thr Glu Gln Leu Pro Pro Ser Gln Pro Val Gln Ile Met Leu Pro Arg Thr Pro Arg Pro Pro Pro Ser Gly Ala Ala Ser Met Val Pro Gly Ala Pro Pro Pro Ser Gln Gln Pro Gly Thr Gly Asp Arg Leu Leu Asn Leu Val Glu Gly Ala Tyr Leu Ala Leu Asn Leu Thr Ser Pro Asp Lys Thr Gln Glu Cys Trp Leu Cys Leu Val Ser Gly Pro Pro

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305					310					315					320
Tyr	Tyr	Glu	Gly	Val 325	Ala	Val	Leu	Gly	Thr 330	-	Ser	Asn	His	Thr 335	Ser
Ala	Pro	Ala	Asn 340		Ser	Val	Thr	Ser 345	Gln	His	Lys	Leu	Thr 350	Leu	Ser
Glu	Val	Thr 355	Gly	Gln	Gly	Leu	Суз 360	Ile	Gly	Ala	Val	Pro 365	Lys	Thr	His
Gln	Ala 370	Leu	Сүз	Asn	Thr	Thr 375	Gln	Lys	Thr	Ser	Asp 380	Gly	Ser	Tyr	Tyr
Leu 385	Ala	Ser	Pro	Ala	Gly 390		Ile	Trp	Ala	Суз 395	Ser	Thr	Gly	Leu	Thr 400
Pro	Cys	Leu	Ser	Thr 405	Thr	Val	Leu	Asn	Leu 410	Thr	Thr	Asp	Tyr	Cys 415	Val
Leu	Val	Glu	Leu 420	Trp	Pro	ГЛа	Val	Thr 425	Tyr	His	Ser	Pro	Asn 430	Tyr	Val
Tyr	Gly	Gln 435	Phe		Lys	Lys	Thr 440	Гла	Tyr	Lys	Arg	Glu 445	Pro	Val	Ser
Leu	Thr 450	Leu	Ala	Leu	Leu	Leu 455	Gly	Gly	Leu	Thr	Met 460	Gly	Gly	Ile	Ala
Ala 465	Gly	Val	Gly	Thr	Gly 470	Thr	Thr	Ala	Leu	Val 475	Ala	Thr	Lys	Gln	Phe 480
Glu	Gln	Leu	Gln	Ala 485	Ala	Ile	His	Thr	Asp 490	Leu	Gly		Leu	Glu 495	Lys
Ser	Val	Ser	Ala 500	Leu	Glu	Lys	Ser	Leu 505	Thr	Ser	Leu	Ser	Glu 510	Val	Val
Leu	Gln	Asn 515	Arg		Gly	Leu	Asp 520	Leu	Leu	Phe	Leu	Lys 525	Glu	Gly	Gly
Leu	Cys 530	Ala	Ala	Leu	Lys	Glu 535	Glu	Суз	Суз	Phe	Tyr 540	Ala	Asp	His	Thr
Gly 545	Val	Val	Arg	Asp	Ser 550	Met	Ala		Leu	Arg 555	Glu	Arg	Leu	Asn	Gln 560
Arg	Gln	Гла	Leu	Phe 565	Glu	Ser	Gly	Gln	Gly 570	Trp	Phe	Glu	Gly	Leu 575	Phe
Asn	Arg	Ser	Pro 580		Phe	Thr	Thr	Leu 585	Ile	Ser	Thr	Ile	Met 590	Gly	Pro
Leu	Ile	Val 595	Leu	Leu	Leu	Ile	Leu 600	Leu	Phe	Gly	Pro	Суз 605	Ile	Leu	Asn
Arg	Leu 610	Val	Gln	Phe	Val	Lys 615	Asp	Arg	Ile	Ser	Val 620	Val	Gln	Ala	Leu
Val 625	Leu	Thr	Gln	Gln	Tyr 630	His	Gln	Leu	Lys	Ser 635	Ile	Asp	Pro	Glu	Glu 640
Val	Glu	Ser	Arg	Glu 645											
<211 <212 <213 <220 <221 <222	.> LH :> T) :> OH :> OH :> NH :> LO	ENGTI (PE : RGAN) EATUI AME / I OCAT	ISM: RE: KEY: ION:	733 Xeno miso (53	otroj c_fea 7)	ature (537	e)								
					TION	: Xa	a cai	n be	any	nati	ural	ту о	ccur	ring	amin
<400)> SI	EQUEI	ICE :	46											

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												COIL	υIII	ueu	
Met 1	Gly	Gln	Thr	Val 5	Thr	Thr	Pro	Leu	Ser 10	Leu	Thr	Leu	Gln	His 15	Trp
Gly	Asp	Val	Gln 20	Arg	Ile	Ala	Ser	Asn 25	Gln	Ser	Val	Asp	Val 30	Lys	Lys
Arg	Arg	Trp 35	Val	Thr	Phe	Сүз	Ser 40	Ala	Glu	Trp	Pro	Thr 45	Phe	Asn	Val
Gly	Trp 50	Pro	Gln	Asp	Gly	Thr 55	Phe	Asn	Leu	Gly	Val 60	Ile	Ser	Gln	Val
Lys 65	Ser	Arg	Val	Phe	Cys 70	Pro	Gly	Pro	His	Gly 75	His	Pro	Asp	Gln	Val 80
Pro	Tyr	Ile	Val	Thr 85	Trp	Glu	Ala	Leu	Ala 90	Tyr	Asp	Pro	Pro	Pro 95	Trp
Val	Lys	Pro	Phe 100	Val	Ser	Pro	Lys	Pro 105	Pro	Pro	Leu	Pro	Thr 110	Ala	Pro
Val	Leu	Pro 115	Pro	Gly	Pro	Ser	Ala 120	Gln	Pro	Pro	Ser	Arg 125	Ser	Ala	Leu
Tyr	Pro 130	Ala	Leu	Thr	Pro	Ser 135	Ile	Lys	Ser	Lys	Pro 140	Pro	Lys	Pro	Gln
Val 145	Leu	Pro	Asp	Ser	Gly 150	Gly	Pro	Leu	Ile	Asp 155	Leu	Leu	Thr	Glu	Asp 160
	Pro	Pro	Tyr	Gly 165		Gln	Pro	Ser	Ser 170		Ala	Arg	Glu	Asn 175	
Glu	Glu	Glu	Ala 180		Thr	Thr	Ser	Glu 185	Val	Ser	Pro	Pro	Ser 190	Pro	Met
Val	Ser	Arg 195		Arg	Gly	Arg	Arg 200		Pro	Pro	Ala	Ala 205	Asp	Ser	Thr
Thr	Ser 210		Ala	Phe	Pro	Leu 215	Arg	Met	Gly	Gly	Asp 220	Gly	Gln	Leu	Gln
Tyr 225	Trp	Pro	Phe	Ser	Ser 230	Ser	Asp	Leu	Tyr	Asn 235	Trp	Lys	Asn	Asn	Asn 240
	Ser	Phe	Ser	Glu 245		Pro	Gly	Lys	Leu 250		Ala	Leu	Ile	Glu 255	
Val	Leu	Ile	Thr 260		Gln	Pro	Thr	Trp 265	Asp	Asp	Сүз	Gln	Gln 270		Leu
Gly	Thr	Leu 275		Thr	Gly	Glu	Glu 280			Arg	Val	Leu 285		Glu	Ala
Arg			Val	Arg	Gly			Gly	Arg	Pro	Thr		Leu	Pro	Asn
	290 Val	Asn	Ala	Ala		295 Pro	Leu	Glu	Arg		300 300	Trp	Asp	Tyr	
305 Thr	Thr	Glu	Gly	-		His	Leu	Val		-	Arg	Gln	Leu		320 Leu
Ala	Gly	Leu		325 Asn		Gly	Arg		330 Pro		Asn	Leu		332 Lys	Val
Lys	Gly	Ile	340 Thr	Gln	Gly	Pro	Asn	345 Glu	Ser	Pro	Ser	Ala	350 Phe	Leu	Glu
Arg	Leu	355 Lys	Glu	Ala	Tyr	Arg	360 Arg	Tyr	Thr	Pro	Tyr	365 Asp	Pro	Glu	Asp
Pro	370 Gly	Gln	Glu	Thr	Asn	375 Val	Ser	Met	Ser	Phe	380 Ile	Trp	Gln	Ser	Ala
385	-				390					395		-			400
0	F		1	405	<i>⊐</i> ,2		<u></u> u	9	410		L		<u> </u>	415	_1 ~

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	COILC		aco

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

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												0011	CIII			
			820					825					830			
Glu	Met	Gly 835	Ile	Ser	Gly	Gln	Leu 840	Thr	Trp	Thr	Arg	Leu 845	Pro	Gln	Gly	
Phe	Lys 850	Asn	Ser	Pro	Thr	Leu 855	Phe	Asp	Glu	Ala	Leu 860	His	Arg	Asp	Leu	
Ala 865	Asp	Phe	Arg	Ile	Gln 870	His	Pro	Asp	Leu	Ile 875	Leu	Leu	Gln	Tyr	Val 880	
Asp	Asp	Leu	Leu	Leu 885	Ala	Ala	Thr	Ser	Glu 890	Gln	Asp	Суз	Gln	Arg 895		
Thr	Arg	Ala	Leu 900	Leu	Gln	Thr	Leu	Gly 905	Asn	Leu	Gly	Tyr	Arg 910	Ala	Ser	
Ala	Lys	Lys 915	Ala	Gln	Ile	Суз	Gln 920	ГÀа	Gln	Val	ГЛа	Tyr 925	Leu	Gly	Tyr	
Leu	Leu 930	Lys	Glu	Gly	Gln	Arg 935	Trp	Leu	Thr	Glu	Ala 940	Arg	Lys	Glu	Thr	
Val 945	Met	Gly	Gln	Pro	Thr 950	Pro	Lys	Thr	Pro	Arg 955	Gln	Leu	Arg	Glu	Phe 960	
Leu	Gly	Thr	Ala	Gly 965	Phe	Сүз	Arg	Leu	Trp 970	Ile	Pro	Gly	Phe	Ala 975		
Met	Ala	Ala	Pro 980	Leu	Tyr	Pro	Leu	Thr 985	ГЛа	Thr	Gly	Thr	Leu 990	Phe	Asn	
Trp	Gly	Pro 995	Asp	Gln	Gln	Lys	Ala 1000		r Glı	n Glu	ı Ile	e Ly 10		ln A	la Leu	
Leu	Thr 1010		a Pro	> Ala	. Leu	ι Glչ 101		eu P:	ro A:	зр Le		hr 1 020	Lys (Pro	Phe	
Glu	Leu 1025		e Val	. Asp	o Glu	ι Ly: 103		ln G	ly Ty	vr Al		ys (035	Gly '	Val	Leu	
Thr	Gln 1040		s Leu	ı Gly	Pro	0 Trp 104		rg A:	rg Pi	co Va		la 050	Tyr :	Leu	Ser	
ГЛа	Lys 1055		ı Asp) Pro	val	. Ala 106		la G	ly Ti	rp Pi		ro 065	Сув	Leu	Arg	
Met	Val 1070		ı Ala	a Ile	e Ala	107 107		eu Tl	nr Ly	/s As		la (080	Gly :	Lya	Leu	
	Met 1085	5				109	90		eu Al		1	095				
Ala	Leu 1100			3 Glr	ı Pro) Pro 110		ab Y:	rg Ti	тр Le		er 1 110	Asn .	Ala	Arg	
Met	Thr 1115		; Tyr	Glr.	ı Ala	112 Met		eu Le	eu As	ap Tł		ap 1 125	Arg `	Val	Gln	
Phe	Gly 1130		> Val	. Val	. Ala	113 Leu		sn P:	ro Al	la Tł		eu 140	Leu :	Pro	Leu	
Pro	Glu 1145		s Glu	ı Ala	l Pro) His 115		ab Ci	ys L€	eu GI		le 155	Leu J	Ala	Glu	
Thr	His 1160		7 Thr	r Arg	Pro) Asp 116		eu Tl	nr Af	ap GI		ro 170	Ile	Pro	Asp	
Ala	Asp 1175		r Thr	Trp	o Tyr	Th: 118		ap Gi	ly Se	er Se		he 185	Leu (Gln	Glu	
Gly	Gln 1190		y Arg	j Ala	Gly	7 Ala 119		la Va	al Tł	ır Tł		lu 200	Thr (Glu	Val	
Ile	Trp 1205		a Arg	g Ala	. Leu	121		la G	ly Th	nr Se		la (215	Gln J	Arg	Ala	

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Glu	Leu 1220	Ile	Ala	Leu	Thr	Gln 1225	Ala	Leu	Lys	Met	Ala 1230	Glu	Gly	Гуз
Lys	Leu 1235	Asn	Val	Tyr	Thr	Asp 1240	Ser	Arg	Tyr	Ala	Phe 1245	Ala	Thr	Ala
His	Val 1250	His	Gly	Glu	Ile	Tyr 1255	Arg	Arg	Arg	Gly	Leu 1260	Leu	Thr	Ser
Glu	Gly 1265	Arg	Glu	Ile	Lys	Asn 1270	Lys	Asn	Glu	Ile	Leu 1275	Ala	Leu	Leu
ГЛа	Ala 1280	Leu	Phe	Leu	Pro	Lys 1285	Arg	Leu	Ser	Ile	Ile 1290	His	Суз	Pro
Gly	His 1295	Gln	Lys	Gly	Asn	Ser 1300	Ala	Glu	Ala	Arg	Gly 1305	Asn	Arg	Met
Ala	Asp 1310	Gln	Ala	Ala	Arg	Glu 1315	Ala	Ala	Met	Lys	Ala 1320	Val	Leu	Glu
Thr	Ser 1325	Thr	Leu	Leu	Ile	Glu 1330	Asp	Ser	Thr	Pro	Tyr 1335	Thr	Pro	Pro
His	Phe 1340	His	Tyr	Thr	Glu	Thr 1345	Asp	Leu	Lys	Arg	Leu 1350	Arg	Glu	Leu
Gly	Ala 1355	Thr	Tyr	Asn	Gln	Thr 1360	Lys	Gly	Tyr	Trp	Val 1365	Leu	Gln	Gly
Гла	Pro 1370	Val	Met	Pro	Asp	Gln 1375	Ser	Val	Phe	Glu	Leu 1380	Leu	Asp	Ser
Leu	His 1385	Arg	Leu	Thr	His	Leu 1390	Ser	Pro	Gln	Lys	Met 1395	Lys	Ala	Leu
Leu	Asp 1400	Arg	Glu	Glu	Ser	Pro 1405	Tyr	Tyr	Met	Leu	Asn 1410	Arg	Asp	Arg
Thr	Ile 1415	Gln	Tyr	Val	Thr	Glu 1420	Thr	Суз	Thr	Ala	Cys 1425	Ala	Gln	Val
Asn	Ala 1430	Ser	Lys	Ala	Lys	Ile 1435	Gly	Ala	Gly	Val	Arg 1440	Val	Arg	Gly
His	Arg 1445	Pro	Gly	Thr	His	Trp 1450	Glu	Val	Asp	Phe	Thr 1455	Glu	Val	Гля
Pro	Gly 1460	Leu	Tyr	Gly	Tyr	Lys 1465	Tyr	Leu	Leu	Val	Phe 1470	Val	Asp	Thr
Phe	Ser 1475	Gly	Trp	Val	Glu	Ala 1480	Phe	Pro	Thr	ГЛа	Arg 1485	Glu	Thr	Ala
ГÀа	Val 1490	Val	Ser	Гла	Lys	Leu 1495	Leu	Glu	Asp	Ile	Phe 1500	Pro	Arg	Phe
Gly	Met 1505	Pro	Gln	Val	Leu	Gly 1510	Ser	Asp	Asn	Gly	Pro 1515	Ala	Phe	Ala
Ser	Gln 1520	Val	Ser	Gln	Ser	Val 1525	Ala	Asp	Leu	Leu	Gly 1530	Ile	Asp	Trp
ГÀа	Leu 1535	His	Cys	Ala	Tyr	Arg 1540	Pro	Gln	Ser	Ser	Gly 1545	Gln	Val	Glu
Arg	Met 1550	Asn	Arg	Thr	Ile	Lys 1555	Glu	Thr	Leu	Thr	Lys 1560	Leu	Thr	Leu
Ala	Ser 1565	Gly	Thr	Arg	Asp	Trp 1570	Val	Leu	Leu	Leu	Pro 1575	Leu	Ala	Leu
Tyr	Arg 1580	Ala	Arg	Asn	Thr	Pro 1585	Gly	Pro	His	Gly	Leu 1590	Thr	Pro	Tyr
Glu	Ile 1595	Leu	Tyr	Gly	Ala	Pro 1600	Pro	Pro	Leu	Val	Asn 1605	Phe	His	Asp

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Pro Glu Met Ser Lys Leu Thr Asn Ser Pro Ser Leu Gln Ala His Leu Gln Ala Leu Gln Ala Val Gln Gln Glu Val Trp Lys Pro Leu Ala Ala Ala Tyr Gln Asp Gln Leu Asp Gln Pro Val Ile Pro His Pro Phe Arg Val Gly Asp Ala Val Trp Val Arg Arg His Gln Thr Lys Asn Leu Glu Pro Arg Trp Lys Gly Pro Tyr Thr Val Leu Leu Thr Thr Pro Thr Ala Leu Lys Val Asp Gly Ile Ser Ala Trp Ile His Ala Ala His Val Lys Ala Ala Thr Thr Pro Pro Ala Gly Thr Ala Trp Lys Val Gln Arg Ser Gln Asn Pro Leu Lys Ile Arg Leu Thr Arg Gly Ala Pro <210> SEQ ID NO 47 <211> LENGTH: 536 <212> TYPE: PRT <213> ORGANISM: Xenotropic MuLV-related Virus VP62 <400> SEOUENCE: 47 Met Gly Gln Thr Val Thr Thr Pro Leu Ser Leu Thr Leu Gln His Trp Gly Asp Val Gln Arg Ile Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Asn Val Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Gly Val Ile Ser Gln Val Lys Ser Arg Val Phe Cys Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile Val Thr Trp Glu Ala Leu Ala Tyr Asp Pro Pro Pro Trp Val Lys Pro Phe Val Ser Pro Lys Pro Pro Pro Leu Pro Thr Ala Pro Val Leu Pro Pro Gly Pro Ser Ala Gln Pro Pro Ser Arg Ser Ala Leu Tyr Pro Ala Leu Thr Pro Ser Ile Lys Ser Lys Pro Pro Lys Pro Gln Val Leu Pro Asp Ser Gly Gly Pro Leu Ile Asp Leu Leu Thr Glu Asp Pro Pro Pro Tyr Gly Ala Gln Pro Ser Ser Ser Ala Arg Glu Asn Asn Glu Glu Glu Ala Ala Thr Thr Ser Glu Val Ser Pro Pro Ser Pro Met Val Ser Arg Leu Arg Gly Arg Arg Asp Pro Pro Ala Ala Asp Ser Thr Thr Ser Gln Ala Phe Pro Leu Arg Met Gly Gly Asp Gly Gln Leu Gln

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Tyr Trp Pro Phe Ser Ser Asp Leu Tyr Asn Trp Lys Asn Asn Asn Pro Ser Phe Ser Glu Asp Pro Gly Lys Leu Thr Ala Leu Ile Glu Ser Val Leu Ile Thr His Gln Pro Thr Trp Asp Asp Cys Gln Gln Leu Leu Gly Thr Leu Leu Thr Gly Glu Glu Lys Gln Arg Val Leu Leu Glu Ala Arg Lys Ala Val Arg Gly Asn Asp Gly Arg Pro Thr Gln Leu Pro Asn Glu Val Asn Ala Ala Phe Pro Leu Glu Arg Pro Asp Trp Asp Tyr Thr Thr Thr Glu Gly Arg Asn His Leu Val Leu Tyr Arg Gln Leu Leu Leu Ala Gly Leu Gln Asn Ala Gly Arg Ser Pro Thr Asn Leu Ala Lys Val Lys Gly Ile Thr Gln Gly Pro Asn Glu Ser Pro Ser Ala Phe Leu Glu Arg Leu Lys Glu Ala Tyr Arg Arg Tyr Thr Pro Tyr Asp Pro Glu Asp Pro Gly Gln Glu Thr Asn Val Ser Met Ser Phe Ile Trp Gln Ser Ala Pro Asp Ile Gly Arg Lys Leu Glu Arg Leu Glu Asp Leu Lys Ser Lys Thr Leu Gly Asp Leu Val Arg Glu Ala Glu Lys Ile Phe Asn Lys Arg Glu Thr Pro Glu Glu Arg Glu Glu Arg Ile Arg Arg Glu Ile Glu Glu Lys Glu Glu Arg Arg Arg Ala Glu Asp Glu Gln Arg Glu Arg Glu Arg Asp Arg Arg Arg His Arg Glu Met Ser Lys Leu Leu Ala Thr Val Val Ile Gly Gln Arg Gln Asp Arg Gln Gly Gly Glu Arg Arg Arg Pro Gln 485 490 495 Leu Asp Lys Asp Gln Cys Ala Tyr Cys Lys Glu Lys Gly His Trp Ala Lys Asp Cys Pro Lys Lys Pro Arg Gly Pro Arg Gly Pro Arg Pro Gln Thr Ser Leu Leu Thr Leu Gly Asp <210> SEO ID NO 48 <211> LENGTH: 409 <212> TYPE: PRT <213> ORGANISM: Friend Spleen Focus-Forming Virus (isolate 502) <400> SEQUENCE: 48 Met Lys Gly Pro Ala Phe Ser Lys Pro Leu Lys Asp Lys Ile Asn Pro Trp Gly Pro Leu Ile Val Leu Gly Ile Leu Ile Arg Ala Gly Val Ser Val Gln His Asp Ser Pro His Gln Val Phe Asn Val Thr Trp Arg Val

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Thr A 5	Asn 50	Leu	Met	Thr	Gly	Gln 55	Thr	Ala	Asn	Ala	Thr 60	Ser	Leu	Leu	Gly
Thr M 65	let	Thr	Asp	Ala	Phe 70	Pro	Met	Leu	His	Phe 75	Asp	Leu	Суз	Asp	Leu 80
Ile G	ly	Asp	Asp	Trp 85	Asp	Glu	Thr	Gly	Leu 90	Glu	Суз	Arg	Thr	Pro 95	Gly
Gly A	Arg	Lys	Arg 100	Ala	Arg	Thr	Phe	Asp 105	Phe	Tyr	Val	Сүз	Pro 110	Gly	His
Thr V	/al	Pro 115	Thr	Gly	Суз	Gly	Gly 120	Pro	Arg	Glu	Gly	Tyr 125	Суз	Gly	Lys
Trp G 1	31y 30	Cys	Glu	Thr	Thr	Gly 135	Gln	Ala	Tyr	Trp	Lys 140	Pro	Ser	Ser	Ser
Trp A 145	/ab	Leu	Ile	Ser	Leu 150	Lys	Arg	Gly	Asn	Thr 155	Pro	Lys	Asp	Arg	Gly 160
Pro C	çÀa	Tyr	Asp	Ser 165	Ser	Val	Ser	Ser	Gly 170	Val	Gln	Gly	Ala	Thr 175	Pro
Gly G	ly	Arg	Cys 180	Asn	Pro	Leu	Val	Leu 185	Lys	Phe	Thr	Asp	Ala 190	Gly	Lys
Lys A	la	Ser 195	Trp	Asp	Ser	Pro	Lys 200	Val	Trp	Gly	Leu	Arg 205	Leu	Tyr	Arg
Pro I 2	hr 10	Gly	Ile	Asp	Pro	Val 215	Thr	Arg	Phe	Ser	Leu 220	Thr	Arg	Gln	Val
Leu A 225	lsn	Ile	Gly	Pro	Arg 230	Ile	Pro	Ile	Gly	Pro 235	Asn	Pro	Val	Ile	Ile 240
Gly G	ln	Leu	Pro	Pro 245	Ser	Arg	Pro	Val	Gln 250	Val	Arg	Leu	Pro	Arg 255	Pro
Pro G	ln	Pro	Pro 260	Pro	Thr	Gly	Ala	Ala 265	Ser	Met	Val	Pro	Gly 270	Thr	Ala
Pro P	ro	Ser 275	Gln	Gln	Pro	Gly	Thr 280	Gly	Asp	Arg	Leu	Leu 285	Asn	Leu	Val
Gln G 2	3ly 290	Ala	Tyr	Gln	Ala	Leu 295	Asn	Leu	Thr	Asn	Pro 300	Asp	Lys	Thr	Gln
Glu C 305	Ç ys	Trp	Leu	Суз	Leu 310	Val	Ser	Gly	Pro	Pro 315	Tyr	Tyr	Glu	Gly	Val 320
Ala V	/al	Leu	Gly	Thr 325	Asn	Ser	Asn	His	Thr 330	Ser	Ala	Leu	Lys	Glu 335	Lys
Суз С	Ç ya	Phe	Tyr 340	Ala	Asp	His	Thr	Gly 345	Leu	Val	Arg	Asp	Ser 350	Met	Ala
Lys L	Jeu	Arg 355	Lys	Arg	Leu	Thr	Gln 360	Arg	Gln	Lys	Leu	Phe 365	Glu	Ser	Ser
Gln G 3	31y 870	Trp	Phe	Glu	Gly	Ser 375	Phe	Asn	Arg	Ser	Pro 380	Trp	Phe	Thr	Thr
Leu I 385	le	Ser	Thr	Ile	Met 390	Gly	Leu	Leu	Ile	Ile 395	Leu	Leu	Leu	Leu	Leu 400
Ile L	Jeu	Leu	Leu	Trp 405	Thr	Leu	His	Ser							
<210> <211> <212> <213>	> LE > TY	NGTH	H: 18 PRT	37	end s	Splee	en Fo	ocus-	- Fort	ning	Viru	ıs (:	isola	ate §	502)

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Met Gly Gln Thr Val Thr Thr Pro Leu Ser Leu Thr Leu Glu His Trp Glu Asp Val Gln Arg Thr Ala Ser Asn Gln Ser Val Asp Val Lys Lys Arg Arg Trp Val Thr Phe Cys Ser Ala Glu Trp Pro Thr Phe Gly Val Gly Trp Pro Gln Asp Gly Thr Phe Asn Leu Asp Ile Ile Leu Gln Val Lys Ser Lys Val Phe Ser Pro Gly Pro His Gly His Pro Asp Gln Val Pro Tyr Ile Val Thr Trp Glu Ala Ile Ala Tyr Glu Pro Pro Trp Val Lys Pro Phe Val Ser Pro Lys Leu Ser Pro Ser Pro Thr Ala Pro Ile Leu Pro Ser Gly Pro Ser Thr Gln Pro Pro Pro Arg Ser Ala Leu Tyr Pro Ala Leu Thr Pro Ser Ile Lys Pro Gly Pro Ser Pro Ile Met Ala Asp Leu Ser Leu Thr Phe Ser Gln Lys Thr Leu Arg Arg Thr Glu Asp Arg Asp Arg Pro Pro Leu Thr Glu Met Ala Thr Glu Lys Arg Pro Pro Pro Leu Leu Arg Phe Leu Pro Pro Leu Pro <210> SEQ ID NO 50 <211> LENGTH: 356 <212> TYPE: PRT <213> ORGANISM: Friend Spleen Focus-Forming Virus (strain BB6) <400> SEQUENCE: 50 Met Glu Gly Pro Ala Phe Ser Lys Pro Leu Lys Asp Lys Ile Asn Pro Trp Gly Pro Leu Ile Val Leu Gly Ile Leu Ile Arg Ala Gly Val Ser Val Gln Arg Asp Ser Pro His Gln Val Phe Asn Val Thr Trp Arg Val Thr Asn Leu Met Thr Gly Gln Thr Ala Asn Ala Thr Ser Leu Leu Gly Thr Met Thr Asp Ala Phe Pro Lys Leu Tyr Phe Asp Leu Cys Asp Leu Glu Gly Lys Arg Ala Arg Thr Phe Asp Leu Tyr Val Cys Pro Gly His Thr Val Pro Thr Gly Cys Gly Gly Pro Arg Glu Gly Tyr Cys Gly Lys Trp Gly Cys Glu Thr Thr Gly Gln Ala Tyr Trp Lys Pro Ser Ser Ser Trp Asp Leu Ile Ser Leu Lys Arg Gly Asn Thr Pro Lys Asp Arg Gly Pro Cys Tyr Asp Ser Ser Val Ser Ser Gly Val Gln Gly Ala Thr Pro

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Gly Gly Arg Cys Asn Pro Leu Val Leu Lys Phe Thr Asp Ala Gly Lys Lys Ala Ser Trp Asp Ala Pro Lys Val Trp Gly Leu Arg Leu Tyr Arg Ser Thr Gly Thr Asp Pro Val Thr Arg Phe Ser Leu Thr Arg Gln Val Leu Asn Ile Gly Pro Arg Val Pro Ile Gly Pro Asn Pro Val Ile Ser Asp Gln Leu Pro Pro Ser Arg Pro Ala Gln Ile Met Leu Pro Arg Pro Pro Gln Pro Pro Pro Pro Gly Thr Ala Ser Ile Val Pro Glu Thr Ala Pro Pro Ser Gln Gln Pro Gly Thr Arg Asp Arg Leu Leu Asn Leu Val Asn Lys Ala Tyr Gln Ala Leu Asn Leu Thr Ser Pro Asp Lys Thr Gln Glu Cys Trp Leu Cys Leu Val Ser Arg Pro Pro Tyr Tyr Glu Gly Val Ala Val Leu Gly Thr Asn Ser Asn His Thr Thr Leu Ile Ser Thr Ile Met Gly Leu Leu Ile Ile Leu Leu Leu Leu Leu Ile Leu Leu Trp Thr Leu His Ser <210> SEQ ID NO 51 <211> LENGTH: 409 <212> TYPE: PRT <213> ORGANISM: Friend Spleen Focus-Forming Virus (strain Lilly-Steeves) <400> SEQUENCE: 51 Met Glu Gly Pro Ala Ser Ser Lys Pro Leu Lys Asp Lys Thr Asn Pro Trp Gly Pro Leu Ile Ile Leu Gly Ile Leu Ile Arg Ala Gly Val Ser Val Gln Leu Asp Ser Pro His Gln Val Ser Asn Val Thr Trp Arg Val Thr Asn Leu Met Thr Gly Gln Thr Ala Asn Ala Thr Ser Leu Leu Gly Thr Met Thr Glu Ala Phe Pro Lys Leu Tyr Phe Asp Leu Cys Asp Leu Met Gly Asp Asp Trp Asp Glu Thr Gly Leu Gly Cys Arg Thr Pro Gly Gly Arg Lys Arg Ala Arg Thr Phe Asp Phe Tyr Val Cys Pro Gly His Thr Val Pro Thr Gly Cys Gly Gly Pro Arg Glu Gly Tyr Cys Gly Lys Trp Gly Cys Glu Thr Thr Gly Gln Ala Tyr Trp Lys Pro Ser Ser Ser Trp Asp Leu Ile Ser Leu Lys Arg Gly Asn Thr Pro Lys Asp Gln Gly Pro Cys Tyr Asp Ser Ser Val Ser Ser Gly Val Leu Gly Ala Thr Pro

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GIN	/ Gly	Ara	Cvs	Asn	Pro	Leu	Val	Leu	Glu	Phe	Thr	Asn	Ala	Glv	Ara
			180					185					190		
LYs	3 Ala	Ser 195	Trp	Asp	Ala	Pro	Lуз 200	Val	Trp	Gly	Leu	Arg 205	Leu	Tyr	Arg
Sei	Thr 210	Gly	Thr	Asp	Pro	Val 215	Thr	Arg	Phe	Ser	Leu 220	Thr	Arg	Gln	Val
Lei 225	ı Asp	Ile	Gly	Pro	Arg 230	Val	Pro	Ile	Gly	Ser 235	Asn	Pro	Val	Thr	Thr 240
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Leu	ı Gln	Pro	Pro 260	Pro	Pro	Gly	Ala	Ala 265	Ser	Ile	Val	Pro	Glu 270	Thr	Ala
Pro) Pro	Pro 275	Gln	Gln	Pro	Gly	Ala 280	Gly	Asp	Arg	Leu	Leu 285	Asn	Leu	Val
Asl	Gly 290	Ala	Tyr	Gln	Ala	Leu 295	Asn	Leu	Thr	Asn	Pro 300	Asp	Lys	Ile	Gln
Glu 309	r CÀa	Trp	Leu	Суз	Leu 310	Val	Ser	Gly	Pro	Pro 315	Tyr	Tyr	Glu	Gly	Val 320
Val	Val	Leu	Gly	Thr 325	Tyr	Phe	Asn	His	Thr 330	Ile	Ala	Leu	Lys	Glu 335	Lys
Cyr	в Сув	Phe	Tyr 340	Ala	Asp	His	Thr	Gly 345	Leu	Val	Arg	Asp	Ser 350	Met	Ala
LY	3 Leu	Arg 355	Lys	Arg	Leu	Thr	Gln 360	Arg	Gln	Lys	Leu	Phe 365	Glu	Ser	Ser
Arç	g Gly 370	Trp	Phe	Glu	Gly	Ser 375	Ser	Asn	Arg	Ser	Pro 380	Trp	Phe	Thr	Thr
Lei 385	ı Ile	Ser	Ala	Ile	Met 390	Gly	Ser	Leu	Ile	Ile 395	Leu	Leu	Leu	Leu	Leu 400
Ile	e Leu	Leu	Ile	Trp 405	Thr	Leu	Tyr	Ser							
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	3> 01		DB.L.												
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	00> SI		ISM:		chei	spl	leen	Focı	ıs-Fo	ormir	ng Vi	irus			
	00> S] : Glu	equei	ISM: NCE:	52									Ile	Asn 15	Pro
Met 1		equei Gly	ISM: NCE: Pro	52 Ala 5	Phe	Ser	Lys	Pro	Leu 10	Гла	Asp	Гла		15	
Met 1 Tr <u>i</u>	: Glu	EQUEI Gly Pro	ISM: NCE: Pro Leu 20	52 Ala 5 Ile	Phe Ile	Ser Leu	Lys Gly	Pro Ile 25	Leu 10 Leu	Lys Ile	Asp Arg	Lys Ala	Gly 30	15 Val	Ser
Met 1 Tr <u>p</u> Val	: Glu o Gly	EQUE Gly Pro His 35	ISM: NCE: Pro Leu 20 Asp	52 Ala 5 Ile Ser	Phe Ile Pro	Ser Leu His	Lys Gly Gln 40	Pro Ile 25 Val	Leu 10 Leu Phe	Lys Ile Asn	Asp Arg Val	Lys Ala Thr 45	Gly 30 Trp	15 Val Arg	Ser Val
Met 1 Tr <u>p</u> Val Thi	Glu Gly Gln Asn	EQUEN Gly Pro His 35 Leu	ISM: NCE: Pro Leu 20 Asp Met	52 Ala 5 Ile Ser Thr	Phe Ile Pro Gly	Ser Leu His Gln 55	Lys Gly Gln 40 Thr	Pro Ile 25 Val Ala	Leu 10 Leu Phe Asn	Lys Ile Asn Ala	Asp Arg Val Thr 60	Lys Ala Thr 45 Ser	Gly 30 Trp Leu	15 Val Arg Leu	Ser Val Gly
Met 1 Try Val Thu 65	: Glu > Gly L Gln : Asn 50	EQUE Gly Pro His 35 Leu Thr	ISM: NCE: Pro Leu 20 Asp Met Asp	52 Ala 5 Ile Ser Thr Ala	Phe Ile Pro Gly Phe 70	Ser Leu His Gln 55 Pro	Lys Gly Gln 40 Thr Lys	Pro Ile 25 Val Ala Leu	Leu 10 Leu Phe Asn Tyr	Lys Ile Asn Ala Phe 75	Asp Arg Val Thr 60 Asp	Lys Ala Thr 45 Ser Leu	Gly 30 Trp Leu Cys	15 Val Arg Leu Asp	Ser Val Gly Leu 80
Met 1 Try Val Thu 65 Ile	: Glu o Gly L Gln : Asn 50 : Met	EQUEN Gly Pro His 35 Leu Thr Asp	ISM: Pro Leu 20 Asp Met Asp Asp	52 Ala 5 Ile Ser Thr Ala Trp 85	Phe Ile Pro Gly Phe 70 Asp	Ser Leu His Gln 55 Pro Glu	Lys Gly Gln 40 Thr Lys Thr	Pro Ile 25 Val Ala Leu Gly	Leu 10 Leu Phe Asn Tyr Leu 90	Lys Ile Asn Ala Phe 75 Gly	Asp Arg Val Thr 60 Asp Cys	Lys Ala Thr 45 Ser Leu Arg	Gly 30 Trp Leu Cys Thr	15 Val Arg Leu Asp Pro 95	Ser Val Gly Leu 80 Gly
Met 1 Try Val Thu 65 Ile Gly	Glu Gly Gly Gln So Met So So So So So So So So So So So So So	EQUE Gly Pro His 35 Leu Thr Asp Lys	ISM: NCE: Pro Leu 20 Asp Met Asp Asp Asp 100	52 Ala 5 Ile Ser Thr Ala Trp 85 Ala	Phe Ile Pro Gly Phe 70 Asp Arg	Ser Leu His Gln 55 Pro Glu Thr	Lys Gly Gln 40 Thr Lys Thr Phe	Pro Ile 25 Val Ala Leu Gly Asp 105	Leu 10 Leu Phe Asn Tyr Leu 90 Phe	Lys Ile Asn Ala Phe 75 Gly Tyr	Asp Arg Val Thr 60 Asp Cys Val	Lys Ala Thr 45 Ser Leu Arg Cys	Gly 30 Trp Leu Cys Thr Pro 110	15 Val Arg Leu Asp Pro 95 Gly	Ser Val Gly Leu 80 Gly His

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Trp Asp Leu Ile 145				Asn Gln Gly 160
Pro Cys Tyr Asp		Val Ser Ser 170	Asp Ile Lys	
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Lys Lys Ala Ser 195	Trp Asp Gly	Pro Lys Val 200	Trp Gly Leu 205	Arg Leu Tyr
Arg Ser Thr Gly 210	Thr Asp Pro 215		Phe Ser Leu 220	Thr Arg Gln
Val Leu Asn Ile 225	Gly Pro Arg 230	Val Pro Ile	Gly Pro Asn 235	Pro Val Ile 240
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Pro Phe Arg Leu 35	Gly Asp Thr	Val Trp Val 40	Arg Arg His 45	Gln Thr Asn
Asn Leu Gln Pro 50	Arg Trp Lys 55	Ala Pro Tyr	Thr Val Leu 60	Leu Thr Thr
Pro Thr Ala Leu 65	Lys Val Asp 70	Gly Ile Ala	Ala Trp Ile 75	His Ala Ala 80

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Thr	Asp	Gln	Leu	Pro 245	Pro	Ser	Arg	Pro	Val 250	Gln	Ile	Met	Leu	Pro 255	Arg				
Pro	Pro	Gln	Pro 260	Pro	Pro	Pro	Gly	Ala 265	Ala	Ser	Ile	Val	Pro 270	Glu	Thr				
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Val	Asp 290	Gly	Ala	Tyr	Gln	Ala 295	Leu	Asn	Leu	Thr	Asn 300	Pro	Asp	Lys	Thr				
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Glu	Cya	Cya	Phe 340	Tyr	Ala	Asp	His	Thr 345	Gly	Leu	Val	Arg	Asp 350	Ser	Met				
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What is claimed is:

1. A method of diagnosing a neuroimmune disease or a retroviral infection in a subject, the method comprising:

comparing a cytokine expression signature of a subject with a control, the cytokine expression signature comprising an expression level of at least three cytokines or chemokines selected from the group consisting of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF; diagnosing the subject with a neuroimmune disease or a retroviral infection where the cytokine expression signature of the subject comprises at least one of

- (i) IL-8 expression of at least about 10-fold higher in the subject, as compared to the control;
- (ii) IL-13 expression of at least about 5-fold lower in the subject, as compared to the control;
- (iii) MIP-1β expression of at least about 10-fold higher in the subject, as compared to the control;

- (iv) TNF- α expression of at least about 10- or more-fold higher in the subject, as compared to the control;
- (v) MCP-1 expression of at least about 1.1-fold higher in the subject, as compared to the control;
- (vi) IL-7 expression of at least about 5-fold lower in the subject, as compared to the control;
- (vii) IFN-α expression of at least about 2-fold lower in the subject, as compared to the control;
- (viii) IL-6 expression of at least about 10- or more-fold higher in the subject, as compared to the control;
- (ix) MIP-1 α expression of at least about 2-fold higher in the subject, as compared to the control; and
- (x) GM-CSF expression of at least about 0.7-fold lower in the subject, as compared to the control.

2. The method of claim 1 for diagnosing a retroviral infection comprising diagnosing the subject with a retroviral infection where the cytokine expression signature of the subject comprises at least one of (i)-(x).

3. The method of claim 1 for diagnosing an neuroimmune disease comprising diagnosing the subject with an neuroimmune disease where the cytokine expression signature of the subject comprises at least one of (i)-(x).

4. The method of claim 1, comprising determining a cytokine expression signature of a subject.

5. A method of claim **1**, wherein the neuroimmune disease is selected from the group consisting of chronic fatigue syndrome, fibromyalgia, myalgic encephalitis, atypical multiple sclerosis, non-epileptic seizures, Gulf War Syndrome and autism.

6. The method of claim 1, wherein the cytokine expression signature comprises an expression level of at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF.

7. The method of claim 1, comprising administering an effective amount of an agent for treatment of a retroviral infection or a neuroimmune disease to a subject diagnosed with a retroviral infection or a neuroimmune disease.

- 8. The method of claim 1, comprising:
- adding a weighted value for a cytokine or chemokine (a) present in the cytokine signature and (b) having an expression level of at least one of (i), (ii), (iii), (iv), (v), (vi), (vii), (ix), or (x), to arrive at a sum of weighted values; and
- diagnosing the subject with a neuroimmune disease or a retroviral infection where the sum of weighted values is about 190 or greater, about 200 or greater, about 210 or greater, about 220 or greater, about 230 or greater, about 240 or greater, or about 250;

wherein the weighted value is selected from the group consisting of IL-8 is 100, IL-13 is 90, MIP-1 β is 80, TNF- α is 70, MCP-1 is 60, IL-7 is 50, IFN- α is 40, IL-6 is 30, MIP-1 α is 20, and GM-CSF is 10.

9. The method of claim 8, comprising diagnosing the subject with a neuroimmune disease or a retroviral infection where the sum of weighted values is about 210 or greater.

10. The method of claim **1**, wherein the retroviral infection comprises an XMRV infection.

11. The method of claim 1, wherein the cytokine expression signature is determined from a culture of plasmacytoid dentritic cells (pDCs) isolated from the subject.

12. The method of claim **1**, comprising determining a cytokine expression signature from a biological sample of the subject.

13. The method of claim **12**, wherein the biological sample comprises a blood sample, a serum sample, a plasma sample, a cerebrospinal fluid sample, or a solid tissue sample.

14. The method of claim 12, wherein the biological sample comprises a serum sample or a plasma sample.

15. A device for detecting a cytokine expression signature of a subject comprising an array, wherein the array detects the presence or expression level at least three cytokines or chemokines selected from the group consisting of IL-8, IL-13, MIP-1 β , TNF- α , MCP-1, IL-7, IFN- α , IL-6, MIP-1 α , and GM-CSF.

16. The device of claim **15**, wherein the array detects expression level of at least three of:

- (i) IL-8 expression of at least about 10-fold higher in the subject, as compared to the control;
- (ii) IL-13 expression of at least about 5-fold lower in the subject, as compared to the control;
- (iii) MIP-1β expression of at least about 10-fold higher in the subject, as compared to the control;
- (iv) TNF-α expression of at least about 10- or more-fold higher in the subject, as compared to the control;
- (v) MCP-1 expression of at least about 1.1-fold higher in the subject, as compared to the control;
- (vi) IL-7 expression of at least about 5-fold lower in the subject, as compared to the control;
- (vii) IFN-α expression of at least about 2-fold lower in the subject, as compared to the control;
- (viii) IL-6 expression of at least about 10- or more-fold higher in the subject, as compared to the control;
- (ix) MIP-1 α expression of at least about 2-fold higher in the subject, as compared to the control; and
- (x) GM-CSF expression of at least about 0.7-fold lower in the subject, as compared to the control.

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