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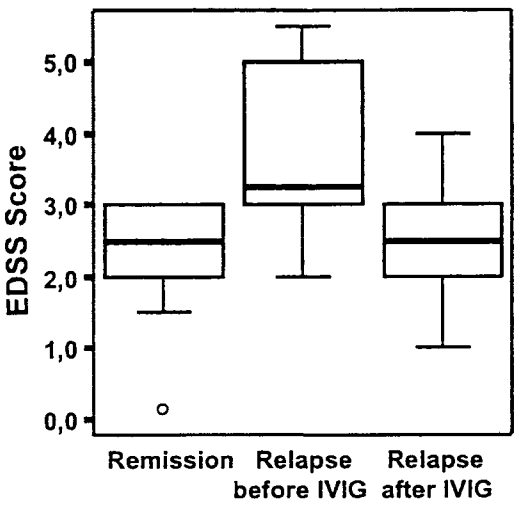

(57) **Abstract:** The present invention provides methods for providing a prognosis of treatment of diseases associated with inflammatory disease of the brain, including MS, e.g., relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, and Parkinson's disease using molecular markers that are shown to be overexpressed or underexpressed in patients treated with intravenous immunoglobulins (IVIG). Also provided are methods to identify compounds that are useful for the treatment or prevention of MS, e.g., relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, and Parkinson's disease.

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IVIG MODULATION OF CHEMOKINES FOR TREATMENT OF MULTIPLE SCLEROSIS, ALZHEIMER'S DISEASE, AND PARKINSON'S DISEASE

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to USSN 60/955,610, filed August 13, 2007, herein incorporated by reference in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Multiple sclerosis (MS) is the most common autoimmune inflammatory disease of the central nervous system. It is characterized by demyelinating lesions in the white matter of the central nervous system that lead to neurological deficits (Sospedra M. and Martin R., *Immunology of Multiple Sclerosis. Annu Rev Immunol.*, **23**:683-747 (2005)). The pathogenesis of the disease is associated with the infiltration of immune cells, mainly activated T cells, into the brain (Sospedra M. and Martin R., *Annu Rev Immunol.*, **23**:683-747 (2005)). This infiltration is accompanied by a disruption of the blood-brain barrier (van Horssen J. *et al.*, *J Neuropathol Exp Neurol.*, **66**:321-8 (2007)).

[0005] Intravenous immunoglobulins (IVIG) have been shown to be effective in the treatment of a number of autoimmune diseases including MS (Sospedra M. and Martin R., *Immunology of Multiple Sclerosis. Annu Rev Immunol.*, **23**:683-747 (2005)), but the exact mechanisms of action underlying the immunomodulatory activities of IVIG have not been fully explained. There are several models that try to explain the immunomodulatory efficacy of IVIG in patients suffering from autoimmune and inflammatory diseases (Kazatchkine

M.D. *et al.*, *Mult Scler*, **2**:24-6; **33**:24-26 (2000); Trebst C. and Stangel M., *Curr. Pharm. Design*, **12**:241-2493 (2006)). These models include Fcγ-receptor-mediated immunomodulation (Sorensen P.S., *Neurol Sci*, **4**:227-230 (2003)), modulation of idiotype/anti-idiotype networks (Samuelsson A. *et al.*, *Science*, **291**:484-6 (2001)), elimination of immunostimulating microbial products (Dalakas M.C., *Ann Intern Med*, **126**:721-30 (1997)) and neutralizing antibodies against cytokines and chemokines (Bayry J. *et al.*, *Transfus Clin Biol.*, **10**:165-9 (2003)). IVIG's potential to modify the balance between Th1 and Th2 cell immunoreactivity and to inhibit the formation of antibody/complement complexes have also been demonstrated (Andersson U. *et al.*, *Immunol Rev*, **139**:21-42 (1994); Bayry J. *et al.*, *Intravenous immunoglobulin in autoimmune disorders: An insight into the immunregulatory mechanisms*).

[0006] The beneficial effects of IVIG in patients with MS were shown by a number of open clinical trials (Basta M. *et al.*, *Blood*, **77**:376-80 (1991)) and by four randomized double-blind clinical studies (Sorensen P.S. *et al.*, *Eur J Neurol*, **9**:557-563 (2002); Strasser-Fuchs S. *et al.*, *Mult Scler*, **2**:9-13 (2000); Sorensen P.S. *et al.*, *Neurology*, **50**:1273-1281 (1998); Lewanska M. *et al.*, *Eur J Neurol*, **9**:565-572 (2002)). IVIG decreased the relapse rate in MS patients and the number of gadolinium-enhancing lesions seen on brain magnetic resonance imaging (MRI) (Dudesek A. and Zettl U.K., *J Neurol*, 253; V/50-V/58)). Furthermore, IVIG was shown to suppress proliferation of activated peripheral T cells (Bayry J. *et al.*, *Neurol Sci*, **4**:217-221 (2003); Stangel M. and Gold R., *Nervenarzt*, (2005)). Auto-reactive peripheral T cells can cross the blood-brain barrier and are believed to be the main effector cells responsible for brain inflammation (Sospedra M. and Martin R., *Annu Rev Immunol.*, **23**:683-747 (2005); Helling N. et al., *Immunol Res.*, **1**:27-51 (2002)). Therefore, a modulation of T cell function by IVIG could explain the beneficial therapeutic effect of IVIG seen in MS patients.

[0007] Recently, we showed that IVIG is an effective alternative treatment for patients with acute exacerbations in relapsing-remitting multiple sclerosis (RRMS) (Elovaara I. et al., *Intravenous Immunoglobulin is effective and well tolerated in the treatment of MS Relapse*, manuscript submitted). Because peripheral auto-reactive T cells are believed to be responsible for brain inflammation in MS, we undertook to identify genes that are differentially regulated in peripheral T cells of patients with MS in acute exacerbation that are treated with IVIG. We reasoned that differences in gene expression profiles could provide important information about the potential mechanisms of action of IVIG treatment.

Furthermore, changes in gene expression profiles could provide prognostic markers to predict treatment success. Such markers could also help to identify targets for developing new therapeutic agents.

[0008] Furthermore, increasing evidence has suggested a role for brain inflammation not only in MS but also in the pathogenesis of Alzheimers`disease and Parkinsons`disease (see, e.g., Wilms *et al., Curr. Pharm. Des.* 13:1925 (2007)). In particular microglia, the resident innate immune cells, play a major role in inflammatory processes of the brain and are known to be associated not only with MS but also with Alzheimers`disease and in Parkinsons`disease (see, e.g, Yamamoto *et al., Am. J. Pathology* 166:1475 (2006); Huang *et al., FASEB* 19:761 (2005); Kim *et al., Exp. And Mol. Med.* 38:333 (2006)). Thus, the present invention provides new prognostic markers to predict treatment success associated with the administration of intravenous immunoglobulin treatment as well as new therapeutic targets that may be exploited in the treatment of MS, e.g., relapsing-remitting multiple sclerosis (RRMS), Parkinsons` disease or Alzheimers disease.`

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides methods for providing a prognosis of treatment of multiple sclerosis, Parkinson's disease and Alzheimer's disease using molecular markers that are overexpressed or underexpressed in patients treated with intravenous immunoglobulins (IVIG). Also provided are methods to identify compounds that are useful for the treatment or prevention of multiple sclerosis. In some aspects, the subtype of multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

[0010] Accordingly, in one embodiment the present invention provides method of providing a prognosis of multiple sclerosis, Parkinson's disease and Alzheimer's disease in a subject treated with intravenous immunoglobulin (IVIG) by contacting a biological sample from the subject treated with IVIG with a reagent that specifically binds to at least one marker selected from any of the nucleic acids and corresponding protein sequences shown in Table 3a, Table 3b, and Table 4, and then determining whether or not the marker is overexpressed or underexpressed in the sample, thus providing a prognosis for MS, Parkinson's disease and Alzheimer's disease in a subject treated with IVIG. In an aspect of this embodiment, the multiple sclerosis is of the relapsing-remitting multiple sclerosis (RRMS) subtype.

[0011] In various aspects of this embodiment, the reagent is an antibody, such as a monoclonal antibody. Alternatively, the reagent can be a nucleic acid, including an oligonucleotide or an RT PCR primer set. In other aspects, the sample is a blood sample, which can contain T cells. The sample can also be cerebrospinal fluid. In some aspects of this embodiment, one of the markers is a chemokine. Examples of chemokines include: CXCL3, CXCL5, CCL13, and XCL2.

[0012] Another embodiment of the invention provides a method of identifying a compound that prevents or treats multiple sclerosis, Parkinson's disease and Alzheimer's disease by contacting a compound with a sample comprising a cell that expresses a marker selected from any of the nucleic acid and corresponding protein sequences shown in Table 3a, Table 3b, Table 3c, Table 3d, and Table 4, and then determining the functional effect of the compound on the marker, thus identifying a compound that prevents or treats MS, Parkinson's disease and Alzheimer's disease. In an aspect of this embodiment, the multiple sclerosis is of the relapsing-remitting multiple sclerosis (RRMS) subtype.

[0013] In various aspects of this embodiment, the functional effect is an increase or decrease in expression of the marker. In other aspects, the functional effect is an increase or decrease in activity of the marker. Examples of compounds used in various aspects of this embodiment include: a small molecule, a siRNA, a ribozyme, an antibody, which can be a monoclonal antibody.

[0014] A further embodiment of the invention provides a method of treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease in a subject by administering to the subject an effective amount of an antibody which binds a chemokine, including CXCL5, CXCL3, and CCL13, in which the effective amount is sufficient to inactivate the chemokine or chemokine cell signaling, thus treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease. In an aspect of this embodiment, the multiple sclerosis is of the relapsing-remitting multiple sclerosis (RRMS) subtype.

[0015] A yet further embodiment of the invention provides a method of treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease in a subject by administering to the subject an effective amount of an antibody which binds a chemokine receptor, including receptors for CXCL5, CXCL3, and CCL13, in which the effective amount is sufficient to inactivate the function of the chemokine receptor, thus treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease. In an aspect of this

embodiment, the multiple sclerosis is of the relapsing-remitting multiple sclerosis (RRMS) subtype.

[0016] Another embodiment of this invention provides a method of treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease in a subject by administering to the subject an effective amount of an antibody which binds to a XCL2 chemokine receptor, in which the effective amount is sufficient to activate the XCL2 chemokine receptor, thus treating or preventing multiple sclerosis, Parkinson's disease and Alzheimer's disease. In an aspect of this embodiment, the multiple sclerosis is of the relapsing-remitting multiple sclerosis (RRMS) subtype.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 shows development of EDSS scores in 10 RRMS patients during treatment with IVIG. Box plots containing the median, 25% and 75% percentile, minimum and maximum, demonstrate the EDSS scores of patients during remission, as well as before and after treatment with IVIG during relapse.

[0018] Figure 2 shows that treatment with IVIG does not alter the cellular composition of cells obtained for isolation of RNA. Relative gene expression data obtained from microarray analysis are presented for CD3, CD4, CD8 and CD14. Gene expression on day 0 was set as 1 and compared with gene expression on day 6 (A) and day 26 (B). Each point represents an individual patient.

[0019] Figure 3 shows real-time PCR demonstrating the expression of representative genes. Box plots containing the median, 25% and 75% percentile, minimum and maximum, demonstrate the relative expression of the indicated genes. Expression of genes was normalized to an endogenous control (glyceraldhyde-3-phosphate dehydrogenase). Real-time PCR experiments were done in triplets and confirmed at least two times on different days.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Multiple sclerosis (MS) refers generally to an inflammatory, demyelinating disease that affects the central nervous system (CNS). During the progression of MS, the myelin surrounding the axons of neurons degenerates, resulting in subsequent axonal degeneration. The pathogenesis of MS is believed to involve an autoimmune response in which T cells attack parts of the central nervous system, triggering inflammatory responses, which results in the stimulation of other immune cells and the secretion of soluble factors such as cytokines and antibodies. The inflammatory processes triggered by T cells create leaks in the blood-

brain barrier formed by endothelial cells. The leaks in the blood-brain barrier, in turn, cause a number of other damaging effects such as brain swelling, activation of macrophages, and further secretion of cytokines and other proteolytic proteins such as matrix metalloproteinases. The final outcome of these pathological processes is neuronal demyelination. *See, e.g.*, Calabresi, P.A., *American Family Physician*, 70: 1935-1944 (2004), for review.

[0021] As MS progresses, gradual demyelination and transection of neuron axons in patches throughout the brain and spinal cord occur. Thus, the term multiple sclerosis refers to the multiple scars (or scleroses) found on myelin sheaths in affected individuals. This scarring causes symptoms which may vary widely depending upon the extent of scarring and which neuronal pathways are disrupted.

[0022] Among the symptoms and manifestations of MS include changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, difficulties in movement; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, bladder and bowel difficulties, cognitive impairment, or emotional symptomatology (e.g., depression).

[0023] The most common initial symptoms reported are: changes in sensation in the arms, legs or face (33%), complete or partial vision loss (optic neuritis) (16%), weakness (13%), double vision (7%), unsteadiness when walking (5%), and balance problems (3%). See Navarro *et al.*, *Rev Neurol* 41: 601-3 (2005); Jongen P., *J Neurol Sci* 245: 59–62 (2006). In some individuals, the initial MS attack is preceded by infection, trauma, or strenuous physical effort.

[0024] A number of diagnostic tests are currently in use for the diagnosis of MS. These include the clinical presentation of two separate episodes of neurologic symptoms characteristic of MS, along with the finding of consistent abnormalities on physical examination. Alternatively, magnetic resonance imaging (MRI) of the brain and spine is often used to evaluate individuals with suspected MS. MRI reveals areas of demyelination as bright lesions on T2-weighted images or FLAIR (fluid attenuated inversion recovery) sequences. Gadolinium contrast can be used to demonstrate active plaques on T1-weighted images.

[0025] The testing of cerebrospinal fluid (CSF) can provide evidence of chronic inflammation of the central nervous system, a characteristic of MS. In such a test, the CSF is tested for oligoclonal bands, which are immunoglobulins found in 85% to 95% of people with definite MS. When combined with MRI and clinical data, the presence of oligoclonal bands can help make a definite diagnosis of MS.

[0026] Because the brains MS-affected individuals often respond less actively to stimulation of the optic nerve and sensory nerves, the measurement of such brain responses can also be used as a diagnostic tool. These brain responses can be examined using visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs). Decreased activity on either test can reveal demyelination which may be otherwise asymptomatic. Along with other data, these exams can help uncover the widespread nerve involvement required for a definite diagnosis of MS.

[0027] Several subtypes, or patterns of progression, of MS have been described. In 1996, the United States National Multiple Sclerosis Society standardized the following four subtype definitions, as described below.

[0028] Relapsing-remitting MS (RRMS) refers to a subtype characterized by unpredictable attacks (relapses) followed by periods of months to years of relative quiet (remission) with no new signs of disease activity. Deficits suffered during the attacks may either resolve or may be permanent. Relapsing-remitting describes the initial course of 85% to 90% of individuals with MS.

[0029] Secondary progressive describes around 80% of those with initial relapsing-remitting MS, who then begin to have neurologic decline between their acute attacks without any definite periods of remission. This decline may include new neurologic symptoms, worsening cognitive function, or other deficits. Secondary progressive is the most common type of MS and causes the greatest amount of disability.

[0030] Primary progressive describes the approximately 10% of individuals who never have remission after their initial MS symptoms. Decline occurs continuously without clear attacks. The primary progressive subtype tends to affect people who are older at disease onset.

[0031] Progressive relapsing describes those individuals who, from the onset of their MS, have a steady neurologic decline but also suffer superimposed attacks; and is the least common of all subtypes.

[0032] While there is currently no definitive cure for MS, a number of therapies have been developed that are directed toward returning function after an attack, preventing new attacks, or preventing disability. Thus, different therapies are used for patients experiencing acute attacks; those who have the relapsing-remitting subtype; those who have the progressive subtypes; those without a diagnosis of MS who have a demyelinating event; and for managing the various consequences of MS attacks.

[0033] The phamacological agents currently in use for MS include interferons, which have been approved for use in relapsing forms of secondary progressive MS; glatiramer acetate, a synthetic medication made of four amino acids that are found in myelin, which stimulates T cells to secrete anti-inflammatory agents that reduce inflammation at lesion sites; mitoxantrone, an agent used to treat progressive, progressive-relapsing, and worsening relapsing-remitting MS; and Natalizumab, a monoclonal antibody that recognizes α4-integrin.

[0034] High doses of intravenous corticosteroids, such as methylprednisolone, are frequently administered in the treatment of RRMS and have been shown to be effective at shortening the length of relapsing-remitting symptomatic attacks. As described in greater detail herein, intravenous IgG immunoglobulins have also been used to treat MS.

[0035] Similarly to MS, other disease states are associated with brain inflammation, such as Parkinson's disease and Alzheimer's disease, as described above. For example, chemokine CCL13, described herein, activates the chemokine receptor CCR2, which is expressed in microglia and astrocytes. Both of these cell types are associated with Parkinson's disease and Alzheimer's disease. This and other markers described herein are therefore useful for drug assays, diagnostic and prognostic assays, and for therapeutic siRNA and antibody treatment for Alzheimer's disease and Parkinson's disesase.

[0036] Intravenous immunoglobulins (IVIG) have been successfully used to treat a number of autoimmune diseases of the central nervous system, including multiple sclerosis (MS). However, the underlying mechanisms of action of IVIG have not been fully explained. Accordingly, we have undertaken the identification of gene expression profiles that are associated with the immunomodulatory activity of IVIG in patients with acute exacerbations in relapsing-remitting MS (RRMS). As described below, HU-133 microarrays from

Affymetrix were used to study gene expression profiles of peripheral T cells in 10 RRMS patients before and after treatment with IVIG. Patients treated with intravenous methylprednisolone were included as controls. The differential expression of representative genes was confirmed by real-time polymerase chain reaction. All patients were analyzed neurologically and by brain and spinal cord magnetic resonance imaging before and after IVIG therapy.

[0037] As shown below in the Examples, 360 genes that were differentially expressed during IVIG treatment were identified. Some encode chemokines such as CXCL3 and CXCL5 that are known to bind to CXCR2, a receptor essential for the regulation of oligodendrocyte migration in the brain. Others encode proteins that are involved in signal transduction, proliferation or apoptosis.

[0038] The studies disclosed herein indicate that among the differentially expressed genes the regulation of chemokine expression in peripheral T cells is an important new mechanism of action of IVIG in patients with acute exacerbations in MS. Thus, the genes disclosed herein may serve as diagnostic markers for predicting treatment success in IVIG therapy and provide new molecular targets for drug development.

DEFINITIONS

[0039] The term "intravenous IgG" or "IVIG" treatment refers generally to a composition of IgG immunoglubulins administered intravenously to treat a number of conditions such as immune deficiencies, inflammatory diseases, and autoimmune diseases. The IgG immunoglobulins are typically pooled and prepared from serum. Whole antibodies or fragments can be used.

[0040] The term "chemokine" refers generally to a family of small cytokines which are secreted by various cells that promote chemotaxis in responsive cells. Chemokines have also gone by the nomenclature of SIS family of cytokines, SIG family of cytokines, SCY family of cytokines, Platelet factor-4 superfamily or intercrines. Cells that are attracted by chemokines follow a signal of increasing chemokine concentration towards the source of the chemokine.

[0041] Some members of the chemokine family control cells of the immune system during the process of immune surveillance, such as by directing lymphocytes to the lymph nodes to allow lymphocyte surveillance invasion of pathogens through interaction with antigen-presenting cells residing in these tissues. Such chemokines are known as homeostatic

chemokines and are produced and secreted without any need to stimulate their source cell(s). Some chemokines have roles in development by, e.g., promoting angiogenesis or guiding cells to tissues that provide specific signals critical for cellular maturation. Other chemokines are inflammatory and are released from a wide variety of cells in response to bacterial infection, viruses and agents that cause physical damage. The release of inflammatory chemokines is often stimulated by pro-inflammatory cytokines such as interleukin 1. Inflammatory chemokines function mainly as chemoattractants for leukocytes, recruiting monocytes, neutrophils and other effector cells from the blood to sites of infection or tissue damage. Certain inflammatory chemokines activate cells to initiate an immune response or promote wound healing. They are released by many different cell types and serve to guide cells of both innate immune system and adaptive immune system.

[0042] Structurally, chemokines are small proteins, with molecular masses of between 8 and 10 kDa. Chemokines also possess conserved amino acids that are important for creating their 3-dimensional or tertiary structure, such as (in most cases) four cysteines that interact with each other in pairs to create a greek key shape that is a characteristic of this class of proteins; intramolecular disulphide bonds typically join the first to third, and the second to fourth cysteine residues, numbered as they appear in the protein sequence of the chemokine.

[0043] Members of the chemokine family are categorized into four groups depending on the spacing of their first two cysteine residues. The CC chemokines (or β-chemokines) have two adjacent cysteines near their amino terminus. There have been at least 27 distinct members of this subgroup reported for mammals, called CC chemokine ligands (CCL)-1 to -28. The first two cysteine residues in CXC chemokines (or α-chemokines) are separated by one amino acid, represented by "X". There have been 17 different CXC chemokines described in mammals, that are subdivided into two categories, those with a specific amino acid sequence (or motif) of Glutamic acid-Leucine-Arginine (ELR) immediately before the first cysteine of the CXC motif (ELR-positive), and those without an ELR motif (ELR-negative). The third group of chemokines is known as the C chemokines (or γ chemokines), and is unlike all other chemokines in that it has only two cysteines; one N-terminal cysteine and one cysteine downstream. A fourth group has three amino acids between the two cysteines and is termed CX_3C chemokine (or δ-chemokines).

[0044] Chemokine receptors are G protein-coupled receptors containing 7 transmembrane domains that are found on the surface of leukocytes. Approximately 19 different chemokine

receptors have been characterized to date, which are divided into four families depending on the type of chemokine they bind; CXCR that bind CXC chemokines, CCR that bind CC chemokines, CX3CR1 that binds the sole CX3C chemokine (CX3CL1), and XCR1 that binds the two XC chemokines (XCL1 and XCL2).

[0045] "Chemokine cell signaling" refers generally to the ability of chemokine receptors to associate with G-proteins to transmit cell signals following ligand binding. Activation of G proteins, by chemokine receptors, causes the subsequent activation of phospholipase C (PLC). PLC cleaves a phosphatidylinositol (4,5)-bisphosphate (PIP2) into two second messenger molecules, inositol triphosphate (IP3) and diacylglycerol (DAG) that trigger intracellular signaling events; DAG activates another enzyme called protein kinase C (PKC), and IP3 triggers the release of calcium from intracellular stores. These events promote signaling cascades such as the MAP kinase pathway that generate responses including chemotaxis, degranulation, release of superoxide anions and changes in the avidity of cell adhesion molecules such as integrins within the cell harboring the chemokine receptor.

[0046] The term "marker" or "biomarker" refers to a molecule (typically protein, nucleic acid, carbohydrate, or lipid) that is expressed in a cell, expressed on the surface of a cell or secreted by a cell and which is useful for providing a prognosis of relapsing-remitting multiple sclerosis (RRMS) in a subject treated with IVIG. Some of the biomarkers disclosed herein are molecules that are overexpressed in individuals with relapsing-remitting multiple sclerosis (RRMS) treated with IVIG, in comparison to individuals not treated IVIG or in RRMS patients prior to treatment with IVIG, for instance, 1-fold overexpression, 2-fold overexpression, 3-fold overexpression, or more. Alternatively, other biomarkers are molecules that are underexpressed in individuals with relapsing-remitting multiple sclerosis (RRMS) treated with IVIG, in comparison to individuals not treated IVIG or in RRMS patients prior to treatment with IVIG, for instance, 1-fold underexpression, 2-fold underexpression, 3-fold underexpression, or more. Further, a marker can be a molecule that is inappropriately synthesized in individuals with relapsing-remitting multiple sclerosis (RRMS) treated with IVIG, in comparison to individuals not treated IVIG or in RRMS patients prior to treatment with IVIG, for instance, a molecule that contains deletions, additions or mutations in comparison to the molecule expressed on a normal cell.

[0047] It will be understood by the skilled artisan that markers may be used singly or in combination with other markers for any of the uses, e.g., prognosis of IVIG treatment of relapsing-remitting multiple sclerosis (RRMS), disclosed herein.

[0048] "Biological sample" includes biological fluid samples, such as blood and cerebrospinal fluid, sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histologic purposes. Such samples include blood and blood fractions or products (e.g., serum, plasma, platelets, red blood cells, and the like), cerebrospinal fluid, sputum, cervicovaginal fluid, lymph and tongue tissue, cultured cells, e.g., primary cultures, explants, and transformed cells, stool, urine, etc. A biological sample is typically obtained from a eukaryotic organism, most preferably a mammal such as a primate e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, Mouse; rabbit; or a bird; reptile; or fish.

[0049] The terms "overexpress," "overexpression" or "overexpressed" or "upregulated" interchangeably refer to a protein or nucleic acid (RNA) that is transcribed or translated at a detectably greater level, usually in an IVIG-treated relapsing-remitting multiple sclerosis (RRMS) patient, in comparison to a patient not undergoing IVIG treatment. The term includes overexpression due to transcription, post transcriptional processing, translation, post-translational processing, cellular localization (*e.g.*, organelle, cytoplasm, nucleus, cell surface), and RNA and protein stability, as compared to a control. Overexpression can be detected using conventional techniques for detecting mRNA (*i.e.*, RT-PCR, PCR, hybridization) or proteins (*i.e.*, ELISA, immunohistochemical techniques). Overexpression can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a normal cell. In certain instances, overexpression is 1-fold, 2-fold, 3-fold, 4-fold or more higher levels of transcription or translation in comparison to a control.

[0050] The terms "underexpress," "underexpression" or "underexpressed" or "downregulated" interchangeably refer to a protein or nucleic acid that is transcribed or translated at a detectably lower level, usually in an IVIG-treated relapsing-remitting multiple sclerosis (RRMS) patient, in comparison to a patient not undergoing IVIG treatment. The term includes underexpression due to transcription, post transcriptional processing, translation, post-translational processing, cellular localization (*e.g.*, organelle, cytoplasm, nucleus, cell surface), and RNA and protein stability, as compared to a control. Underexpression can be detected using conventional techniques for detecting mRNA (*i.e.*, RT-PCR, PCR, hybridization) or proteins (*i.e.*, ELISA, immunohistochemical techniques).

Underexpression can be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or less in comparison to a control. In certain instances, underexpression is 1-fold, 2-fold, 3-fold, 4-fold or more lower levels of transcription or translation in comparison to a control.

[0051] The term "differentially expressed" or "differentially regulated" refers generally to a protein or nucleic acid that is overexpressed (upregulated) or underexpressed (downregulated) in one sample compared to at least one other sample, generally in an IVIG-treated relapsing-remitting multiple sclerosis (RRMS) patient, in comparison to a patient not undergoing IVIG treatment, in the context of the present invention.

[0052] "Therapeutic treatment" refers to drug therapy, hormonal therapy, immunotherapy, and biologic (targeted) therapy.

[0053] By "therapeutically effective amount or dose" or "sufficient amount or dose" herein is meant a dose that produces effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0054] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site http://www.ncbi.nlm.nih.gov/BLAST/ or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0055] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Preferably, default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0056] A "comparison window," as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g., Current Protocols in Molecular Biology* (Ausubel *et al.*, eds. 1987-2005, Wiley Interscience)).

[0057] A preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al., Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990), respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs

containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0058] "Nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0059] "RNAi molecule" or an "siRNA" refers to a nucleic acid that forms a double stranded RNA, which double stranded RNA has the ability to reduce or inhibit expression of a gene or target gene when the siRNA expressed in the same cell as the gene or target gene. "siRNA" thus refers to the double stranded RNA formed by the complementary strands. The complementary portions of the siRNA that hybridize to form the double stranded molecule typically have substantial or complete identity. In one embodiment, an siRNA refers to a nucleic acid that has substantial or complete identity to a target gene and forms a double stranded siRNA. The sequence of the siRNA can correspond to the full length target gene, or a subsequence thereof. Typically, the siRNA is at least about 15-50 nucleotides in length (e.g., each complementary sequence of the double stranded siRNA is 15-50 nucleotides in

length, and the double stranded siRNA is about 15-50 base pairs in length, preferable about preferably about 20-30 base nucleotides, preferably about 20-25 nucleotides in length, e.g., 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

[0060] An "antisense" polynucleotide is a polynucleotide that is substantially complementary to a target polynucleotide and has the ability to specifically hybridize to the target polynucleotide.

[0061] Ribozymes are enzymatic RNA molecules capable of catalyzing specific cleavage of RNA. The composition of ribozyme molecules preferably includes one or more sequences complementary to a target mRNA, and the well known catalytic sequence responsible for mRNA cleavage or a functionally equivalent sequence (see, e.g., U.S. Pat. No. 5,093,246, which is incorporated herein by reference in its entirety). Ribozyme molecules designed to catalytically cleave target mRNA transcripts can also be used to prevent translation of subject target mRNAs.

[0062] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, *Nucleic Acid Res.* 19:5081 (1991); Ohtsuka *et al.*, *J. Biol. Chem.* 260:2605-2608 (1985); Rossolini *et al.*, *Mol. Cell. Probes* 8:91-98 (1994)). The term nucleic acid is used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

[0063] A particular nucleic acid sequence also implicitly encompasses "splice variants" and nucleic acid sequences encoding truncated forms of a protein. Similarly, a particular protein encoded by a nucleic acid implicitly encompasses any protein encoded by a splice variant or truncated form of that nucleic acid. "Splice variants," as the name suggests, are products of alternative splicing of a gene. After transcription, an initial nucleic acid transcript may be spliced such that different (alternate) nucleic acid splice products encode different polypeptides. Mechanisms for the production of splice variants vary, but include alternate splicing of exons. Alternate polypeptides derived from the same nucleic acid by read-through transcription are also encompassed by this definition. Any products of a splicing reaction, including recombinant forms of the splice products, are included in this definition. Nucleic

acids can be truncated at the 5' end or at the 3' end. Polypeptides can be truncated at the N-terminal end or the C-terminal end. Truncated versions of nucleic acid or polypeptide sequences can be naturally occurring or recombinantly created.

[0064] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0065] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0066] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0067] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the

corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

[0068] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

[0069] The following eight groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M). *See, e.g.*, Creighton, *Proteins* (1984).

[0070] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes (*e.g.*, as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins which can be made detectable, *e.g.*, by incorporating a radiolabel into the peptide or used to detect antibodies specifically reactive with the peptide.

[0071] The term "recombinant" when used with reference, *e.g.*, to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic

acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0072] The phrase "stringent hybridization conditions" refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acids, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, *Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Probes*, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993). Generally, stringent conditions are selected to be about 5-10°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength pH. The T_m is the temperature (under defined ionic strength, pH, and nucleic concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at T_m, 50% of the probes are occupied at equilibrium). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide. For selective or specific hybridization, a positive signal is at least two times background, preferably 10 times background hybridization. Exemplary stringent hybridization conditions can be as following: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C, or, 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C.

[0073] Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the polypeptides which they encode are substantially identical. This occurs, for example, when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code. In such cases, the nucleic acids typically hybridize under moderately stringent hybridization conditions. Exemplary "moderately stringent hybridization conditions" include a hybridization in a buffer of 40% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 1X SSC at 45°C. A positive hybridization is at least twice background. Those of ordinary skill will readily recognize that alternative hybridization and wash conditions can be utilized to provide conditions of similar stringency. Additional guidelines for determining hybridization parameters are provided in numerous reference, e.g., and *Current Protocols in Molecular Biology*, ed. Ausubel, *et al.*, *supra.*

[0074] For PCR, a temperature of about 36°C is typical for low stringency amplification, although annealing temperatures may vary between about 32°C and 48°C depending on primer length. For high stringency PCR amplification, a temperature of about 62°C is typical, although high stringency annealing temperatures can range from about 50°C to about 65°C, depending on the primer length and specificity. Typical cycle conditions for both high and low stringency amplifications include a denaturation phase of 90°C - 95°C for 30 sec - 2 min., an annealing phase lasting 30 sec. - 2 min., and an extension phase of about 72°C for 1 - 2 min. Protocols and guidelines for low and high stringency amplification reactions are provided, e.g., in Innis *et al.* (1990) *PCR Protocols, A Guide to Methods and Applications*, Academic Press, Inc. N.Y.).

[0075] "Antibody" refers to a polypeptide comprising a framework region from an immunoglobulin gene or fragments thereof that specifically binds and recognizes an antigen. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. Typically, the antigen-binding region of an antibody will be most critical in specificity and affinity of binding. Antibodies can be polyclonal or monoclonal, derived from serum, a hybridoma or recombinantly cloned, and can also be chimeric, primatized, or humanized.

[0076] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively.

[0077] Antibodies exist, *e.g.*, as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab)'$_2$, a dimer of Fab which itself is a light chain joined to V_H-C_H1 by a disulfide bond. The F(ab)'$_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab)'$_2$ dimer into an Fab' monomer. The Fab' monomer is

essentially Fab with part of the hinge region (*see Fundamental Immunology* (Paul ed., 3d ed. 1993). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized *de novo* using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990)).

[0078] An antibody immunologically reactive with a particular biomarker protein of the present invention can be generated by recombinant methods such as selection of libraries of recombinant antibodies in phage or similar vectors, see, *e.g.*, Huse *et al.*, *Science,* 246:1275-1281 (1989); Ward *et al.*, *Nature,* 341:544-546 (1989); and Vaughan *et al.*, *Nature Biotech.,* 14:309-314 (1996), or by immunizing an animal with the antigen or with DNA encoding the antigen.

[0079] Methods of preparing polyclonal antibodies are known to the skilled artisan (*e.g.*, Harlow & Lane, 1988, Antibodies: A Laboratory Manual. (Cold Spring Harbor Press)). Polyclonal antibodies can be raised in a mammal, *e.g.*, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include a protein encoded by a nucleic acid of the figures or fragment thereof or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

[0080] The antibodies can, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler & Milstein, *Nature,* 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce

or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized in vitro. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if nonhuman mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp. 59-103 (1986)). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

[0081] Human antibodies can be produced using various techniques known in the art, including phage display libraries (Hoogenboom & Winter, *J. Mol. Biol.*, 227:381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581 (1991)). The techniques of Cole *et al.* and Boemer *et al.* are also available for the preparation of human monoclonal antibodies (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, p. 77 (1985) and Boemer *et al.*, *J. Immunol.*, 147(1):86-95 (1991)). Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, *e.g.*, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, *BioTechnology,* 10:779-783 (1992); Lonberg *et al.*, *Nature,* 368:856-859 (1994); Morrison, *Nature,* 368:812-13 (1994); Fishwild *et al.*, *Nature Biotechnology,* 14:845-51 (1996); Neuberger, *Nature Biotechnology,* 14:826 (1996); Lonberg & Huszar, *Inter. Rev. Immunol.*, 13:65-93 (1995).

[0082] In one embodiment, the antibody is conjugated to an "effector" moiety. The effector moiety can be any number of molecules, including labeling moieties such as radioactive labels or fluorescent labels, or can be a therapeutic moiety. In one aspect the antibody modulates the activity of the protein.

[0083] The nucleic acids of the differentially expressed genes of this invention or their encoded polypeptides refer to all forms of nucleic acids (*e.g.*, gene, pre-mRNA, mRNA) or proteins, their polymorphic variants, alleles, mutants, and interspecies homologs that (as applicable to nucleic acid or protein): (1) have an amino acid sequence that has greater than about 60% amino acid sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, preferably 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or greater amino acid sequence identity, preferably over a region of at least about 25, 50, 100, 200, 500, 1000, or more amino acids, to a polypeptide encoded by a referenced nucleic acid or an amino acid sequence described herein; (2) specifically bind to antibodies, *e.g.*, polyclonal antibodies, raised against an immunogen comprising a referenced amino acid sequence, immunogenic fragments thereof, and conservatively modified variants thereof; (3) specifically hybridize under stringent hybridization conditions to a nucleic acid encoding a referenced amino acid sequence, and conservatively modified variants thereof; (4) have a nucleic acid sequence that has greater than about 95%, preferably greater than about 96%, 97%, 98%, 99%, or higher nucleotide sequence identity, preferably over a region of at least about 25, 50, 100, 200, 500, 1000, or more nucleotides, to a reference nucleic acid sequence. A polynucleotide or polypeptide sequence is typically from a mammal including, but not limited to, primate, *e.g.*, human; rodent, *e.g.*, rat, mouse, hamster; cow, pig, horse, sheep, or any mammal. The nucleic acids and proteins of the invention include both naturally occurring or recombinant molecules. Truncated and alternatively spliced forms of these antigens are included in the definition.

[0084] The phrase "specifically (or selectively) binds" when referring to a protein, nucleic acid, antibody, or small molecule compound refers to a binding reaction that is determinative of the presence of the protein or nucleic acid, such as the differentially expressed genes of the present invention, often in a heterogeneous population of proteins or nucleic acids and other biologics. In the case of antibodies, under designated immunoassay conditions, a specified antibody may bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies can be selected to obtain only those polyclonal antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays

are routinely used to select antibodies specifically immunoreactive with a protein (*see, e.g.*, Harlow & Lane, *Antibodies, A Laboratory Manual* (1988) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0085] The phrase "functional effects" in the context of assays for testing compounds that modulate a marker protein includes the determination of a parameter that is indirectly or directly under the influence of a biomarker of the invention, e.g., a chemical or phenotypic effect such as altered chemokine cell signaling. A functional effect therefore includes ligand binding activity, transcriptional activation or repression, the ability of cells to proliferate, the ability to migrate, among others. "Functional effects" include *in vitro*, *in vivo*, and *ex vivo* activities.

[0086] By "determining the functional effect" is meant assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of a biomarker of the invention, e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled in the art, e.g., changes in spectroscopic characteristics (e.g., fluorescence, absorbance, refractive index); hydrodynamic (e.g., shape), chromatographic; or solubility properties for the protein; ligand binding assays, e.g., binding to antibodies; measuring inducible markers or transcriptional activation of the marker; measuring changes in enzymatic activity; the ability to increase or decrease cellular proliferation, apoptosis, cell cycle arrest, measuring changes in cell surface markers. The functional effects can be evaluated by many means known to those skilled in the art, e.g., microscopy for quantitative or qualitative measures of alterations in morphological features, measurement of changes in RNA or protein levels for other genes expressed in chemokine-responsive cells, measurement of RNA stability, identification of downstream or reporter gene expression (CAT, luciferase, β-gal, GFP and the like), e.g., via chemiluminescence, fluorescence, colorimetric reactions, antibody binding, inducible markers, etc.

[0087] "Inhibitors," "activators," and "modulators" of the markers are used to refer to activating, inhibitory, or modulating molecules identified using *in vitro* and *in vivo* assays of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS). Inhibitors are compounds that, e.g., bind to, partially or totally block activity, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity or expression of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis

(RRMS). "Activators" are compounds that increase, open, activate, facilitate, enhance activation, sensitize, agonize, or up regulate activity of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS), e.g., agonists. Inhibitors, activators, or modulators also include genetically modified versions of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS), e.g., versions with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, antibodies, peptides, cyclic peptides, nucleic acids, antisense molecules, ribozymes, RNAi molecules, small organic molecules and the like. Such assays for inhibitors and activators include, e.g., expressing biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS) *in vitro*, in cells, or cell extracts, applying putative modulator compounds, and then determining the functional effects on activity, as described above.

[0088] Samples or assays comprising biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS) that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of inhibition. Control samples (untreated with inhibitors) are assigned a relative protein activity value of 100%. Inhibition of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS) is achieved when the activity value relative to the control is about 80%, preferably 50%, more preferably 25-0%. Activation of biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS) is achieved when the activity value relative to the control (untreated with activators) is 110%, more preferably 150%, more preferably 200-500% (i.e., two to five fold higher relative to the control), more preferably 1000-3000% higher.

[0089] The term "test compound" or "drug candidate" or "modulator" or grammatical equivalents as used herein describes any molecule, either naturally occurring or synthetic, e.g., protein, oligopeptide (e.g., from about 5 to about 25 amino acids in length, preferably from about 10 to 20 or 12 to 18 amino acids in length, preferably 12, 15, or 18 amino acids in length), small organic molecule, polysaccharide, peptide, circular peptide, lipid, fatty acid, siRNA, polynucleotide, oligonucleotide, etc., to be tested for the capacity to directly or indirectly modulate biomarkers responsive to IVIG treatment of relapsing-remitting multiple sclerosis (RRMS). The test compound can be in the form of a library of test compounds, such as a combinatorial or randomized library that provides a sufficient range of diversity. Test compounds are optionally linked to a fusion partner, e.g., targeting compounds, rescue compounds, dimerization compounds, stabilizing compounds, addressable compounds, and

other functional moieties. Conventionally, new chemical entities with useful properties are generated by identifying a test compound (called a "lead compound") with some desirable property or activity, e.g., inhibiting activity, creating variants of the lead compound, and evaluating the property and activity of those variant compounds. Often, high throughput screening (HTS) methods are employed for such an analysis.

[0090] A "small organic molecule" refers to an organic molecule, either naturally occurring or synthetic, that has a molecular weight of more than about 50 daltons and less than about 2500 daltons, preferably less than about 2000 daltons, preferably between about 100 to about 1000 daltons, more preferably between about 200 to about 500 daltons.

PROGNOSTIC METHODS

[0091] The present invention provides methods of providing a prognosis of IVIG treatment of multiple sclerosis, including relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, or Parkinson's disease by detecting the expression of markers overexpressed or underexpressed in patients treated with IVIG. Providing a prognosis involves determining the level of one or more IVIG responsive biomarker polynucleotides or the corresponding polypeptides in a patient or patient sample and then comparing the level to a baseline or range. Typically, the baseline value is representative of levels of the polynucleotide or nucleic acid in a relapsing-remitting multiple sclerosis (RRMS) patient prior to IVIG treatment, as measured using a biological sample such as a sample of a bodily fluid (e.g., blood or cerebrospinal fluid). Variation of levels of a polynucleotide or corresponding polypeptides of the invention from the baseline range (either up or down) indicates that the patient is benefiting from IVIG treatment of relapsing-remitting multiple sclerosis (RRMS).

[0092] As used herein, the term "providing a prognosis" refers to providing a prediction of the probable course and outcome of treatment of a patient suffering from multiple sclerosis, including relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, or Parkinson's disease with IVIG. The methods can also be used to devise a suitable alternative or additional therapy for multiple sclerosis, including relapsing-remitting multiple sclerosis (RRMS) treatment, Alzheimer's disease, or Parkinson's disease, e.g., by indicating the failure of IVIG treatment to alleviate multiple sclerosis, including relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, or Parkinson's disease. The prognosis can be used to adjust dose or frequency of IVIG administration as well.

[0093] Antibody reagents can be used in assays to detect expression levels of the biomarkers of the invention in patient samples using any of a number of immunoassays known to those skilled in the art. Immunoassay techniques and protocols are generally described in Price and Newman, "Principles and Practice of Immunoassay," 2nd Edition, Grove's Dictionaries, 1997; and Gosling, "Immunoassays: A Practical Approach," Oxford University Press, 2000. A variety of immunoassay techniques, including competitive and non-competitive immunoassays, can be used. *See, e.g.,* Self *et al.*, *Curr. Opin. Biotechnol.*, 7:60-65 (1996). The term immunoassay encompasses techniques including, without limitation, enzyme immunoassays (EIA) such as enzyme multiplied immunoassay technique (EMIT), enzyme-linked immunosorbent assay (ELISA), IgM antibody capture ELISA (MAC ELISA), and microparticle enzyme immunoassay (MEIA); capillary electrophoresis immunoassays (CEIA); radioimmunoassays (RIA); immunoradiometric assays (IRMA); fluorescence polarization immunoassays (FPIA); and chemiluminescence assays (CL). If desired, such immunoassays can be automated. Immunoassays can also be used in conjunction with laser induced fluorescence. *See, e.g.,* Schmalzing *et al.*, *Electrophoresis*, 18:2184-93 (1997); Bao, *J. Chromatogr. B. Biomed. Sci.*, 699:463-80 (1997). Liposome immunoassays, such as flow-injection liposome immunoassays and liposome immunosensors, are also suitable for use in the present invention. *See, e.g.,* Rongen *et al.*, *J. Immunol. Methods*, 204:105-133 (1997). In addition, nephelometry assays, in which the formation of protein/antibody complexes results in increased light scatter that is converted to a peak rate signal as a function of the marker concentration, are suitable for use in the methods of the present invention. Nephelometry assays are commercially available from Beckman Coulter (Brea, CA; Kit #449430) and can be performed using a Behring Nephelometer Analyzer (Fink *et al.*, *J. Clin. Chem. Clin. Biochem.*, 27:261-276 (1989)).

[0094] Specific immunological binding of antibodies can be detected directly or indirectly. Direct labels include fluorescent or luminescent tags, metals, dyes, radionuclides, and the like, attached to the antibody. An antibody labeled with iodine-125 (^{125}I) can be used. A chemiluminescence assay using a chemiluminescent antibody specific for the nucleic acid is suitable for sensitive, non-radioactive detection of protein levels. An antibody labeled with fluorochrome is also suitable. Examples of fluorochromes include, without limitation, DAPI, fluorescein, Hoechst 33258, R-phycocyanin, B-phycoerythrin, R-phycoerythrin, rhodamine, Texas red, and lissamine. Indirect labels include various enzymes well known in the art, such as horseradish peroxidase (HRP), alkaline phosphatase (AP), β-galactosidase, urease, and the

like. A horseradish-peroxidase detection system can be used, for example, with the chromogenic substrate tetramethylbenzidine (TMB), which yields a soluble product in the presence of hydrogen peroxide that is detectable at 450 nm. An alkaline phosphatase detection system can be used with the chromogenic substrate p-nitrophenyl phosphate, for example, which yields a soluble product readily detectable at 405 nm. Similarly, a β-galactosidase detection system can be used with the chromogenic substrate o-nitrophenyl-β-D-galactopyranoside (ONPG), which yields a soluble product detectable at 410 nm. An urease detection system can be used with a substrate such as urea-bromocresol purple (Sigma Immunochemicals; St. Louis, MO).

[0095] A signal from the direct or indirect label can be analyzed, for example, using a spectrophotometer to detect color from a chromogenic substrate; a radiation counter to detect radiation such as a gamma counter for detection of ^{125}I; or a fluorometer to detect fluorescence in the presence of light of a certain wavelength. For detection of enzyme-linked antibodies, a quantitative analysis can be made using a spectrophotometer such as an EMAX Microplate Reader (Molecular Devices; Menlo Park, CA) in accordance with the manufacturer's instructions. If desired, the assays of the present invention can be automated or performed robotically, and the signal from multiple samples can be detected simultaneously.

[0096] The antibodies can be immobilized onto a variety of solid supports, such as magnetic or chromatographic matrix particles, the surface of an assay plate (*e.g.*, microtiter wells), pieces of a solid substrate material or membrane (*e.g.*, plastic, nylon, paper), and the like. An assay strip can be prepared by coating the antibody or a plurality of antibodies in an array on a solid support. This strip can then be dipped into the test sample and processed quickly through washes and detection steps to generate a measurable signal, such as a colored spot.

[0097] Alternatively, nucleic acid binding molecules such as probes, oligonucleotides, oligonucleotide arrays, and primers can be used in assays to detect differential RNA expression in patient samples, *e.g.*, RT-PCR. In one embodiment, RT-PCR is used according to standard methods known in the art. In another embodiment, PCR assays such as Taqman® assays available from, *e.g.*, Applied Biosystems, can be used to detect nucleic acids and variants thereof. In other embodiments, qPCR and nucleic acid microarrays can be used to

detect nucleic acids. Reagents that bind to selected biomarkers can be prepared according to methods known to those of skill in the art or purchased commercially.

[0098] Analysis of nucleic acids can be achieved using routine techniques such as Southern analysis, reverse-transcriptase polymerase chain reaction (RT-PCR), or any other methods based on hybridization to a nucleic acid sequence that is complementary to a portion of the marker coding sequence (*e.g.*, slot blot hybridization) are also within the scope of the present invention. Applicable PCR amplification techniques are described in, *e.g.*, Ausubel *et al.* and Innis *et al.*, *supra*. General nucleic acid hybridization methods are described in Anderson, "Nucleic Acid Hybridization," BIOS Scientific Publishers, 1999. Amplification or hybridization of a plurality of nucleic acid sequences (*e.g.*, genomic DNA, mRNA or cDNA) can also be performed from mRNA or cDNA sequences arranged in a microarray. Microarray methods are generally described in Hardiman, "Microarrays Methods and Applications: Nuts & Bolts," DNA Press, 2003; and Baldi *et al.*, "DNA Microarrays and Gene Expression: From Experiments to Data Analysis and Modeling," Cambridge University Press, 2002.

[0099] Analysis of nucleic acid markers and their variants can be performed using techniques known in the art including, without limitation, microarrays, polymerase chain reaction (PCR)-based analysis, sequence analysis, and electrophoretic analysis. A non-limiting example of a PCR-based analysis includes a Taqman® allelic discrimination assay available from Applied Biosystems. Non-limiting examples of sequence analysis include Maxam-Gilbert sequencing, Sanger sequencing, capillary array DNA sequencing, thermal cycle sequencing (Sears *et al.*, *Biotechniques*, 13:626-633 (1992)), solid-phase sequencing (Zimmerman *et al.*, *Methods Mol. Cell Biol.*, 3:39-42 (1992)), sequencing with mass spectrometry such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS; Fu *et al.*, *Nat. Biotechnol.*, 16:381-384 (1998)), and sequencing by hybridization. Chee *et al.*, *Science*, 274:610-614 (1996); Drmanac *et al.*, *Science*, 260:1649-1652 (1993); Drmanac *et al.*, *Nat. Biotechnol.*, 16:54-58 (1998). Non-limiting examples of electrophoretic analysis include slab gel electrophoresis such as agarose or polyacrylamide gel electrophoresis, capillary electrophoresis, and denaturing gradient gel electrophoresis. Other methods for detecting nucleic acid variants include, *e.g.*, the INVADER® assay from Third Wave Technologies, Inc., restriction fragment length polymorphism (RFLP) analysis, allele-specific oligonucleotide hybridization, a heteroduplex

mobility assay, single strand conformational polymorphism (SSCP) analysis, single-nucleotide primer extension (SNUPE) and pyrosequencing.

[0100] A detectable moiety can be used in the assays described herein. A wide variety of detectable moieties can be used, with the choice of label depending on the sensitivity required, ease of conjugation with the antibody, stability requirements, and available instrumentation and disposal provisions. Suitable detectable moieties include, but are not limited to, radionuclides, fluorescent dyes (*e.g.,* fluorescein, fluorescein isothiocyanate (FITC), Oregon Green™, rhodamine, Texas red, tetrarhodimine isothiocynate (TRITC), Cy3, Cy5, *etc.*), fluorescent markers (*e.g.,* green fluorescent protein (GFP), phycoerythrin, *etc.*), autoquenched fluorescent compounds that are activated by tumor-associated proteases, enzymes (*e.g.,* luciferase, horseradish peroxidase, alkaline phosphatase, *etc.*), nanoparticles, biotin, digoxigenin, and the like.

[0101] Useful physical formats comprise surfaces having a plurality of discrete, addressable locations for the detection of a plurality of different markers. Such formats include microarrays and certain capillary devices. *See, e.g.,* Ng *et al., J. Cell Mol. Med.,* 6:329-340 (2002); U.S. Pat. No. 6,019,944. In these embodiments, each discrete surface location may comprise antibodies to immobilize one or more markers for detection at each location. Surfaces may alternatively comprise one or more discrete particles (*e.g.,* microparticles or nanoparticles) immobilized at discrete locations of a surface, where the microparticles comprise antibodies to immobilize one or more markers for detection.

[0102] Analysis can be carried out in a variety of physical formats. For example, the use of microtiter plates or automation could be used to facilitate the processing of large numbers of test samples. Alternatively, single sample formats could be developed to facilitate a prognosis in a timely fashion.

[0103] Alternatively, the antibodies or nucleic acid probes of the invention can be applied to sections of patient biopsies immobilized on microscope slides. The resulting antibody staining or in situ hybridization pattern can be visualized using any one of a variety of light or fluorescent microscopic methods known in the art.

[0104] In another format, the various markers of the invention also provide reagents for in vivo imaging such as, for instance, the imaging of labeled regents that detect the nucleic acids or encoded proteins of the biomarkers of the invention. For in vivo imaging purposes, reagents that detect the presence of proteins encoded by IVIG-responsive relapsing-remitting

multiple sclerosis (RRMS) biomarkers, such as antibodies, may be labeled using an appropriate marker, such as a fluorescent marker.

PREPARATIONS AND ADMINISTRATION OF IVIG

[0105] IVIG compositions comprising whole antibodies have been described for the treatment of certain autoimmune conditions. (*See, e.g.*, U.S. Patent Publication US 2002/0114802, US 2003/0099635, and US 2002/0098182.) The IVIG compositions disclosed in these references include polyclonal antibodies.

[0106] Immunoglobulin preparations according to the present invention can be prepared from any suitable starting materials. For example, immunoglobulin preparations can be prepared from donor serum or monoclonal or recombinant immunoglobulins. In a typical example, blood is collected from healthy donors. Usually, the blood is collected from the same species of animal as the subject to which the immunoglobulin preparation will be administered (typically referred to as "homologous" immunoglobulins). The immunoglobulins are isolated from the blood by suitable procedures, such as, for example, Cohn fractionation, ultracentrifugation, electrophoretic preparation, ion exchange chromatography, affinity chromatography, immunoaffinity chromatography, polyethylene glycol fractionation, or the like. (*See, e.g.*, Cohn *et al.*, *J. Am. Chem. Soc.* 68:459-75 (1946); Oncley *et al.*, *J. Am. Chem. Soc.* 71:541-50 (1949); Barundern *et al.*, *Vox Sang.* 7:157-74 (1962); Koblet *et al.*, *Vox Sang.* 13:93-102 (1967); U.S. Patent Nos. 5,122,373 and 5,177,194; the disclosures of which are incorporated by reference herein.)

[0107] In certain embodiments, immunoglobulin is prepared from gamma globulin-containing products produced by the alcohol fractionation and/or ion exchange and affinity chromatography methods well known to those skilled in the art. Purified Cohn Fraction II is commonly used. The starting Cohn Fraction II paste is typically about 95 percent IgG and is comprised of the four IgG subtypes. The different subtypes are present in Fraction II in approximately the same ratio as they are found in the pooled human plasma from which they are obtained. The Fraction II is further purified before formulation into an administrable product. For example, the Fraction II paste can be dissolved in a cold purified aqueous alcohol solution and impurities removed via precipitation and filtration. Following the final filtration, the immunoglobulin suspension can be dialyzed or diafiltered (*e.g.*, using ultrafiltration membranes having a nominal molecular weight limit of less than or equal to

100,000 daltons) to remove the alcohol. The solution can be concentrated or diluted to obtain the desired protein concentration and can be further purified by techniques well known to those skilled in the art.

[0108] Preparative steps can be used to enrich a particular isotype or subtype of immunoglobulin. For example, protein A, protein G or protein H sepharose chromatography can be used to enrich a mixture of immunoglobulins for IgG, or for specific IgG subtypes. (*See generally* Harlow and Lane, *Using Antibodies*, Cold Spring Harbor Laboratory Press (1999); Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1988); U.S. Patent No. 5,180,810.)

[0109] Commercial sources of immunoglobulins can also be used. Such sources include but are not limited to: Gammagard S/D® (Baxter Healthcare); BayRho-D® products (Bayer Biological); Gamimune N®, 5% (Bayer Biological); Gamimune N®, 5% Solvent/Detergent Treated (Bayer Biological); Gamimune N®, 10% (Bayer Biological); Sandoglobulin I.V.® (Novartis); Polygam S/D® (American Red Cross); Venoglobulin-S® 5% Solution Solvent Detergent Treated (Alpha Therapeutic); Venoglobulin-S® 10% Solution Solvent Detergent/Treated (Alpha Therapeutic); and VZIG® (American Red Cross). The commercial source of immunoglobulin preparation for use in the methods of the present invention is not critical.

[0110] An alternative approach is to use fragments of antibodies, such as Fc fragments of immunoglobulins. An Fc preparation comprises Fc fragments of immunoglobulins. The term "Fc fragment" refers to a portion of an immunoglobulin heavy chain constant region containing at least one heavy chain constant region domain (*e.g.*, C_H2, C_H3 and/or C_H4) or an antigenic portion thereof, but excluding the variable regions of the immunoglobulin. (As used herein, a variable region refers to region of the immunoglobulin that binds to an antigen, but excludes the C_H1 and C_L domains.) The Fc preparation can contain entire Fc fragments and/or portions thereof (*e.g.*, one or more heavy chain constant region domains or portions thereof containing an epitope(s) bound by the rheumatoid factors). An Fc fragment optionally can include an immunoglobulin hinge region, a heavy chain C_H1 domain, and/or a heavy chain C_H1 domain joined to a light chain C_L domain.

[0111] An Fc preparation includes Fc fragments of at least one Fc isotype and can contain a mixture of immunoglobulin Fc fragments of different isotypes (*e.g.*, IgA, IgD, IgE, IgG and/or IgM). The Fc preparation also can contain predominantly (at least 60%, at least 75%,

at least 90%, at least 95%, or at least 99%) Fc fragments from one immunoglobulin isotype, and can contain minor amounts of the other subtypes. For example, an Fc preparation can contain at least at least about 75%, at least about 90%, at least about 95%, or at least about 99% IgG Fc fragments. In addition, the Fc preparation can comprise a single IgG subtype or a mixture two or more of IgG Fc subtypes. Suitable IgG subtypes include IgG1, IgG2, IgG3, and IgG4. In a specific embodiment, the Fc preparation comprises IgG1 Fc fragments.

[0112] An Fc preparation is substantially free of $F(ab')_2$ fragments (*i.e.*, heavy and light chain variable and first constant regions and a portion of the hinge region, which can be produced by pepsin digestion of the antibody molecule), Fab' fragments (*i.e.*, Fab' fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragment), or Fab fragments (*i.e.*, which can be generated by treating the antibody molecule with papain and a reducing agent). In this context, "substantially free" means the Fc preparation contains less than about 30%, less than about 20%, less than about 10%, less than about 5%, or less than about 1% $F(ab')_2$, Fab' or Fab fragments. In another embodiment, the Fc preparation contains Fc fragments which are essentially free of $F(ab')_2$, Fab' or Fab fragments. The Fc preparations are typically substantially free of whole (*i.e.*, full length) immunoglobulins. In this context, "substantially free" means less than about 25%, or less than about 10%, or less than about 5%, or less than about 2%, less than about 1% or are free of full length immunoglobulins.

[0113] Immunoglobulins can be cleaved at any suitable time during preparation to separate the Fc fragments from the Fab, F(ab') and/or $F(ab')_2$ fragments, as applicable. A suitable enzyme for cleavage is, for example, papain, pepsin or plasmin. (*See, e.g.*, Harlow and Lane, *Using Antibodies*, Cold Spring Harbor Laboratory Press (1999); Plan and Makula, *Vox Sanguinis* 28:157-75 (1975).) After cleavage, the Fc portions can be separated from the Fab F(ab') and/or $F(ab')_2$ fragments by, for example, affinity chromatography, ion exchange chromatography, gel filtration, or the like. In a specific example, immunoglobulins are digested with papain to separate the Fc fragment from the Fab fragments. The digestion mixture is then subjected to cationic exchange chromatography to separate the Fc fragments from the Fab fragments.

[0114] Immunoglobulin or Fc fragments can also be prepared from hybridomas or other culture system which express monoclonal antibody. (*See, e.g.*, Kohler and Milstein, *Nature* 256:495-97 (1975); Hagiwara and Yuasa, Hum. *Antibodies Hybridomas* 4:15-19 (1993);

Kozbor *et al.*, *Immunology Today* 4:72 (1983); Cole *et al.*, in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96 (1985).) Human monoclonal antibodies can be obtained, for example, from human hybridomas (*see, e.g.*, Cote *et al.*, *Proc. Natl. Acad. Sci. USA* 80:2026-30 (1983)) or by transforming human B cells with EBV virus *in vitro* (*see, e.g.*, Cole *et al.*, *supra*). Monoclonal antibodies produced from hybridomas can be purified and the Fc fragments separated from the Fab, F(ab') and/or $F(ab')_2$ fragments as described herein or as known to the skilled artisan.

[0115] Immunoglobulin or Fc fragments also can be produced recombinantly, such as from eukaryotic cell culture systems. For example, an Fc fragment of an immunoglobulin can be recombinantly produced by Chinese hamster ovary (CHO) cells transfected with a vector containing a DNA sequence encoding the Fc fragment. Methods for creating such recombinant mammalian cells are described in, for example, Sambrook and Russell, *Molecular Cloning, A Laboratory Manual*, 3rd ed. (Cold Spring Harbor Laboratory Press (New York) 2001) and Ausubel *et al.*, *Short Protocols in Molecular Biology*, 4th ed. (John Wiley & Sons, Inc. (New York) 1999) and are known to the skilled artisan. Recombinant Fc can also be produced in other mammalian cell lines, such as baby hamster kidney (BHK) cells. Methods of culturing recombinant cells to produce recombinant proteins are also known to the art.

[0116] A variety of other expression systems can be utilized to express recombinant immunoglobulins or Fc fragments. These include, but are not limited to, insect cell systems and microorganisms such as yeast or bacteria which have been transfected or transformed with an expression cassette encoding the desired Fc fragment. In certain embodiments, the microorganism optionally can be engineered to reproduce glycosylation patterns of mammalian or human Fc fragments.

[0117] In certain embodiments, further preparative steps can be used in order to render an immunoglobulin or Fc preparation safe for use in the methods according to the present invention. Such steps can include, for example, treatment with solvent/detergent, pasteurization and sterilization. Additional preparative steps may be used in order to ensure the safety of an Fc preparation. Such preparative steps can include, for example, enzymatic hydrolysis, chemical modification via reduction and alkylation, sulfonation, treatment with ß-propiolactone, treatment at low pH, or the like. Descriptions of suitable methods can also be found in, for example, U.S. Patent Nos. 4,608,254; 4,687,664; 4,640,834; 4,814,277;

5,864,016; 5,639,730 and 5,770,199; Romer *et al.*, *Vox Sang.* 42:62-73 (1982); Romer *et al.*, *Vox Sang.* 42:74-80 (1990); and Rutter, *J. Neurosurg. Psychiat.* 57 (Suppl.):2-5 (1994) (the disclosures of which are incorporated by reference herein).

[0118] An effective amount of an immunoglobulin or Fc preparation is administered to the subject generally by intravenous means. The term "effective amount" refers to an amount of an immunoglobulin or Fc preparation that results in an improvement or remediation of RRMS in the subject. An effective amount to be administered to the subject can be determined by a physician with consideration of individual differences in age, weight, disease severity and response to the therapy. In certain embodiments, an immunoglobulin or Fc preparation can be administered to a subject at about 5 mg/kilogram to about 500 mg/kilogram each day. In additional embodiments, an mmunoglobulin or Fc preparation can be administered in amounts of at least about 10 mg/kilogram, at last 15 mg/kilogram, at least 20 mg/kilogram, at least 25 mg/kilogram, at least 30 mg/kilogram or at least 50 mg/kilogram. In additional embodiments, an mmunoglobulin or Fc preparation can be administered to a subject at doses up to about 100 mg/kilogram, to about 150 mg/kilogram, to about 200 mg/kilogram, to about 250 mg/kilogram, to about 300 mg/kilogram, to about 400 mg/kilogram each day. In other embodiments, the doses of the mmunoglobulin or Fc preparation can be greater or less. Immunoglobulin or Fc preparations can be administered in one or more doses per day.

[0119] In accordance with the present invention, the time needed to complete a course of the treatment can be determined by a physician and may range from as short as one day to more than a month. In certain embodiments, a course of treatment can be from 1 to 6 months.

COMPOSITIONS, KITS AND INTEGRATED SYSTEMS

[0120] The invention provides compositions, kits and integrated systems for practicing the assays described herein using antibodies specific for the polypeptides or nucleic acids specific for the polynucleotides of the invention.

[0121] Kits for carrying out the diagnostic assays of the invention typically include a probe that comprises an antibody or nucleic acid sequence that specifically binds to polypeptides or polynucleotides of the invention, and a label for detecting the presence of the probe. The kits may include several antibodies or polynucleotide sequences encoding polypeptides of the

invention, e.g., a cocktail of antibodies that recognize the proteins encoded by the biomarkers of the invention.

METHODS TO IDENTIFY COMPOUNDS

[0122] A variety of methods may be used to identify compounds that prevent or treat multiple sclerosis, including relapsing-remitting multiple sclerosis (RRMS), Alzheimer's disease, or Parkinson's disease. Typically, an assay that provides a readily measured parameter is adapted to be performed in the wells of multi-well plates in order to facilitate the screening of members of a library of test compounds as described herein. Thus, in one embodiment, an appropriate number of cells, e.g., T cells, can be plated into the cells of a multi-well plate, and the effect of a test compound on the expression of an IVIG-responsive relapsing-remitting multiple sclerosis (RRMS) biomarker can be determined.

[0123] The compounds to be tested can be any small chemical compound, or a macromolecule, such as a protein, sugar, nucleic acid or lipid. Typically, test compounds will be small chemical molecules and peptides. Essentially any chemical compound can be used as a test compound in this aspect of the invention, although most often compounds that can be dissolved in aqueous or organic (especially DMSO-based) solutions are used. The assays are designed to screen large chemical libraries by automating the assay steps and providing compounds from any convenient source to assays, which are typically run in parallel (*e.g.*, in microtiter formats on microtiter plates in robotic assays). It will be appreciated that there are many suppliers of chemical compounds, including Sigma (St. Louis, MO), Aldrich (St. Louis, MO), Sigma-Aldrich (St. Louis, MO), Fluka Chemika-Biochemica Analytika (Buchs Switzerland) and the like.

[0124] In one preferred embodiment, high throughput screening methods are used which involve providing a combinatorial chemical or peptide library containing a large number of potential therapeutic compounds. Such "combinatorial chemical libraries" or "ligand libraries" are then screened in one or more assays, as described herein, to identify those library members (particular chemical species or subclasses) that display a desired characteristic activity. In this instance, such compounds are screened for their ability to reduce or increase the expression of the relapsing-remitting multiple sclerosis (RRMS) biomarkers of the invention.

[0125] A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis, by combining a number of

chemical "building blocks" such as reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining a set of chemical building blocks (amino acids) in every possible way for a given compound length (*i.e.*, the number of amino acids in a polypeptide compound). Millions of chemical compounds can be synthesized through such combinatorial mixing of chemical building blocks.

[0126] Preparation and screening of combinatorial chemical libraries are well known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries (*see, e.g.,* U.S. Patent 5,010,175, Furka, *Int. J. Pept. Prot. Res.*, 37:487-493 (1991) and Houghton *et al.*, *Nature,* 354:84-88 (1991)). Other chemistries for generating chemical diversity libraries can also be used. Such chemistries include, but are not limited to: peptoids (*e.g.*, PCT Publication No. WO 91/19735), encoded peptides (*e.g.*, PCT Publication No. WO 93/20242), random bio-oligomers (*e.g.*, PCT Publication No. WO 92/00091), benzodiazepines (*e.g.*, U.S. Patent No. 5,288,514), diversomers such as hydantoins, benzodiazepines and dipeptides (Hobbs *et al.*, *PNAS USA,* 90:6909-6913 (1993)), vinylogous polypeptides (Hagihara *et al.*, *J. Amer. Chem. Soc.*, 114:6568 (1992)), nonpeptidal peptidomimetics with glucose scaffolding (Hirschmann *et al.*, *J. Amer. Chem. Soc.,* 114:9217-9218 (1992)), analogous organic syntheses of small compound libraries (Chen *et al.*, *J. Amer. Chem. Soc.,* 116:2661 (1994)), oligocarbamates (Cho *et al.*, *Science*, 261:1303 (1993)), and/or peptidyl phosphonates (Campbell *et al.*, *J. Org. Chem.*, 59:658 (1994)), nucleic acid libraries (*see* Ausubel, Berger and Sambrook, all *supra*), peptide nucleic acid libraries (*see, e.g.,* U.S. Patent No. 5,539,083), antibody libraries (*see, e.g.,* Vaughn *et al.*, *Nature Biotechnology*, 14(3):309-314 (1996) and PCT/US96/10287), carbohydrate libraries (*see, e.g.,* Liang *et al.*, *Science*, 274:1520-1522 (1996) and U.S. Patent No. 5,593,853), small organic molecule libraries (*see, e.g.,* benzodiazepines, Baum C&EN, Jan 18, page 33 (1993); isoprenoids, U.S. Patent No. 5,569,588; thiazolidinones and metathiazanones, U.S. Patent No. 5,549,974; pyrrolidines, U.S. Patent Nos. 5,525,735 and 5,519,134; morpholino compounds, U.S. Patent No. 5,506,337; benzodiazepines, 5,288,514, and the like).

[0127] Devices for the preparation of combinatorial libraries are commercially available (*see, e.g.,* 357 MPS, 390 MPS, Advanced Chem Tech, Louisville KY, Symphony, Rainin, Woburn, MA, 433A Applied Biosystems, Foster City, CA, 9050 Plus, Millipore, Bedford, MA). In addition, numerous combinatorial libraries are themselves commercially available (*see, e.g.,* ComGenex, Princeton, N.J., Asinex, Moscow, Ru, Tripos, Inc., St. Louis, MO,

ChemStar, Ltd, Moscow, RU, 3D Pharmaceuticals, Exton, PA, Martek Biosciences, Columbia, MD, *etc.*).

[0128] In the high throughput assays of the invention, it is possible to screen up to several thousand different modulators or ligands in a single day. In particular, each well of a microtiter plate can be used to run a separate assay against a selected potential modulator, or, if concentration or incubation time effects are to be observed, every 5-10 wells can test a single modulator. Thus, a single standard microtiter plate can assay about 96 modulators. If 1536 well plates are used, then a single plate can easily assay from about 100- about 1500 different compounds. It is possible to assay many plates per day; assay screens for up to about 6,000, 20,000, 50,000, or 100,000 or more different compounds is possible using the integrated systems of the invention.

METHODS TO INHIBIT OR ACTIVATE BIOMARKER PROTEINS OR BIOMARKER RECEPTOR FUNCTION USING ANTIBODIES

[0129] Because the biomarkers of the present invention are overexpressed or underexpressed in response to IVIG treatment of multiple sclerosis, Alzheimer's disease, or Parkinson's disease, the biomarker proteins or their cellular receptors, may serve as targets for multiple sclerosis therapy using antibodies. In the case of, for instance, of chemokines, such as CXCL5, CXCL3, and CCL13, whose expression is decreased upon treatment of RRMS with IVIG, antibodies that bind to and inactivate these chemokines or their receptors can be used in the treatment of multiple sclerosis, Alzheimer's disease, or Parkinson's disease. Alternatively, in the case of chemokines, such as XCL2, whose expression is increased upon IVIG treatment, antibodies may be generated which bind to and activate XCL2 receptors, thus mimicking the effect of XCL2 binding.

[0130] The antibodies described above may be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material which when combined with the antibody does not interfere with function of the antibody and is non-reactive with the subject's immune systems. Examples include, but are not limited to, any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like (see, generally, *Remington's Pharmaceutical Sciences*, 20th ed., 2003).

[0131] Antibody formulations may be administered via any route capable of delivering the antibodies to an individual suffering from multiple sclerosis. Potentially effective routes of

administration include, but are not limited to, intravenous, intraperitoneal, intramuscular, intradermal, and the like. One preferred route of administration is by intravenous injection. A preferred formulation for intravenous injection comprises the antibodies in a solution of preserved bacteriostatic water, sterile unpreserved water, and/or diluted in polyvinylchloride or polyethylene bags containing 0.9% sterile Sodium Chloride for Injection, USP. The antibody preparation may be lyophilized and stored as a sterile powder, preferably under vacuum, and then reconstituted in bacteriostatic water containing, for example, benzyl alcohol preservative, or in sterile water prior to injection.

[0132] Treatment will generally involve the repeated administration of antibody preparations via an acceptable route of administration such as intravenous injection (IV), at an effective dose. Dosages will depend upon various factors generally appreciated by those of skill in the art, including without limitation the type, stage, the severity, grade, or stage of multiple sclerosis, the binding affinity and half life of the antibody used, the degree of biomarker or receptor expression in the patient, the desired steady-state antibody concentration level, frequency of treatment, and the influence of any other agents used in combination with the treatment method of the invention. Typical daily doses may range from about 0.1 to 100 mg/kg. Doses in the range of 10-500 mg mAb per week may be effective and well tolerated, although even higher weekly doses may be appropriate and/or well tolerated. The principal determining factor in defining the appropriate dose is the amount of a particular antibody necessary to be therapeutically effective in a particular context. Repeated administrations may be required in order to achieve longer lasting remission in RRMS. Initial loading doses may be higher. The initial loading dose may be administered as an infusion. Periodic maintenance doses may be administered similarly, provided the initial dose is well tolerated.

METHODS TO INHIBIT MARKER PROTEIN EXPRESSION USING NUCLEIC ACIDS

[0133] A variety of nucleic acids, such as antisense nucleic acids, siRNAs or ribozymes, may be used to inhibit the function of the markers of this invention. Ribozymes that cleave mRNA at site-specific recognition sequences can be used to destroy target mRNAs, particularly through the use of hammerhead ribozymes. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. Preferably, the target mRNA has the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art.

[0134] Gene targeting ribozymes necessarily contain a hybridizing region complementary to two regions, each of at least 5 and preferably each 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous nucleotides in length of a target mRNA. In addition, ribozymes possess highly specific endoribonuclease activity, which autocatalytically cleaves the target sense mRNA.

[0135] With regard to antisense, siRNA or ribozyme oligonucleotides, phosphorothioate oligonucleotides can be used. Modifications of the phosphodiester linkage as well as of the heterocycle or the sugar may provide an increase in efficiency. Phophorothioate is used to modify the phosphodiester linkage. An N3'-P5' phosphoramidate linkage has been described as stabilizing oligonucleotides to nucleases and increasing the binding to RNA. Peptide nucleic acid (PNA) linkage is a complete replacement of the ribose and phosphodiester backbone and is stable to nucleases, increases the binding affinity to RNA, and does not allow cleavage by RNAse H. Its basic structure is also amenable to modifications that may allow its optimization as an antisense component. With respect to modifications of the heterocycle, certain heterocycle modifications have proven to augment antisense effects without interfering with RNAse H activity. An example of such modification is C-5 thiazole modification. Finally, modification of the sugar may also be considered. 2'-O-propyl and 2'-methoxyethoxy ribose modifications stabilize oligonucleotides to nucleases in cell culture and *in vivo*.

[0136] Inhibitory oligonucleotides can be delivered to a cell by direct transfection or transfection and expression via an expression vector. Appropriate expression vectors include mammalian expression vectors and viral vectors, into which has been cloned an inhibitory oligonucleotide with the appropriate regulatory sequences including a promoter to result in expression of the antisense RNA in a host cell. Suitable promoters can be constitutive or development-specific promoters. Transfection delivery can be achieved by liposomal transfection reagents, known in the art (*e.g.*, Xtreme transfection reagent, Roche, Alameda, CA; Lipofectamine formulations, Invitrogen, Carlsbad, CA). Delivery mediated by cationic liposomes, by retroviral vectors and direct delivery are efficient. Another possible delivery mode is targeting using antibody to cell surface markers for the target cells.

[0137] For transfection, a composition comprising one or more nucleic acid molecules (within or without vectors) can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in

pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described, for example, in Gilmore, *et al.*, *Curr Drug Delivery* (2006) 3:147-5 and Patil, *et al.*, *AAPS Journal* (2005) 7:E61-E77, each of which are incorporated herein by reference. Delivery of siRNA molecules is also described in several U.S. Patent Publications, including for example, 2006/0019912; 2006/0014289; 2005/0239687; 2005/0222064; and 2004/0204377, the disclosures of each of which are hereby incorporated herein by reference. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, by electroporation, or by incorporation into other vehicles, including biodegradable polymers, hydrogels, cyclodextrins (*see, for example* Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang et al., International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example U.S. Pat. No. 6,447,796 and US Patent Application Publication No. 2002/130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

[0138] Examples of liposomal transfection reagents of use with this invention include, for example: CellFectin, 1:1.5 (M/M) liposome formulation of the cationic lipid N,NI,NII,NIII-tetramethyl-N,NI,NII,NIII-tetrapalmit-y-spermine and dioleoyl phosphatidylethanolamine (DOPE) (GIBCO BRL); Cytofectin GSV, 2:1 (M/M) liposome formulation of a cationic lipid and DOPE (Glen Research); DOTAP (N-[1-(2,3-dioleoyloxy)-N,N,N-tri-methyl-ammoniummethylsulfate) (Boehringer Manheim); Lipofectamine, 3:1 (M/M) liposome formulation of the polycationic lipid DOSPA and the neutral lipid DOPE (GIBCO BRL); and (5) siPORT (Ambion); HiPerfect (Qiagen); X-treme GENE (Roche); RNAicarrier (Epoch Biolabs) and TransPass (New England Biolabs).

[0139] In some embodiments, antisense, siRNA, or ribozyme sequences are delivered into the cell via a mammalian expression vector. For example, mammalian expression vectors suitable for siRNA expression are commercially available, for example, from Ambion (*e.g.*, pSilencer vectors), Austin, TX; Promega (*e.g.*, GeneClip, siSTRIKE, SiLentGene), Madison,

WI; Invitrogen, Carlsbad, CA; InvivoGen, San Diego, CA; and Imgenex, San Diego, CA. Typically, expression vectors for transcribing siRNA molecules will have a U6 promoter.

[0140] In some embodiments, antisense, siRNA, or ribozyme sequences are delivered into cells via a viral expression vector. Viral vectors suitable for delivering such molecules to cells include adenoviral vectors, adeno-associated vectors, and retroviral vectors (including lentiviral vectors). For example, viral vectors developed for delivering and expressing siRNA oligonucleotides are commercially available from, for example, GeneDetect, Bradenton, FL; Ambion, Austin, TX; Invitrogen, Carlsbad, CA; Open BioSystems, Huntsville, AL; and Imgenex, San Diego, CA.

EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1: Methods and Materials

Patients Involved in the Study

[0141] 10 consecutive patients with acute MS relapse as rated on McDonald's criteria (McDonald W.I. et al., *Ann Neurol*, **50**:121-27 (2001)) were included. The diagnosis of definite MS was based on McDonald's criteria (Kurtzke J.F., *Neurology*, **33**:1444-1452 (1983)). The EDSS (Dastidar P. et al., *Med Biol Eng Comput*, **37**:104-7 (1999)) and volumetric brain MRI were evaluated at baseline (at relapse immediately before treatment) and 3 weeks after completion of IVIG therapy (Elovaara I. et al., *Intravenous Immunoglobulin is effective and well tolerated in the treatment of MS Relapse*, Manuscript submitted). The primary outcome measure of the study was a change in the EDSS score from baseline to week 3 after the start of IVIG therapy on day 21. Secondary outcome measures were changes in the volumes of T1-, T2-, Flair- and gadolinium (Gd)-enhanced lesions, the number of Gd-enhanced lesions, and brain volumes (Elovaara I. et al., *Intravenous Immunoglobulin is effective and well tolerated in the treatment of MS Relapse*, Manuscript submitted; Dastidar P. et al., *Med Biol Eng Comput*, **37**:104-7 (1999)).

[0142] Patients' characteristics are listed in Table 1. Before entry into the study each patient signed a form of consent. The study was approved by the Ethics Committee of Tampere University, Tampere, Finland.

[0143] Patients who received treatment with immunosuppressants in the preceding nine months or patients who received corticosteroids in the preceding 8 weeks were excluded. All patients received 0.4g/kg/day Endobulin (Baxter AG, Vienna, Austria) for 5 days. Clinical evaluation of the patients was done before treatment with IVIG, 1 day after completion of therapy on day 6 as well as 3 weeks after the beginning of therapy on day 21. Clinical evaluation included neurological examination, determination of the EDSS score, arm index and ambulation index. A control group of five patients received standard treatment of IVMP 100 mg/day for 3 days.

Table 1. Characteristics of patients included in the study

Characteristics	IVIG Patients	IVMP Patients (controls)
Number of patients	10	5
Age (years, average ± SD)	40 ± 10.6	35.3 ± 8.8
Sex (male vs female)	3 vs 7	0 vs 5
Disease duration (years, average ± SD)	5.6 ± 3.5	5.2 ± 3.6
Time current vs previous relapse (months, average ± SD)	17.6 ± 21.0	5 ± 3.2
EDSS score during remission (average ± SD)	2.3 ± 0.95	3.2 ± 2.4
EDSS score at acute relapse (average ± SD)	3.7 ± 1.1	4.2 ± 2.0

MRI Analysis

[0144] Brain MRI examinations were done using a 1.5 Tesla MRI unit (Philips Gyroscan ACS NT Intera, Best, Netherlands) as described (Kurtzke J.F., *Neurology*, **33**:1444-1452 (1983)). The MRI protocol included sagittal T1 localizer, axial fluid attenuated inversion recovery (FLAIR), T1 magnetization transfer contrast (MTC), T1 spin echo (SE) , T2 turbo spin echo (TSE) (3mm thick and 0mm gap) and gadolinium-enhanced T1 MTC sequences. T1 axial SE (3mm thick and 0mm gap) and axial FLAIR (5mm thick and 1mm gap) sequences were used for volumetric analyses of plaques. Computerized semiautomatic segmentation and volumetric analyses were done using Anatomatic software operating in a Windows environment. The inter- and intra- observer variability of the volumetric results has been reported elsewhere (Dastidar P. et al., *Med Biol Eng Comput*, **37**:104-7 (1999); Heinonen T. et al., *J Med Eng Technol*, **22**:173-8 (1998)). The volumetric accuracy of the Anatomatic program was analyzed as described (Dastidar P. et al., *Med Biol Eng Comput*, **37**:104-7 (1999)). Good head repositioning was controlled using the same head coil, the same anatomic locations and the same pack of images in different MRI sequences. Whole spinal cords were scanned separating into upper and lower parts. The same scanner was used for all MRI examinations.

Preparation of RNA Samples

[0145] Blood samples were obtained using Vacutainer CPTTM Cell Preparation Tubes (Becton Dickinson, Franklin Lakes, NJ). Peripheral blood mononuclear cells (PBMC) were separated from peripheral blood within 60 min after blood sampling using density gradient (Lymphoprep, Nycomed, Roskilde, DK) centrifugation according to the manufacturer's protocol. The cells were separated into T cells and non-T cells using a mixture of non-stimulating anti-CD4+ and anti-CD8+ magnetic Dynabeads (Dynal Biotech, Oslo, N) at 4°C. Cell pellets obtained from $5x10^6$ cells were thoroughly mixed with 1ml TRIzol (Invitrogen, Carlsbad, CA). Aliquots were frozen and stored at –80°C until further processing. Total RNA was isolated according to the manufacturer's protocol. RNA pellets were dissolved in nuclease-free water (Invitrogen, Carlsbad, CA) and stored at –80° C.

Microarray Analysis

[0146] The HU-133A Genechip (Affymetrix, Santa Clara, CA) containing approximately 33,000 human genes was used. 5µg of total RNA were transcribed, labelled and hybridized *in vitro* on the array according to the manufacturer's protocol (see Affymetrix.com). The quality of the RNA was checked before in vitro processing using a Bioanalyzer (Agilent Technologies, Palo Alto, CA).

Statistical Analysis of Gene Expression Data

[0147] Statistical analysis of gene expression data was done at the Microarray Facility Tübingen, Eberhard-Karls-University Tübingen, Germany. The Affymetrix CHP files were imported into Genespring 7.1 for statistical data analysis. The signals of each array were divided by the median of all signals of the arrays from time point zero. Subsequently, a "per-gene" normalization was done by dividing all signals of a gene by the median signal of this gene. Thus the signals of each gene start at time point zero around 1 and display values greater than 1 upon increase and vice versa. The signals were log-transformed, and fold change and p-values (Welch's t-test) (Han T. et al., *BMC bioinformatics*, 7:9 (2006)) were calculated for each gene in pair-wise comparisons. Probe sets with a fold change of more than 2 and a p-value of less than 0.05 were identified in volcano plots and called statistically significant.

Real Time Polymerase Chain Reaction

[0148] The gene expression data obtained by microarray analysis for four representative genes were confirmed by quantitative real-time polymerase chain reaction (PCR). For this purpose, 1µg of total T cell RNA was used for reverse transcription into cDNA according to the manufacturer's protocol (MBI Fermentas, Burlington, Canada). For each sample to be analyzed, 100 mg cDNA were dissolved in 5µl nuclease-free water (Invitrogen, Carlsbad, CA) and quantitatively analyzed using different TaqMan Assays-on-Demand and the ABPrism 7000 (both from Applied Biosystems, Foster City, CA). Data were analyzed using the ^^CT-method, which is commonly used for relative quantification (Livak K.J. and Schmittgen T.D., *Methods*, **25**:402-40 (2001)). For normalization of expression data human glyceraldhyde-3 phosphate dehydrogenase was included as a housekeeping gene. For verification of normalization, a second housekeeping gene, β-2microglobulin, was used as a control (data not shown).

Example 2: Clinical Outcome of Treatment of Subjects with IVIG

[0149] Analysis of the clinical outcome of the study showed that a 5-day course of IVIG therapy resulted in a significant reduction of the EDSS score in all 10 patients (Fig. 1). The effectiveness of the IVIG therapy was supported by an improvement of most MRI variables (Table 2). Although similar effects were observed in the control group that received standard treatment with IVMP (Table 2), the changes in MRI variables in the control group did not reach statistical significance. Treatment with IVIG was safe and well-tolerated.

Table 2. MRI analysis of brain abnormalities before and after treatment with IVIG and IVMP

	Before IVIG	After IVIG
Parameter	Lesion vol cm^3	Lesion vol cm^3
	mean ± SE	mean ± SE
T1	1. 76 ± 0.55	1.73 ± 0.59
T2	5.49 ± 1.09	5.08 ± 1.03*
Flair	15.76 ± 2.23	14.09 ± 1.94**
Gd-enhanced	0.32 ± 0.27	0.21 ± 0.24**
Brain volume	1124.94 ± 40.61	1120.31± 40.72
Gd+lesion N	2.83 ± 0.71	2.00 ± 0.60**
EDSS score	3.8 ± 0.3	2.6 ± 0.2**

	Before IVMP	After IVMP
Parameter	Lesion vol cm^3	Lesion vol cm^3
	mean ± SE	mean ± SE
T1	1.41 ± 0.60	1.64 ± 0.84
T2	11.15 ± 4.59	9.83 ± 4.17
Flair	24.37 ± 8.19	23.18 ± 8.05
Gd-enhanced	0.70 ± 0.39	0.63 ± 0.37
Brain volume	1056.32 ± 47.78	1045.07 ± 52.53
Gd+lesion N	3.0 ± 1.5	2.7 ± 1.4
EDSS score	4.2 ± 2.0	3.3 ± 2.4

* p<0.05; ** p<0.01
EDSS = Kurtzke's Expanded Disability Status Scale
Gd = Gadolinium-enhanced lesion volumes

Example 3: Treatment With IVIG does not Significantly Alter the Cellular Composition of Cells Obtained for Isolation of RNA

[0150] PBMCs obtained from peripheral blood were separated into T cells and non-T cells using a mixture of non-stimulating anti-CD4+ and anti-CD8+ magnetic Dynabeads at 4°C. This procedure was chosen to prevent stimulation of T cells during cell separation. To ensure that potential differences in gene expression profiles are not due to differences in the cellular composition of the different samples, we compared the expression of genes that encode CD3, CD4, CD8 and CD14 between samples obtained at different time points for each patient. Our results show that the cellular composition of the samples obtained from each patient on different days is similar (Figures 2A, 2B). No statistically significant differences were observed.

Example 4: Analysis of Gene Expression Data Obtained from Patients Treated With IVIG

[0151] Statistic analysis of gene expression data included all results obtained from microarray analysis done at three different time points (before treatment, 1 day and 21 days after beginning of treatment) and included all 10 patients treated with IVIG. The analysis revealed that 360 genes in peripheral T cells were significantly changed in expression during the course of IVIG treatment. The expression of 91 of these genes changed between day 0 and day 6, the expression of 147 genes changed between day 0 and day 21, and the expression of 122 genes changed between day 6 and day 21.

[0152] Statistical analysis of the control-patient group treated with IVMP showed differential expression of 583 genes, with the majority (218 genes) being changed between day 0 and day 6.

[0153] Tables 3a-3d present the 20 most significant changes in gene expression observed in patients treated with IVIG and IVMP.

[0154] Table 3a: 10 genes that were most extensively up-regulated in peripheral T cells of patients during IVIG therapy

Fold Change	Time Point	Gene Title	Gene Symbol	Ref Seq ID
4.37	21 vs 6	Transcriptional regulating factor 1	TRERF1	NM_018415
4.26	21 vs 0	chromosome 19 open reading frame 28	C19orf28	NM_174983
4	6 vs 0	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	NM_000076
3.86	21 vs 6	breast cancer 1, early onset	BRCA1	NM_007294
3.83	6 vs 0	Clone 23555 mRNA sequence	---	---
3.54	21 vs 6	---	---	---
3.52	21 vs 6	SH3-domain binding protein 4	SH3BP4	NM_014521
3.5	6 vs 0	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	COL3A1	NM_000090
3.41	21 vs 0	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 2	B3GALT2	NM_003783
3.36	21 vs 6	glycosylphosphatidylinositol specific phospholipase D1	GPLD1	NM_001503

Table 3b: 10 genes that were most extensively down-regulated in peripheral T cells of patients during IVIG therapy

Fold Change	Time Point	Gene Title	Gene Symbol	Ref Seq ID
-4.82	6 vs 0	myotubularin related protein 7	MTMR7	NM_004686
-3.96	6 vs 0	transmembrane protein with EGF-like and two follistatin-like domains 1	TMEFF1	NM_003692
-3.9	21 vs 0	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa	NDUFA5	NM_005000
-3.89	21 vs 6	collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant)	COL3A1	NM_000090
-3.59	21 vs 6	FAT tumor suppressor homolog 2 (Drosophila)	FAT2	NM_001447
-3.57	21 vs 6	DNA damage repair and recombination protein RAD52 pseudogene	---	---
-3.34	21 vs 0	chemokine (C-X-C motif) ligand 5	CXCL5	NM_002994
-3.34	21 vs 0	mesenchymal stem cell protein DSC43	LOC51333	NM_016643
-3.26	21 vs 6	natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C)	NPR3	NM_000908
-3.22	21 vs 6	early growth response 2 (Krox-20 homolog, Drosophila)	EGR2	NM_000399

Table 3a/b: Timepoints: 6 vs) represents genes with a different expression between day 0 and day 6; 21 vs 0 represents genes with a differential expression between day 21 and day 0; and 21 vs 6 refers to genes with a change in expression between day 6 and day 21.

Table 3c: 10 genes that were most extensively up-regulated in peripheral T cells of patients during IVMP therapy

Fold Change	Time Point	Gene Title	Gene Symbol	Ref Seq ID
15.94	21 vs 6	leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 4	ILT7	NM_012276
9.26	21 vs 6	prostaglandin D2 synthase 21kDa (brain)	PTGDS	NM_000954
8.91	21 vs 6	Periostin, osteoblast specific factor	POSTN	NM_006475
8.64	21 vs 6	wingless-type MMTV integration site family, member 5A	WNT5A	NM_003392
8.31	21 vs 6	prostaglandin D2 synthase 21kDa (brain) /// prostaglandin D2 synthase 21kDa (brain)	PTGDS	NM_000954
7.94	21 vs 6	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	NM_000076
7.41	21 vs 6	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	NM_000076
7.33	6 vs 0	defensin, alpha 1, myeloid-related sequence /// defensin, alpha 3, neutrophil-specific	DEFA1 ///	NM_005217
6.48	6 vs 0	POU domain, class 1, transcription factor 1 (Pit1, growth hormone factor 1)	POU1F1	NM_000306
6	6 vs 0	cadherin 13, H-cadherin (heart)	CDH13	NM_001257

Table 3d: 10 genes that were most extensively down-regulated in peripheral blood cells of patients during IVMP therapy

Fold Change	Time Point	Gene Title	Gene Symbol	Ref Seq ID
-11.52	6 vs 0	leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 4	ILT7	NM_012276
-9.73	6 vs 0	tripartite motif-containing 58	TRIM58	NM_015431
-9.11	21 vs 6	Zwilch	FLJ10036	NM_017975
-8.24	21 vs 0	Integrin, alpha 1	PELO	NM_015946
-7.86	21 vs 0	zinc finger protein 6 (CMPX1)	ZNF6	NM_021998
-7.36	21 vs 6	intersectin 1 (SH3 domain protein)	ITSN1	NM_003024
-7.3	21 vs 6	phorbol-12-myristate-13-acetate-induced protein 1	PMAIP1	NM_021127
-7.28	21 vs 0	transmembrane protein 47	TMEM47	NM_031442
-6.84	6 vs 0	---	---	---
-6.82	6 vs 0	prostaglandin D2 synthase 21kDa (brain)	PTGDS	NM_000954

Table 3c/d: Timepoints: 6 vs 0 represents genes with a differential expression between day 0 and day 6; 21 vs 0 represents genes with a differential expression between day 21 and day 0; and 21 vs 6 refers to genes with a change in expression between day 6 and day 21.

[0155] Genes mostly affected in expression by IVIG treatment include genes that encode proteins that regulate cell cycle (transcriptional regulating factor 1, TRERF1; cyclin-dependent kinase inhibitor 1C, CDKN1C; breast cancer 1, BRCA1; SH3-domain binding protein 4, SH3BP4); but also proteins that regulate inflammation [chemokine (C-X-C motif) ligand 5, CXCL5], cell adhesion (FAT tumor suppressor homolog 2, FAT2) or cell differentiation (early growth response, EGR2). Other genes included in the list encode proteins that are involved in electron transport, phosphorylation, glycosylation, skeletal development or proteins that have not yet been defined in function.

[0156] Other genes of interest that were differentially regulated upon IVIG treatment encoded proteins involved in immune regulation such as interleukin 11 (IL11), chemokine (C motif) ligand 2 (XCL2), prostaglandin E receptor 4 (PTGER4), caspase 2 (CASP2), killer cell immunoglobin-like receptor, two domains, short cytoplasmic tail 1 (KIR2DS1), mitogen-activated protein kinase kinase kinase kinase 2 (MAP4K2), chemokine (C-X-C motif) ligand 5 (CXCL5), chemokine (C-X-C motif) ligand 3 (CXCL3), C-type lectin domain family 4, member E (CLEC4E), chemokine (C-C motif) ligand 13 (CCL13) and alpha-fetoprotein (AFP) (see Table 4).

[0157] Table 4. Genes differentially expressed under IVIG treatment that encode proteins involved in immune regulation (note that accession number for CLEC4E should be NM_014358, not NM_013458 in Table 4).

Fold Change	Time Point	Gene Title	Gene Symbol	Ref Seq ID
2.00	6 vs 0	interleukin 11	IL11	NM_000641
2.38	21 vs 0	chemokine (C motif) ligand 2	XCL2	NM_003175
2.28	21 vs 0	prostaglandin E receptor 4 (subtype EP4)	PTGER4	NM_000958
2.02	21 vs 0	caspase 2, apoptosis-related cysteine protease (neural precursor cell expressed)	CASP2	NM_032982
2.37	21 vs 6	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1	KIR2DS1	NM_014512
2.35	21 vs 0	mitogen-activated protein kinase kinase kinase kinase 2	MAP4K2	NM_004579
-3.34	21 vs 0	chemokine (C-X-C motif) ligand 5	CXCL5	NM_002994
-2.46	21 vs 0	chemokine (C-X-C motif) ligand 3	CXCL3	NM_002090
-2.26	21 vs 0	C-type lectin domain family 4, member E	CLEC4E	NM_013458
-3.06	21 vs 6	chemokine (C-C motif) ligand 13	CCL13	NM_005408
-2.53	21 vs 6	alpha-fetoprotein	AFP	NM_001134

Table 4: Timepoints: 6 vs 0 represents genes with a differential expression between day 0 and day 6; 21 vs 0 represents genes with a differential expression between day 21 and day 0; and 21 vs 6 refers to genes with a change in expression between day 6 and day 21.

Example 5: Comparison of Gene Expression Data Obtained From Patients Treated With IVIG and Patients Treated With IVMP

[0158] When gene expression data obtained from patients treated with IVIG were compared with gene expression data obtained from patients treated with IVMP, 17 genes

were identified that significantly changed in expression in both groups of patients (Table 5). Most of the proteins that are encoded by these 17 genes regulate cell cycle (HABP4, STAT1, CDKN1, SH3BP4 and ORC1L). These results indicate that cell cycle regulation might be a mechanism of therapeutic effectiveness that both drugs have in common. The other genes that were found to be differentially regulated were only found in one of the two treatment groups and, therefore, reflect mechanisms of action that are specific for only one of the two drugs.

[0159] Table 5. Intersection of genes differentially expressed under both IVIG treatment and IVMP treatment

Gene Title	Gene Symbol	GO Biological Process Description	Ref Seq ID
cadherin 5, type 2, VE-cadherin (vascular epithelium)	CDH5	cell adhesion /// homophilic cell adhesion	NM_001795
hyaluronan binding protein 4	HABP4	---	NM_014282
signal transducer and activator of transcription 1, 91kDa	STAT1	regulation of cell cycle /// transcription /// regulation of transcription, DNA-dependent /// transcription from RNA polymerase II promoter /// caspase activation /// intracellular signaling cascade /// I-kappaB kinase/NF-kappaB cascade /// tyrosine phosp	NM_007315
cyclin-dependent kinase inhibitor 1C (p57, Kip2)	CDKN1C	regulation of cyclin dependent protein kinase activity /// G1 phase of mitotic cell cycle /// cell cycle /// cell cycle arrest /// negative regulation of cell proliferation /// negative regulation of cell cycle	NM_000076
actinin, alpha 2	ACTN2	---	NM_001103
histone 1, H2bh	HIST1H2BH	nucleosome assembly /// nucleosome assembly /// chromosome organization and biogenesis (sensu Eukaryota)	NM_003524
SH3-domain binding protein 4	SH3BP4	endocytosis /// cell cycle	NM_014521
origin recognition complex, subunit 1-like (yeast)	ORC1L	DNA replication /// DNA replication initiation	NM_004153
KIAA0644 gene product	KIAA0644	---	NM_014817
Heparan sulfate (glucosamine) 3-O-sulfotransferase 1	HS3ST1	---	NM_005114
ropporin, rhophilin associated protein 1B	ROPN1B	cytokinesis /// signal transduction /// Rho protein signal transduction /// spermatogenesis /// acrosome reaction /// fusion of sperm to egg plasma membrane /// cell-cell adhesion /// sperm motility	NM_001012337
outer dense fiber of sperm tails 2	ODF2	---	NM_002540
---	---	---	
unknown protein	---	---	
1-acylglycerol-3-phosphate O-acetyltransferase 7	AGPAT7	metabolism	NM_153613
zinc finger protein 804A	ZNF804A	---	NM_194250
TRAF-type zinc finger domain containing 1	TRAFD1	---	NM_006700

Example 6: Confirmation of Gene Expression Data Obtained with Microarray Analysis by Real-Time PCR

[0160] Data obtained with microarray analysis were confirmed by quantitative real-time PCR. For this purpose, 4 genes were selected that encoded proteins known to regulate immune regulation (see Table 4): PTGER4, CXCL5, IL11 and CASP2. Results of real-time PCR are shown in Figure 3A-D. Results obtained with real-time PCR confirm the data obtained with microarray analysis (Figure 3A-D, and Tables 3 and 4).

DISCUSSION

[0161] The present study was designed to identify genes that are differentially expressed in peripheral T cells of patients with RRMS in acute exacerbation after treatment with IVIG. Peripheral T cells (CD4+ and CD8+ T cells) have been shown to be involved in the disease pathogenesis, in particular in the process of demyelination and axonal damage (Stinissen P. et al., *Mult Scler.*, **4**:203-11 (1998)). This is supported by a recent study in which a number of genes in peripheral blood cells of MS patients were shown to be differentially expressed compared with those in healthy twins (Särkijärvi S. et al., *BMC Medical Genetics*, **7**:11 (2006)).

[0162] Statistical data analysis revealed 360 genes that were at least 2-fold up- or down-regulated in all patients following IVIG treatment. The effect of IVIG treatment was most prominent at 21 days after the beginning of IVIG treatment. Genes mostly affected in expression by IVIG treatment included genes that encode proteins that regulate cell cycle, signal transduction, transcription, inflammation, cell-cell interactions and apoptosis. These processes are likely to be involved in the pathogenesis of MS. When we compared the effects on gene expression caused by IVIG treatment with the effects caused by IVMP treatment, we found 583 genes to be differentially regulated upon IVMP treatment. The majority of these genes was altered in expression at day 6 compared to day 0 after the beginning of therapy. These results indicate that IVMP might be a faster acting drug than IVIG.

[0163] We identified 17 genes that were significantly changed in expression in both groups of patients. Most of the proteins that are encoded by these 17 genes regulate cell cycle. These results strongly suggest that the regulation of cell proliferation, in particular the regulation of T cell proliferation, is a mechanism of action that both drugs have in common. These results agree with published data that indicate that IVIG suppresses the proliferation of activated T cells when given to patients with MS (Andersson U. et al., *Immunol Rev*, **139**:21-42 (1994); Bayry J. et al., *Intravenous immunoglobulin in autoimmune disorders: An insight into the immunregulatory mechanisms*).

[0164] An important mechanism of action of IVIG in MS seems to be the modulation of chemokine expression. This conclusion is based on our findings that a number of genes that encode chemokines (CXCL3, CXCL5, CCL13 and XCL2) are differentially expressed upon IVIG treatment. These changes in gene expression were not found in patients treated with

IVMP. Therefore, we believe that the modulation of chemokine expression in peripheral T cells might be a specific mechanism of action of IVIG in MS. Several studies have shown that chemokines and chemokine receptors are involved in the pathogenesis of MS (Trebst C. and Ransohoff R.M., *Arch Neurol*, **58**:1975-80 (2001)). Chemokines have been shown to mediate trafficking of immune cells across the blood-brain barrier and to direct migration of immune cells towards sites of active lesions (Szczucinski A. and Losy J., *Acta Neurol Scand*, **115**:137-146 (2007)). Moreover, chemokines were detected in active lesions and were found to be elevated in the cerebrospinal fluid of patients with MS during relapse (Sindern E. et al., *J Neuroimmunol*, **131**:186-90 (2002)). Two of the chemokines (CXCL3 and CXCL5) that were significantly down-regulated in our study are known to specifically interact with the chemokine receptor CXCR2 (Omari K. et al., *Brain*, **128**:1003-1015 (2005)). Previous studies have shown that CXCR2 is not only expressed on peripheral blood cells such as granulocytes, monocytes or lymphocytes (Murdoch C. et al., *Brain*, **128**:1003-1015 (2005(?)); Murphy P.M. et al., *Pharmacol Rev.*, **52**:145-76 (2000)) but also on oligodendrocytes in the brain. Oligodendrocytes are most essential for the myelination of axons in the white matter of the Central Nervous System and for remyelination after demyelination of axons during inflammation in MS (Blakemore W.F., *J Neurol Sci.*, (2007)). Recently it was shown that CXCR2 expressed on oligodendrocytes is essential for the development and maintenance of the oligodendrocyte lineage, myelination and white matter in the vertebrate CNS (Tsai H.H. et al., *Cell*, **110**:373-83 (2002); Padovani-Claudio D. et al., *Glia*, **54**:471-483 (2006)). The regulation of oligodendrocyte development and migration depends on the localized expression of the chemokine CXCL1 and its interaction with CXCR2 expressed on oligodendrocyte precursor cells and oligodendrocytes (Padovani-Claudio D. et al., *Glia*, **54**:471-483 (2006)). Any event that disrupts the interaction between CXCL1 and CXCR2 expressed on oligodendrocytes or the signalling induced by this interaction could therefore cause a disruption of the remyelination processes in MS patients. Based on these findings we propose the following hypothesis for a new mechanism of action of IVIG in RRMS patients during relapse. Peripheral T cells and monocytes enter the CNS in response to chemokines produced by the inflammation in the brain. The disrupted blood-brain barrier (Man S. et al., *Brain Pathol.*, **17**:243-50 (2007)) facilitates this process. Both T cells and monocytes produce chemokines in the brain that interfere with the tightly regulated activity of oligodendrocyte precursor cells and oligodendrocytes. This interference could be caused by either a desensitization of the CXCR2 receptor expressed on oligodendrocytes or by interference with the interaction between locally expressed CXCL1

and CXCR2 on oligodendrocytes. IVIG down-regulates the expression of chemokines in peripheral T cells, monocytes or both. Consequently, the interference of chemokines produced by these cells with the function of oligodendrocytes would be prevented and the natural process of remyelination induced by oligodendrocytes would be re-established. It remains to be shown whether IVIG might not only modulate the expression of chemokines in peripheral T cells but also the expression of chemokines in cells of the CNS, e.g., in astrocytes.

[0165] The aim of our study was to identify genes that are likely to be associated with T cell responses in MS. The strategy that we used for positive cell selection does not exclude the possibility that some of the identified genes are associated with peripheral monocytes rather than T cells. This has to be taken into consideration when interpreting the above data. The genes that we found to be differentially expressed under IVIG treatment will be confirmed in a second clinical trial with a larger study group. Differentially expressed genes can be used as diagnostic markers for the therapeutic efficacy of IVIG treatment. Furthermore, some of the proteins encoded by the genes of interest will provide suitable targets for future drug development.

[0166] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

INFORMAL SEQUENCE LISTING

SEQ ID NO: 1: Homo sapiens transcriptional regulating factor 1 (TRERF1) (NM_018415)

ctctgctcgc cccccatctc acccccaag cggatactgg tcttctcgtc ggattgccca
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SEQ ID NO: 2 Homo sapiens transcriptional regulating factor 1 (TRERF1) (NP_060885.1)

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SEQ ID NO: 3 Homo sapiens chromosome 19 open reading frame 28 (C19orf28) (NM_174983)

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SEQ ID NO: 4 Homo sapiens chromosome 19 open reading frame 28 (C19orf28) (NP_778148.2)

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SEQ ID NO: 5 Homo sapiens cyclin-dependent kinase inhibitor 1C (p57, Kip2) (NM_000076)

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SEQ ID NO: 6 Homo sapiens cyclin-dependent kinase inhibitor 1C (p57, Kip2) (NP_000067.1)

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SEQ ID NO: 7 Homo sapiens breast cancer 1, early onset (BRCA1) (NM_007294)

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SEQ ID NO: 8 Homo sapiens breast cancer 1, early onset (BRCA1) (NP_009225.1)

MDLSALRVEEVQNVINAMQKILECPICLELIKEPVSTKCDHIFCKFCMLKLLNQKKGPSQCPLCKNDITKRSLQE
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SEQ ID NO: 9 Homo sapiens SH3-domain binding protein 4 (SH3BP4)(NM_014521)

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SEQ ID NO: 10 Homo sapiens SH3-domain binding protein 4 (SH3BP4) (NP_055336.1)

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SEQ ID NO: 11 Homo sapiens collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant) (COL3A1)(NM_000090)

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cacccataat aaaatatcat attaaaattc

SEQ ID NO: 12 Homo sapiens collagen, type III, alpha 1 (Ehlers-Danlos syndrome type IV, autosomal dominant) (COL3A1) (NP_000081.1)

MMSFVQKGSWLLLALLHPTIILAQQEAVEGGCSHLGQSYADRDVWKPEPCQICVCDSGSVLCDDIICDDQELDCP
NPEIPFGECCAVCPQPPTAPTRPPNGQGPQGPKGDPGPPGIPGRNGDPGIPGQPGSPGSPGPPGICESCPTGPQN
YSPQYDSYDVKSGVAVGGLAGYPGPAGPPGPPGPPGTSGHPGSPGSPGYQGPPGEPGQAGPSGPPGPPGAIGPSG
PAGKDGESGRPGRPGERGLPGPPGIKGPAGIPGFPGMKGHRGFDGRNGEKGETGAPGLKGENGLPGENGAPGPMG
PRGAPGERGRPGLPGAAGARGNDGARGSDGQPGPPGPPGTAGFPGSPGAKGEVGPAGSPGSNGAPGQRGEPGPQG
HAGAQGPPGPPGINGSPGGKGEMGPAGIPGAPGLMGARGPPGPAGANGAPGLRGGAGEPGKNGAKGEPGPRGERG
EAGIPGVPGAKGEDGKDGSPGEPGANGLPGAAGERGAPGFRGPAGPNGIPGEKGPAGERGAPGPAGPRGAAGEPG
RDGVPGGPGMRGMPGSPGGPGSDGKPGPPGSQGESGRPGPPGPSGPRGQPGVMGFPGPKGNDGAPGKNGERGGPG
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PPGPVGPAGKSGDRGESGPAGPAGAPGPAGSRGAPGPQGPRGDKGETGERGAAGIKGHRGFPGNPGAPGSPGPAG
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EYWVDPNQGCKLDAIKVFCNMETGETCISANPLNVPRKHWWTDSSAEKKHVWFGESMDGGFQFSYGNPELPEDVL
DVQLAFLRLLSSRASQNITYHCKNSIAYMDQASGNVKKALKLMGSNEGEFKAEGNSKFTYTVLEDGCTKHTGEWS
KTVFEYRTRKAVRLPIVDIAPYDIGGPDQEFGVDVGPVCFL

SEQ ID NO: 13 Homo sapiens UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 2 (B3GALT2) (NM_003783)

cctgtgcagc agctgaggaa ccgtggattt catattatag actaaaaccc cattaaaact
gctcaaaatc cttcctgcag ctgccaggca acaacgaaag aagagaggta aatcctattc
ttttccaata caactgaagc actacatttt agctctggct gctttacatt gcagctcagt
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tgtaaaggat aatcgaagca aaagtaatca cttaaaggca caaataggat gtactgttga
aaaagataaa gagtgcaggt gcagtttcat tcaacacatt tttaagatgc atgtctgcca

aaatgcaaca tacgggaagt ttatttcctg acagcaggtg tacacatgcc aacacttaat
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ttggtagatg acaaatattc tgaatcacca attaaaaacc tttttgggag ggatggggaa
aactacaaac gtttgacaaa cacaattcta ggatgaacaa tgtatacaat gcacttttat
gaagttttta aaaataaagg aaaacaaaaa acttt

SEQ ID NO: 14 Homo sapiens UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 2 (B3GALT2) (NP_003774.1)

MLQWRRRHCCFAKMTWNAKRSLFRTHLIGVLSLVFLFAMFLFFNHHDWLPGRAGFKENPVTYTFRGFRSTKSETN
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PFLILLIAAEPGQIEARRAIRQTWGNESLAPGIQITRIFLLGLSIKLNGYLQRAILEESRQYHDIIQQEYLDTYY
NLTIKTLMGMNWVATYCPHIPYVMKTDSDMFVNTEYLINKLLKPDLPPRHNYFTGYLMRGYAPNRNKDSKWYMPP
DLYPSERYPVFCSGTGYVFSGDLAEKIFKVSLGIRRLHLEDVYVGICLAKLRIDPVPPPNEFVFNHWRVSYSSCK
YSHLITSHQFQPSELIKYWNHLQQNKHNACANAAKEKAGRYRHRKLH

SEQ ID NO: 15 Homo sapiens glycosylphosphatidylinositol specific phospholipase D1 (GPLD1)(NM_001503)

gtgacctgct tagagagaag cggtgggtct gcacctggat tttggagtcc cagtgctgct
gcagctctga gcattcccac gtcaccagag aagccggtgg gcaatgagat catgtctgct
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aaaaaagttg aacttaaaaa taacagattg gcccatgcca atcaaagtat aatagaaagc atagtatac

SEQ ID NO: 16 Homo sapiens glycosylphosphatidylinositol specific phospholipase D1 (GPLD1) (NP_001494.2)

MSAFRLWPGLLIMLGSLCHRGSPCGLSTHVEIGHRALEFLQLHNGRVNYRELLLEHQDAYQAGIVFPDCFYPSIC
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HGSYSEAHSAGDFGGDVLSQFEFNFNYLARRWYVPVKDLLGIYEKLYGRKVITENVIVDCSHIQFLEMYGEMLAV
SKLYPTYSTKSPFLVEQFQEYFLGGLDDMAFWSTNIYHLTSFMLENGTSDCNLPENPLFIACGGQQNHTQGSKMQ
KNDFHRNLTTSLTESVDRNINYTERGVFFSVNSWTPDSMSFIYKALERNIRTMFIGGSQLSQKHVSSPLASYFLS
FPYARLGWAMTSADLNQDGHGDLVVGAPGYSRPGHIHIGRVYLIYGNDLGLPPVDLDLDKEAHRILEGFQPSGRF
GSALAVLDFNVDGVPDLAVGAPSVGSEQLTYKGAVYVYFGSKQGGMSSSPNITISCQDIYCNLGWTLLAADVNGD
SEPDLVIGSPFAPGGGKQKGIVAAFYSGPSLSDKEKLNVEAANWTVRGEEDFSWFGYSLHGVTVDNRTLLLVGSP
TWKNASRLGHLLHIRDEKKSLGRVYGYFPPNGQSWFTISGDKAMGKLGTSLSSGHVLMNGTLKQVLLVGAPTYDD
VSKVAFLTVTLHQGGATRMYALTSDAQPLLLSTFSGDRRFSRFGGVLHLSDLDDDGLDEIIMAAPLRIADVTSGL
IGGEDGRVYVYNGKETTLGDMTGKCKSWITPCPEEKAQYVLISPEASSRFGSSLITVRSKAKNQVVIAAGRSSLG
ARLSGALHVYSLGSD

SEQ ID NO: 17 Homo sapiens myotubularin related protein 7 (MTMR7) (NM_004686)

gcgcccgccc gggaccctgc agacgtgggc cagccatgga gcacatccgc acgcccaagg
ttgaaaatgt ccgcttggta gatcgagtgt ctcctaaaaa agcagctcta ggtactttgt
atttgacggc tacccatgtc atattcgtgg aaaattcacc tgacgcaaga aaagaaacat
ggattcttca cagtcagatt tccaccattg agaaacaggc aacaaccgct accggatgcc
ctctgctgat tcgctgcaag aactttcaga taatacagct catcatacct caggaaagag
attgccacga cgtgtacatc tccctgatac gccttgcaag gccagtgaaa tatgaggagt
tatactgctt ttcattcaac cccatgctgg ataaagaaga aagagagcaa ggctgggtgc
tgatcgatct tagtgaagaa tacacgcgga tgggcctccc taatcattac tggcagctca
gcgatgtgaa tagagactac agagtctgtg actcttatcc tactgaactg tacgttccca
aatcggccac ggcacacatc atagtgggga gttccaaatt ccggagtaga cggcgatttc
ctgtcctttc ttactattat aaagataacc acgcctccat ctgccggagc agccagcccc
tgtccggctt cagtgcccgg tgcctggagg acgagcagat gctccaggcc attaggaaag
ccaatccagg aagtgacttc gtttatgtcg ttgacgcccg gcctaaactt aatgcaatgg
caaatcgtgc tgcagggaaa ggctatgaga atgaagacaa ttattccaat atcaagtttc
agtttatcgg gatagagaac atccatgtca tgaggaacag tctgcagaaa atgctggaag
tgtgtgaact taaatctccc tccatgagtg atttcctgtg gggtctggag aactctggct
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aactcaagat tcaagaaaga acatactcat tatgggctca cctgtggaag aatcgggccg
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aggggatgca gccccgacag tcagttacag attacctaat ggcagtgaag gaagaaactc

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gtaaaggaca cataagcaac acttccaaaa acaagggaac aaggtggttt attgtaaaaa
caggaaatgg tgcatgtcat tgagaactat tttaatgcag ctatgaaaag ggaaaaaagt
gcccagttct tgatttctta gatactgaag aggacgtagt catttcattt atcaaatata
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atctctcaaa aagcctccac tcctttccct cacatctgtg atcatcatga ttcttttagt
tcacttctag atgcatattt tgtgttttct aaagcatctg acattatcct cctttccgac
cctcttatac atatttctaa aaacaggcac attggtgaga tgcacccttt ttagttaata
gatgcattcc taaggagctt ttaattgctt atctttcagg cataatcatc actttaactt
ttccttggag catatatttt gaattgtgag aataattttg ttgcttttct ctgagatcta
tagtctgttt ctcctcatta tttaaaaatg ctaaaccttg tatctcactt tttctctaac
actgatttaa tagctaacga ggtagaagca acattcattc tcctggtctt acatatgaat
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agtgtgggcc agccaccagc ctgatctcaa agtatcacat tataaagtta gtagataaaa
catctgtgag tgaaaatcca gtttcaggaa ccagagaatt gggttgtcat gtctgtttaa
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gttttgttac actgcacatt taagggagag tccctcccct atcttatgag ttaaaaaaga
cttcactagg tgacctaaat taaacttagt ggggaaaagt ggccatgttt ggacataaat
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ggagtgttgc aatatatata aatgaaaaca tttaattgtg ttcatcatat ttaaaaatat
agaatatatt agagaactgt gatttaaaag tactgttaat gtaaaaaata aagcaagtgt
aattaattct ttcagaatat aaaatttggg cattctctgc tgagcagttc ccaaattaag
tacaaggaat gtttattcat tttctgcaat atactatatg taatagggaa taccttgcta
aaataaaact taggatatag tggtaatggc tttcacattt ttataacata acataactca
cttcacaacc ttcttggagc tgtccactct tagaaactct gttgcctaat attgaggatg
tggctttaat ttcttccgtt tgacagtgta tgtctataaa aacaataaac atttttaaa
aaatgacaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa

SEQ ID NO: 18 Homo sapiens myotubularin related protein 7 (MTMR7)(NP_004677.2)

MEHIRTPKVENVRLVDRVSPKKAALGTLYLTATHVIFVENSPDARKETWILHSQISTIEKQATTATGCPLLIRCK
NFQIIQLIIPQERDCHDVYISLIRLARPVKYEELYCFSFNPMLDKEEREQGWVLIDLSEEYTRMGLPNHYWQLSD
VNRDYRVCDSYPTELYVPKSATAHIIVGSSKFRSRRRFPVLSYYYKDNHASICRSSQPLSGFSARCLEDEQMLQA
IRKANPGSDFVYVVDARPKLNAMANRAAGKGYENEDNYSNIKFQFIGIENIHVMRNSLQKMLEVCELKSPSMSDF
LWGLENSGWLRHIKAIMDAGIFIAKAVSEEGASVLVHCSDGWDRTAQVCSVASLLLDPHYRTLKGFMVLIEKDWI
SFGHKFNHRYGNLDGDPKEISPVIDQFIECVWQLMEQFPCAFEFNERFLIHIQHHIYSCQFGNFLCNSQKERREL
KIQERTYSLWAHLWKNRADYLNPLFRADHSQTQGTLHLPTTPCNFMYKFWSGMYNRFEKGMQPRQSVTDYLMAVK
EETQQLEEELEALEERLEKIQKVQLNCTKVKSKQSEPSKHSGFSTSDNSIANTPQDYSGNMKSFPSRSPSQGDED
SALILTQDNLKSSDPDLSANSDQESGVEDLSCRSPSGGEHAPSEDSGKDRDSDEAVFLTA

SEQ ID NO: 19 Homo sapiens transmembrane protein with EGF-like and two follistatin-like domains 1 (TMEFF1)(NM_003692)

agcgggcggc tgctaggagg caccgaggca gcggcggggc tctgggcgcg cggctggatg
cccccggcct gcggctccct gcgcttcccg ccgtccaggg gcaccagtca tgggcgccgc
agccgctgag gcgccgctcc ggctgcctgc cgcgcctccg ctcgccttct gctgctacac
gtcggtgctt ctgctcttcg ccttctctct gccagggagc cgcgcgtcca accagccccc
gggtggtggc ggcggcagcg gcggggactg tcccggcggc aaaggcaaga gcatcaactg
ctcagaatta aatgtgaggg agtctgacgt aagagtttgt gatgagtcat catgtaaata
tggaggagtc tgtaaagaag atggagatgg tttgaaatgt gcatgccaat ttcagtgcca

tacaaattat attcctgtct gtggatcaaa tggggacact tatcaaaatg aatgctttct
cagaagggct gcttgtaagc accagaaaga gataacagta atagcaagag gaccatgcta
ctctgataat ggatctggat ctggagaagg agaagaggaa gggtcagggg cagaagttca
cagaaaacac tccaagtgtg gaccctgcaa atataaagct gagtgtgatg aagatgcaga
aaatgttggg tgtgtatgta atatagattg cagtggatac agttttaatc ctgtgtgtgc
ttctgatggg agttcctata acaatccctg ttttgttcga gaagcatctt gtataaagca
agaacaaatt gatataaggc atcttggtca ttgcacagat acagatgaca ctagtttgtt
gggaaagaaa gatgatggac tacaatatcg accagatgtg aaagatgcta gtgatcaaag
agaagatgtt tatattggaa accacatgcc ttgccctgaa aacctcaatg gttactgcat
ccatggaaaa tgtgaattca tctattctac tcagaaggct tcttgtagat gtgaatctgg
ctacactgga cagcactgtg aaaagacaga ctttagtatt ctctatgtag tgccaagtag
gcaaaagctc actcatgttc ttattgcagc aattattgga gctgtacaga ttgccatcat
agtagcaatt gtaatgtgca taacaagaaa atgccccaaa aacaatagag gacgtcgaca
gaagcaaaac ctaggtcatt ttacttcaga tacgtcatcc agaatggttt aaactgatga
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aatatttatt tcagaggcct tatttttgga catttttagt gtagtactgt tggctcgtat
ttagaatatt cagctacgac agttttggac tgtttagtag tctttgtttt atgtttttaa
atacagaaat tgctttcaca aatttgtacc acatggtaat tctaagactt gttctttacc
catggaatgt aatatttttg caaagatgga ctacttcaca aatggttata aagtcatatc
cacttcttcc acaatgacca cagcaaatga ccaagcatga actaaaggta aagatgttta
cagattactt ttcttacaaa aaaatctaga agacactgtg tttaaataga tatttaaatg
tttttgagat ttagtaactg atttttttaga cactgcctat cgcatgaact gtaaagctgt
gtgtattagg tgtaaaatat ttataagata tatggactgg ggaatttgat tattcctccc
tttgaaaaaa tagtcctaat aatttgaaca aatatgttag taatgatgga acagatcaat
gaaaagtaga tatagatatt gtgaaaatag gctgtttaac aaacagattg gaataaagcc
tattctacca gttaaactac tttaatacac attcattttt aaagaaaatg tttgttttaa
cataaataaa caaatcgtat cagtgtttgt gaataaaata caaaaatgat tgttaatgat
tggtgctctt aaagtgagct taaaatttat ccaagacgta tatccaaatt tgtcctgtag
taatagatta atattcatag attgttggtg tttaaagatc tgaagtgtga gtagaatgta
ttcagctgtt taacatgtag tttagatatt caaaagtatg catgtagaat ttaaagaata
tgttaaaaat tattaatctt aatattttgt ttggaaaagc atgttataat ataatgtttt
cacaaaaaaa aaaaaaaaa

SEQ ID NO: 20 Homo sapiens transmembrane protein with EGF-like and two follistatin-like domains 1 (TMEFF1)(NP_003683.2)

MGAAAAEAPLRLPAAPPLAFCCYTSVLLLFAFSLPGSRASNQPPGGGGGSGGDCPGGKGKSINCSELNVRESDVR
VCDESSCKYGGVCKEDGDGLKCACQFQCHTNYIPVCGSNGDTYQNECFLRRAACKHQKEITVIARGPCYSDNGSG
SGEGEEEGSGAEVHRKHSKCGPCKYKAECDEDAENVGCVCNIDCSGYSFNPVCASDGSSYNNPCFVREASCIKQE
QIDIRHLGHCTDTDDTSLLGKKDDGLQYRPDVKDASDQREDVYIGNHMPCPENLNGYCIHGKCEFIYSTQKASCR
CESGYTGQHCEKTDFSILYVVPSRQKLTHVLIAAIIGAVQIAIIVAIVMCITRKCPKNNRGRRQKQNLGHFTSDT
SSRMV

SEQ ID NO: 21 Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa (NDUFA5), nuclear gene encoding mitochondrial protein (NM_005000)

tggagctaag ctgtttccag ggtgacagag tggcgacctc ggtggtcgat tgagcaggtc
tgagaattgt tcccaaaggg ttgtgcgtca ccgagtcgtt ggcgctgtca tggcgggtgt
gctgaagaag accactggcc ttgtgggatt ggctgtgtgc aatactcctc acgagaggct
aagaatattg tacacaaaga ttcttgatgt tcttgaggaa atccctaaaa atgcagcata
tagaaagtat acagaacaga ttacaaatga gaagctggct atggttaaag cggaaccaga
tgttaaaaaa ttagaagacc aacttcaagg cggtcaatta gaagaggtga ttcttcaggc
tgaacatgaa ctaaatctgg caagaaaaat gagggaatgg aaactatggg agccattagt
ggaagagcct cctgccgatc agtggaaatg gccaatataa ttattaagtg actttggtgt
gttcatggga aactgatgta attaaatatt ctgttatatt aagagcgtgt tcttattact
gacattttgt aatcaagaaa agtgatatag aaaatatgta ggagactgtt aaaattggtg
attatggtaa tatggtcatg tgaatcaatt tttgatttat aaagtactca cacaagttgt
ttcaaagatg atatttctgt gaacagagag gccatgggaa gatttgaaaa ttattaaaga
aaaattccta cagattttca atgcagagac cataatcaaa aagtaaactt tctttagtag
tatgttcaat acatcattta atttttaag ttatcctgaa gaaggaaagg tccttaatta
ttatagtcta aacaaattta tagattactg tttgaagtaa ataatacgag tgaatatttt

caaatgtgat aaaatagcac aagtggctgg tgataaaatt tgaaattatg gttaacctca
gctgtgatct tatgtatgta aagtgaaatt taaatagata attataggtt gattacaaaa
tccatagtgt cattttattt tagtcattat tgaattatac catttactct gttttcttat
agtcttaatt ttattatatt ttgttgttac tgtattatat ttgaaaacct tcaaattaga
atacattgta cagttaaaga aattgacttg gtacttaaaa gaaagatttc ccattgcata
caggttattg gagaaatttt ccttttgttg catttgtgga agttagtttt ctggcccgtg
gcctttaatt ttcttaatca acctaattac atcaggatag aggtagagtt tctgtaaaag
aagagacatt aagagttcct gaaatttata tctggcatac cgataggctt atattcaaaa
catcttagtc atacgaccat aaattaaaag tggagtcact aaatagtttg cagtacgttt
ctaatataag tgtaggtggg tatcaaaaca agacaaatgc tgttcaggga aagaagttgg
caagcttaag gttaaacaaa aataaaatta catgtgtttt cgccttccta

SEQ ID NO: 22 Homo sapiens NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 5, 13kDa (NDUFA5), nuclear gene encoding mitochondrial protein (NP_004991.1)

MAGVLKKTTGLVGLAVCNTPHERLRILYTKILDVLEEIPKNAAYRKYTEQITNEKLAMVKAEPDVKKLEDQLQGG
QLEEVILQAEHELNLARKMREWKLWEP LVEEPPADQWKWPI

SEQ ID NO: 23 Homo sapiens FAT tumor suppressor homolog 2 (Drosophila) (FAT2) (NM_001447)

ggagttttcc accatgacta ttgccctgct gggttttgcc atattcttgc tccattgtgc
gacctgtgag aagcctctag aagggattct ctcctcctct gcttggcact tcacacactc
ccattacaat gccaccatct atgaaaattc ttctcccaag acctatgtgg agagcttcga
gaaaatgggc atctacctcg cggagccaca gtgggcagtg aggtaccgga tcatctctgg
ggatgtggcc aatgtattta aaactgagga gtatgtggtg ggcaacttct gcttcctaag
aataaggaca aagagcagca acacagctct tctgaacaga gaggtgcgag acagctacac
cctcatcatc caagccacag agaagacctt ggagttggaa gctttgaccc gtgtggtggt
ccacatcctg gaccagaatg acctgaagcc tctcttctct ccaccttcgt acagagtcac
catctctgag gacatgcccc tgaagagccc catctgcaag gtgactgcca cagatgctga
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ccatcccacc agcggtgtgg tcactgtggc tgggaagctt aacgtcacct ggcgaggaaa
gcatgagctc caggtgctag ctgtggaccg catgcggaaa atctctgagg gcaatgggtt
tggcagcctg gctgcacttg tggttcatgt ggagcctgcc ctcaggaagc ccccagccat
tgcttcggtg gtggtgactc caccagacag caatgatggt accacctatg ccactgtact
ggtcgatgca aatagctcag gagctgaagt ggagtcagtg gaagttgttg gtggtgaccc
tggaaagcac ttcaaagcca tcaagtctta tgcccggagc aatgagttca gtttggtgtc
tgtcaaagac atcaactgga tggagtacct tcatgggttc aacctcagcc tccaggccag
gagtgggagc ggcccttatt tttattccca gatcaggggc tttcacctac caccttccaa
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cctcttcaac aggtcttcct atgatggtac cttggatgag aacatccctc caggcaccag
tgttttggct gtgactgcca ctgaccggga tcatggggaa aatggatatg tcacctattc
cattgctgga ccaaaagctt tgccattttc tattgacccc tacctgggga tcatctccac
ctccaaaccc atggactatg aactcatgaa aagaatttat accttccggg taagagcatc
agactgggga tccccttttc gccgggagaa ggaagtgtcc atttttcttc agctcaggaa
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cctaaaatac gagattgtat caggcaatga actagagtat tttgatctaa atcatttctc
cggagtgata tccctcaaac gccctttat caatcttact gctggtcaac ccaccagtta
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tactgtggtg aaggaccctc attttgaagt tcctgtaaca tgtgataaaa caggggtatt
gacacaattc acaaagacta tcctccactt tattgggctt cagaaccagg agtccagtga
tgaggaattc acttctttaa gcacatatca gattaatcat tacaccccac agtttgagga
ccacttcccc caatccattg atgtccttga gagtgtccct atcaacaccc ccttggcccg
cctagcagcc actgaccctg atgctggttt taatggcaaa ctggtctatg tgattgcaga
tggcaatgag gagggctgct ttgacataga gctggagaca gggctgctca ctgtagctgc
tcccttggac tatgaagcca ccaatttcta catcctcaat gtaacagtat atgacctggg

cacaccccag aagtcctcct ggaagctgct gacagtgaat gtgaaagact ggaatgacaa
cgcacccaga tttcctcccg gtgggtacca gttaaccatc tcggaggaca cagaagttgg
aaccacaatt gcagagctga caaccaaaga tgctgactcg gaagacaatg gcagggttcg
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cgcaggtgaa gtgcgatatg ttctgatgga tggcgcccat gggaccttcc gggtggacct
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ccgagaattt gcatcttact actggttgac ggtattagca gtggacaggg gttctgtgcc
cctctcttct gtaactgaag tctacatcga ggttacggat gccaatgaca acccacccca
gatgtcccaa gctgtgttct acccctccat ccaggaggat gctcccgtgg gcacctctgt
gcttcaactg gatgcctggg acccagactc cagctccaaa gggaagctga ccttcaacat
caccagtggg aactacatgg gattctttat gattcaccct gttacaggtc tcctatctac
agcccagcag ctggacagag agaacaagga tgaacacatc ctggaggtga ctgtgctgga
caatggggaa ccctcactga agtccacctc cagggtggtg gtaggcatct tggacgtcaa
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cacaggtgtg gtttcatcca gcagcacttt tacagctgga gagtacaaca tcctaacgat
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acccggactc ttctggttca acatctcagg tggggataag gacatggact ttgacattga
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taacttgact gttgaggtga cagatgggtc ccgcaccatt gccacacagg tccacatctt
catgattgcc aacattaacc accatcggcc ccagtttctg gaaactcgtt atgaagtcag
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NELVTFGPNSKQRPVVCSVPPRLPPAAVPSHSDNEPVIKRTWSSEEMVYPGGAMVWPPTYSRNERWEYPHSEVTQ
GPLPPSAHRHSTPVVMPEPNGLYGGFPFPLEMENKRAPLPPRYSNQNLEDLMPSRPPSPRERLVAPCLNEYTAIS
YYHSQFRQGGGGPCLADGGYKGVGMRLSRAGPSYAVCEVEGAPLAGQGQPRVPPNYEGSDMVESDYGSCEEVMF

SEQ ID NO: 25 Homo sapiens chemokine (C-X-C motif) ligand 5 (CXCL5) (NM_002994)

gtgcagaagg cacgaggaag ccacagtgct ccggatcctc caatcttcgc tcctccaatc
tccgctcctc cacccagttc aggaacccgc gaccgctcgc agcgctctct tgaccactat
gagcctcctg tccagccgcg cggcccgtgt ccccggtcct tcgagctcct tgtgcgcgct
gttggtgctg ctgctgctgc tgacgcagcc agggcccatc gccagcgctg gtcctgccgc
tgctgtgttg agagagctgc gttgcgtttg tttacagacc acgcaaggag ttcatcccaa
aatgatcagt aatctgcaag tgttcgccat aggcccacag tgctccaagg tggaagtggt
agcctccctg aagaacggga aggaaatttg tcttgatcca gaagcccctt ttctaaagaa
agtcatccag aaaattttgg acggtggaaa caaggaaaac tgattaagag aaatgagcac
gcatggaaaa gtttcccagt cttcagcaga gaagttttct ggaggtctct gaacccaggg
aagacaagaa ggaaagattt tgttgttgtt tgtttatttg tttttccagt agttagcttt
cttcctggat tcctcacttt gaagagtgtg aggaaaacct atgtttgccg cttaagcttt
cagctcagct aatgaagtgt ttagcatagt acctctgcta tttgctgtta ttttatctgc
tatgctattg aagttttggc aattgactat agtgtgagcc aggaatcact ggctgttaat
ctttcaaagt gtcttgaatt gtaggtgact attatatttc caagaaatat tccttaagat
attaactgag aaggctgtgg atttaatgtg gaaatgatgt ttcataagaa ttctgttgat
ggaaatacac tgttatcttc acttttataa gaaataggaa atattttaat gtttcttggg
gaatatgtta gagaatttcc ttactcttga ttgtgggata ctatttaatt atttcacttt
agaaagctga gtgtttcaca ccttatctat gtagaatata tttccttatt cagaatttct
aaaagtttaa gttctatgag ggctaatatc ttatcttcct ataattttag acattcttta
tctttttagt atggcaaact gccatcattt acttttaaac tttgatttta tatgctattt
attaagtatt ttattaggag taccataatt ctggtagcta aatatatatt ttagatagat
gaagaagcta gaaaacaggc aaattcctga ctgctagttt atatagaaat gtattctttt
agtttttaaa gtaaaggcaa acttaacaat gacttgtact ctgaaagttt tggaaacgta
ttcaaacaat ttgaatataa atttatcatt tagttataaa aatatatagc gacatcctcg
aggccctagc atttctcctt ggatagggga ccagagagag cttggaatgt taaaaacaaa
acaaaacaaa aaaaaacaag gagaagttgt ccaagggatg tcaatttttt atccctctgt
atgggttaga ttttccaaaa tcataatttg aagaaggcca gcatttatgg tagaatatat
aattatatat aaggtggcca cgctggggca agttccctcc ccactcacag ctttggcccc
tttcacagag tagaacctgg gttagaggat tgcagaagac gagcggcagc ggggagggca
gggaagatgc ctgtcgggtt tttagcacag ttcatttcac tgggattttg aagcatttct
gtctgaatgt aaagcctgtt ctagtcctgg tgggacacac tggggttggg ggtgggggaa
gatgcggtaa tgaaaccggt tagtcagtgt tgtcttaata tccttgataa tgctgtaaag
tttatttta caaatatttc tgtttaagct atttcacctt tgtttggaaa tccttccctt
ttaaagagaa aatgtgacac ttgtgaaaag gcttgtagga aagctcctcc ctttttttct
ttaaaccttt aaatgacaaa cctaggtaat taatggttgt gaatttctat ttttgctttg
tttttaatga acatttgtct ttcagaatag gattctgtga taatatttaa atggcaaaaa

caaaacataa ttttgtgcaa ttaacaaagc tactgcaaga aaaataaaac atttcttggt
aaaaacgtat gtatttatat attatatatt tatatataat atatattata tatttagcat
tgctgagctt tttagatgcc tattgtgtat cttttaaagg ttttgaccat tttgttatga
gtaattacat atatattaca ttcactatat taaaattgta ctttttttact atgtgtctca
ttggttcata gtctttattt tgtcctttga ataaacatta aaagatttct aaacttcaaa
aaaaaaaaaa aaaaa

SEQ ID NO: 26 Homo sapiens chemokine (C-X-C motif) ligand 5 (CXCL5) (NP_002985.1)

MSLLSSRAARVPGPSSSLCALLVLLLLLTQPGPIASAGPAAAVLRELRCVCLQTTQGVHPKMISNLQVFAIGPQC
SKVEVVASLKNGKEICLDPEAPFLKKVIQKILDGGNKEN

SEQ ID NO: 27 Homo sapiens zinc finger protein 771 (ZNF771) (NM_016643)

gaggtggtga aactcaagat ccccatggac aacaaggagg tcccgggcga ggcgcccgcg
ccgtccgccg acccggcgcg tccccacgcg tgccccgact gcggccgcgc cttcgcgcgc
cgctccacgc tggcgaagca cgcgcgcacg cacacgggcg aacggccctt cgggtgcacc
gagtgcgggc ggcgcttctc acagaagtcg gcgctgacca aacacggccg cacgcacacg
ggcgagcggc cctacgagtg ccccgagtgc gacaaacgct tctcggccgc ctcgaacctg
cggcagcacc gacggcggca cacgggcgag aagccgtacg catgcgcgca ctgcggccgc
cgcttcgcgc agagctccaa ctacgcacag cacctgcgcg tgcacacggg cgagaagccg
tacgcgtgcc cggactgcgg acgcgccttt ggcggcagct cgtgcctggc gcgccaccga
cgcacgcaca cgggcgagcg gccctacgct tgcgccgact gcggcacgcg cttcgctcag
agctcggcgc tggccaagca ccggcgcgtg cacacgggcg agaagccgca ccgctgcgct
gtgtgtggcc gtcgcttcgg ccaccgctcc aacctggcgg agcacgcgcg cacgcacaca
ggcgagcggc cctacccctg cgccgagtgc ggccgccgct tccgcctaag ctcgcacttc
attcgccacc gacgcgcgca catgcggcgc cgcctgtata tttgcgccgg ctgcggcagg
gacttcaagc tgccccctgg cgccacggcc gccactgcca ccgagcgttg cccggagtgt
gagggcagct gagtcccgca gggctgcgga ggggcgcgct ggggcttcga cctggctgca
ctaacccagg ctcctcctcg ccccggcctc cgggtctggg aaattgaggg gacggcaggc
ccggctgccc tggaactggg agacagggag aatcccctgc cggggtccct ggaaacagtg
cccaccccac atcactacat tccctcggcc cgtgttagtg aataaagtat tatatcctca
ccccacccgt gcctgtgagt gaggtgggtg ggagaggaag aaagttgggg ttctccaggc
tcaggtgcca agtgagttgt caaggaacca aatggggatg taaacctaaa aggggttccc
ggcacctcgg tttgtgttgg ttggaggtga tcgcacactt ggcccttggt tacgtcctca
taaccttaga cctgaaaggg cccataaata tactatgttc acgatcagac acgcactgca
ttcggcagag ctccagtgag caaggcacga ccctcagatc tcagtctagt gaaggagaga
aaactgtaat aacactacgt taaaggtttt aactgctttg ttatgtaagc ttacccagcc
cggcgcacag tgactcacgc ctgtaatccc agcactttgg gagggcgagg ctagcagatc
acttgaggtt aggagttcga taccagcctg gccaacatgg tgaaacccgg tctctactaa
aaatacaaaa attaactggg tgtggtggcg ggcgcctgta atcccagcta ctgaggggc
tgaggcatga gaatcacttg aacctgggag acagaggttg caatgaaccg agatagtgcc
attgcactcc ggcctgggca acagaggaag actgcctcaa acaaacaaaa aacaacaaac
caaaccaaac caaaaaaatc tcaaagcgat tggacctagc agctcatgcc tgtaatctcc
agcactttgg gaggcggagg caggaggatc tcttgaagtc aagagtttga gatcagcctg
gagaacaaag tgagaccccc atctattaaa aaaaaaaaaa aaaaa

SEQ ID NO: 28 Homo sapiens zinc finger protein 771 (ZNF771)(NP_057727.1)

MDNKEVPGEAPAPSADPARPHACPDCGRAFARRSTLAKHARTHTGERPFGCTECGRRFSQKSALTKHGRTHTGER
PYECPECDKRFSAASNLRQHRRRHTGEKPYACAHCGRRFAQSSNYAQHLRVHTGEKPYACPDCGRAFGGSSCLAR
HRRTHTGERPYACADCGTRFAQSSALAKHRRVHTGEKPHRCAVCGRRFGHRSNLAEHARTHTGERPYPCAECGRR
FRLSSHFIRHRRAHMRRRLYICAGCGRDFKLPPGATAATATERCPECEGS

SEQ ID NO: 29 Homo sapiens natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C)(NPR3)(NM_000908)

tctttttctt ttttttttaa gaaaaactag tgacattgca gagaaggacg cttcctctct
atcttttggc gcattagtga agggggtatt ctattttgtt aaagcgccca agggggcgca
gggaccttgg agagaagagt ggggaggaaa gaggaagggt gggtgggggg cagagggcga
gtcggcggcg gcgagggcaa gctctttctt gcggcacgat gccgtctctg ctggtgctca

ctttctcccc gtgcgtacta ctcggctggg cgttgctggc cggcggcacc ggtggcggtg
gcgttggcgg cggcggcggt ggcgcgggca taggcggcgg acgccaggag agagaggcgc
tgccgccaca gaagatcgag gtgctggtgt tactgcccca ggatgactcg tacttgtttt
cactcacccg ggtgcggccg gccatcgagt atgctctgcg cagcgtggag ggcaacggga
ctgggaggcg gcttctgccg ccgggcactc gcttccaggt ggcttacgag gattcagact
gtgggaaccg tgcgctcttc agcttggtgg accgcgtggc ggcggcgcgg ggcgccaagc
cagaccttat cctggggcca gtgtgcgagt atgcagcagc gccagtggcc cggcttgcat
cgcactggga cctgcccatg ctgtcggctg gggcgctggc cgctggcttc cagcacaagg
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tgctcgccct gttccgccac caccactgga gccgcgctgc actggtctac agcgacgaca
agctggagcg gaactgctac ttcaccctcg agggggtcca cgaggtcttc caggaggagg
gtttgcacac gtccatctac agtttcgacg agaccaaaga cttggatctg gaagacatcg
tgcgcaatat ccaggccagt gagagagtgg tgatcatgtg tgcgagcagt gacaccatcc
ggagcatcat gctggtggcg cacaggcatg gcatgaccag tggagactac gccttcttca
acattgagct cttcaacagc tcttcctatg gagatggctc atggaagaga ggagacaaac
acgactttga agctaagcaa gcatactcgt ccctccagac agtcactcta ctgaggacag
tgaaacctga gtttgagaag ttttccatgg aggtgaaaag ttcagttgag aaacaagggc
tcaatatgga ggattacgtt aacatgtttg ttgaaggatt ccacgatgcc atcctcctct
acgtcttggc tctacatgaa gtactcagag ctggttacag caaaaaggat ggagggaaaa
ttatacagca gacttggaac agaacatttg aaggtatcgc cgggcaggtg tccatagatg
ccaacggaga ccgatatggg gatttctctg tgattgccat gactgatgtg gaggcgggca
cccaggaggt tattggtgat tattttggaa aagaaggtcg ttttgaaatg cggccgaatg
tcaaatatcc ttggggccct ttaaaactga gaatagatga aaaccgaatt gtagagcata
caaacagctc tccctgcaaa tcatgtggcc tagaagaatc ggcagtgaca ggaattgtcg
tgggggcttt actaggagct ggcttgctaa tggccttcta ctttttcagg aagaaataca
gaataaccat tgagaggcga acccagcaag aagaaagtaa ccttggaaaa catcgggaat
tacgggaaga ttccatcaga tcccattttt cagtagctta aaggaagccc cccacttttt
ttttttctgc ctgagattct ttaaggagat agacgggttg aaagacatca atgaaacaga
aggggcgttc ttgaagaatt cataatttta agcagttagt aatttcattt taaaatttct
gtagaagctc aggaattatg attaatcacc atctgcctcc aggcctttca tctcatgaca
aacaaatata ataatgatat cgtgtcactc tgttaaatgt tcatactgtt tcaagcccat
atgattagat ttatgttttt aaaatctgtt gtctccatat cttgatggct tttgggagca
tttcacacaa ggatataaaa tgcggttttc ttaaatgaaa tgttttgtag ctagaataaa
atcatttta caagtacagc attcttggaa agaatttaac acccaaaaag gggaaaatgt
aatgaaaaat ctcaaggttg gaaatacagc cttactctct ctagagctgg aggacaggtt
tgtggttgag gacttctctg tccgatgtct acattcaggt tctgacttca tatcttgaaa
aaggatttcc tccctgtctt tttcagtgtc tcataaacgc tactctggat tgttgtaaat
attagtgaga tgggaggatt tacagaagaa aagcaagtca aaaatatttc ctttttgatg
taaaaaaaaa aagccctatt tcgcactaac attttatttt acaagtattt taatcttata
ttttggtatt agaaaaattt gtctattttt tcattttgaa gattaaatgt tgcttacatt
ttaaaaaaaa a

SEQ ID NO: 30 Homo sapiens natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C) (NPR3) (NP_000899.1)

MPSLLVLTFSPCVLLGWALLAGGTGGGGVGGGGGGAGIGGGRQEREALPPQKIEVLVLLPQDDSYLFSLTRVRPA
IEYALRSVEGNGTGRRLLPPGTRFQVAYEDSDCGNRALFSLVDRVAAARGAKPDLILGPVCEYAAAPVARLASHW
DLPMLSAGALAAGFQHKDSEYSHLTRVAPAYAKMGEMMLALFRHHHWSRAALVYSDDKLERNCYFTLEGVHEVFQ
EEGLHTSIYSFDETKDLDLEDIVRNIQASERVVIMCASSDTIRSIMLVAHRHGMTSGDYAFFNIELFNSSSYGDG
SWKRGDKHDFEAKQAYSSLQTVTLLRTVKPEFEKFSMEVKSSVEKQGLNMEDYVNMFVEGFHDAILLYVLALHEV
LRAGYSKKDGGKIIQQTWNRTFEGIAGQVSIDANGDRYGDFSVIAMTDVEAGTQEVIGDYFGKEGRFEMRPNVKY
PWGPLKLRIDENRIVEHTNSSPCKSCGLEESAVTGIVVGALLGAGLLMAFYFFRKKYRITIERRTQQEESNLGKH
RELREDSIRSHFSVA

SEQ ID NO: 31 Homo sapiens early growth response 2 (Krox-20 homolog, Drosophila) (EGR2) (NM_000399)

taactgagcg aggagcaatt gattaatagc tcggcgaggg gactcactga ctgttataat
aacactacac cagcaactcc tggcttccca gcagccggaa cacagacagg agagagtcag
tggcaaatag acatttttct tatttcttaa aaaacagcaa cttgtttgct acttttattt
ctgttgattt ttttttcttg gtgtgtgtgg tggttgtttt taagtgtgga gggcaaaagg
agataccatc ccaggctcag tccaacccct ctccaaaacg gcttttctga cactccaggt

agcgagggag ttgggtctcc aggttgtgcg aggagcaaat gatgaccgcc aaggccgtag
acaaaatccc agtaactctc agtggttttg tgcaccagct gtctgacaac atctacccgg
tggaggacct cgccgccacg tcggtgacca tctttcccaa tgccgaactg ggaggcccct
ttgaccagat gaacggagtg gccggagatg gcatgatcaa cattgacatg actggagaga
agaggtcgtt ggatctccca tatcccagca gctttgctcc cgtctctgca cctagaaacc
agaccttcac ttacatgggc aagttctcca ttgaccctca gtaccctggt gccagctgct
acccagaagg cataatcaat attgtgagtg caggcatctt gcaaggggtc acttccccag
cttcaaccac agcctcatcc agcgtcacct ctgcctcccc caacccactg gccacaggac
ccctgggtgt gtgcaccatg tcccagaccc agcctgacct ggaccacctg tactctccgc
caccgcctcc tcctccttat tctggctgtg caggagacct ctaccaggac ccttctgcgt
tcctgtcagc agccaccacc tccacctctt cctctctggc ctacccacca cctccttcct
atccatcccc caagccagcc acggacccag gtctcttccc aatgatccca gactatcctg
gattctttcc atctcagtgc cagagagacc tacatggtac agctggccca gaccgtaagc
cctttccctg cccactggac accctgcggg tgccccctcc actcactcca ctctctacaa
tccgtaactt taccctgggg ggccccagtg ctggggtgac cggaccaggg gccagtggag
gcagcgaggg accccggctg cctggtagca gctcagcagc agcagcagcc gccgccgccg
ccgcctataa cccacaccac ctgccactgc ggcccattct gaggcctcgc aagtacccca
acagacccag caagacgccg gtgcacgaga ggccctaccc gtgcccagca gaaggctgcg
accggcggtt ctcccgctct gacgagctga cacggcacat ccgaatccac actgggcata
agcccttcca gtgtcggatc tgcatgcgca acttcagccg cagtgaccac ctcaccaccc
atatccgcac ccacaccggt gagaagccct tcgcctgtga ctactgtggc cgaaagtttg
cccggagtga tgagaggaag cgccacacca agatccacct gagacagaaa gagcggaaaa
gcagtgcccc ctctgcatcg gtgccagccc cctctacagc ctcctgctct gggggcgtgc
agcctggggg taccctgtgc agcagtaaca gcagcagtct tggcggaggg ccgctcgccc
cttgctcctc tcggacccgg acaccttgag atgagactca ggctgataca ccagctccca
aaggtcccgg aggccctttg tccactggag ctgcacaaca aacactacca ccctttcctg
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ctagaagcag gttcttccta aaacttagcc cattctagtc tctcttaggt gagttgacta
tcaacccaag gcaaagggga ggctcagaag gaggtggtgt ggggatcccc tggccaagag
ggctgaggtc tgaccctgct ttaaagggtt gtttgactag gttttgctac cccacttccc
cttattttga cccatcacag gtttttgacc ctggatgtca gagttgatct aagacgtttt
ctacaatagg ttgggagatg ctgatccctt caagtgggga cagcaaaaag acaagcaaaa
ctgatgtgca ctttatggct tgggactgat ttgggggaca ttgtacagtg agtgaagtat
agcctttatg ccacactctg tggccctaaa atggtgaatc agagcatatc tagttgtctc
aacccttgaa gcaatatgta ttatatactc agagaacaga agtgcaatgt gatgggagga
acgtagcaat atctgctcct tttcgagttg tttgagaaat gtaggctatt ttttcagtgt
atatccactc agattttgtg tatttttgat gtacccacac tgttctctaa attctgaatc
tttgggaaaa aatgtaaagc atttatgatc tcagaggtta acttatttaa gggggatgta
catattctct gaaactagga tgcatgcaat tgtgttggaa gtgtccttgg tcgccttgtg
tgatgtagac aaatgttaca aggctgcatg taaatgggtt gccttattat ggagaaaaaa
atcactccct gagtttagta tggctgtata tttatgccta ttaatatttg gaatttttt
tagaaagtat atttttgtat gctttgtttt gtgacttaaa agtgttacct ttgtagtcaa
atttcagata agaatgtaca taatgttacc ggagctgatt tgtttggtca ttagctctta
atagttgtga aaaaataaat ctattctaac gcaaaaccac taactgaagt tcagatataa
tggatggttt gtgactatag tgtaaataaa tacttttcaa caat

SEQ ID NO: 32 Homo sapiens early growth response 2 (Krox-20 homolog, Drosophila) (EGR2) (NP_000390.2)

MMTAKAVDKIPVTLSGFVHQLSDNIYPVEDLAATSVTIFPNAELGGPFDQMNGVAGDGMINIDMTGEKRSLDLPY
PSSFAPVSAPRNQTFTYMGKFSIDPQYPGASCYPEGIINIVSAGILQGVTSPASTTASSSVTSASPNPLATGPLG
VCTMSQTQPDLDHLYSPPPPPPPYSGCAGDLYQDPSAFLSAATTSTSSSLAYPPPPSYPSPKPATDPGLFPMIPD
YPGFFPSQCQRDLHGTAGPDRKPFPCPLDTLRVPPPLTPLSTIRNFTLGGPSAGVTGPGASGGSEGPRLPGSSSA
AAAAAAAAAYNPHHLPLRPILRPRKYPNRPSKTPVHERPYPCPAEGCDRRFSRSDELTRHIRIHTGHKPFQCRIC
MRNFSRSDHLTTHIRTHTGEKPFACDYCGRKFARSDERKRHTKIHLRQKERKSSAPSASVPAPSTASCSGGVQPG
GTLCSSNSSSLGGGPLAPCSSRTRTP

SEQ ID NO: 33 Homo sapiens leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4 (LILRA4) (NM_012276)

ctacgggcac cgtggccaca cctgcctgca cagccagggc caggaggagg agatgccatg
accctcattc tcacaagcct gctcttcttt gggctgagcc tgggccccag gacccgggtg

caggcagaaa acctacccaa acccatcctg tgggccgagc caggtcccgt gatcacctgg
cataaccccg tgaccatctg gtgtcagggc accctggagg cccaggggta ccgtctggat
aaagagggaa actcaatgtc gaggcacata ttaaaaacac tggagtctga aaacaaggtc
aaactctcca tcccatccat gatgtgggaa catgcagggc gatatcactg ttactatcag
agccctgcag gctggtcaga gcccagcgac cccctggagc tggtggtgac agcctacagc
agacccaccc tgtccgcact gccaagccct gtggtgacct caggagtgaa cgtgaccctc
cggtgtgcct cacggctggg actgggcagg ttcactctga ttgaggaagg agaccacagg
ctctcctgga ccctgaactc acaccaacac aaccatggaa agttccaggc cctgttcccc
atgggccccc tgaccttcag caacaggggt acattcagat gctacggcta tgaaaacaac
accccatacg tgtggtcgga acccagtgac cccctgcagc tactggtgtc aggcgtgtct
aggaagccct ccctcctgac cctgcagggc cctgtcgtga cccccggaga gaatctgacc
ctccagtgtg gctctgatgt cggctacatc agatacactc tgtacaagga gggggccgat
ggcctccccc agcgccctgg ccggcagccc caggctgggc tctcccaggc caacttcacc
ctgagccctg tgagccgctc ctacgggggc cagtacagat gctacggcgc acacaacgtc
tcctccgagt ggtcggcccc cagtgacccc ctggacatcc tgatcgcagg acagatctct
gacagaccct ccctctcagt gcagccgggc cccacggtga cctcaggaga gaaggtgacc
ctgctgtgtc agtcatggga cccgatgttc actttccttc tgaccaagga gggggcagcc
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atgagtcctg tgacctcagc ccacgcgggg acctacaggt gctacggctc acgcagctcc
aacccctacc tgctgtctca ccccagtgag cccctggagc tcgtggtctc aggagcaact
gagaccctca atccagcaca aaagaagtca gattccaaga ctgccccaca cctccaggat
tacacagtgg agaatctcat ccgcatgggt gtggctggct tggtcctgct gttcctcggg
attctgttat ttgaggctca gcacagccag agaagccccc caaggtgcag ccaggaggca
aacagcagaa aggacaatgc acccttcaga gtggtggagc cttgggaaca gatctgatga
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ggggaagaag catgggtcag gtgcaggaag atgtctgggt gtctgtagaa gatgcttcct
ccattaaact gtggtgcttt cctcctcaaa aaaaaaaaaa aaaaa

SEQ ID NO: 34 Homo sapiens leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4 (LILRA4) (NP_036408.3)

MTLILTSLLFFGLSLGPRTRVQAENLPKPILWAEPGPVITWHNPVTIWCQGTLEAQGYRLDKEGNSMSRHILKTL
ESENKVKLSIPSMMWEHAGRYHCYYQSPAGWSEPSDPLELVVTAYSRPTLSALPSPVVTSGVNVTLRCASRLGLG
RFTLIEEGDHRLSWTLNSHQHNHGKFQALFPMGPLTFSNRGTFRCYGYENNTPYVWSEPSDPLQLLVSGVSRKPS
LLTLQGPVVTPGENLTLQCGSDVGYIRYTLYKEGADGLPQRPGRQPQAGLSQANFTLSPVSRSYGGQYRCYGAHN
VSSEWSAPSDPLDILIAGQISDRPSLSVQPGPTVTSGEKVTLLCQSWDPMFTFLLTKEGAAHPPLRLRSMYGAHK
YQAEFPMSPVTSAHAGTYRCYGSRSSNPYLLSHPSEPLELVVSGATETLNPAQKKSDSKTAPHLQDYTVENLIRM
GVAGLVLLFLGILLFEAQHSQRSPPRCSQEANSRKDNAPFRVVEPWEQI

SEQ ID NO: 35 Homo sapiens prostaglandin D2 synthase 21kDa (brain) (PTGDS) (NM_000954)

gctcctcctg cacacctccc tcgctctccc acaccactgg caccaggccc cggacacccg
ctctgctgca ggagaatggc tactcatcac acgctgtgga tgggactggc cctgctgggg
gtgctgggcg acctgcaggc agcaccggag gcccaggtct ccgtgcagcc caacttccag
caggacaagt tcctggggcg ctggttcagc gcgggcctcg cctccaactc gagctggctc
cgggagaaga aggcggcgtt gtccatgtgc aagtctgtgg tggcccctgc cacggatggt
ggcctcaacc tgacctccac cttcctcagg aaaaaccagt gtgagacccg aaccatgctg
ctgcagcccg cggggtccct cggctcctac agctaccgga gtccccactg gggcagcacc
tactccgtgt cagtggtgga gaccgactac gaccagtacg cgctgctgta cagccagggc
agcaagggcc ctggcgagga cttccgcatg gccaccctct acagccgaac ccagacccca
agggctgagt taaaggagaa attcaccgcc ttctgcaagg cccagggctt cacagaggat
accattgtct tcctgcccca aaccgataag tgcatgacgg aacaatagga ctccccaggg
ctgaagctgg gatcccggcc agccaggtga cccccacgct ctggatgtct ctgctctgtt
ccttccccga gcccctgccc cggctccccg ccaaagcaac cctgcccact caggcttcat
cctgcacaat aaactccgga agcaagtcag taaaaaaaaa aaaaaaaaaa aaaaaaa

SEQ ID NO: 36 Homo sapiens prostaglandin D2 synthase 21kDa (brain) (PTGDS) (NP_000945.3)

MATHHTLWMGLALLGVLGDLQAAPEAQVSVQPNFQQDKFLGRWFSAGLASNSSWLREKKAALSMCKSVVAPATDG
GLNLTSTFLRKNQCETRTMLLQPAGSLGSYSYRSPHWGSTYSVSVVETDYDQYALLYSQGSKGPGEDFRMATLYS
RTQTPRAELKEKFTAFCKAQGFTEDTIVFLPQTDKCMTEQ

SEQ ID NO: 37 Homo sapiens periostin, osteoblast specific factor (POSTN) (NM_006475)

agagactcaa gatgattccc tttttaccca tgttttctct actattgctg cttattgtta
accctataaa cgccaacaat cattatgaca agatcttggc tcatagtcgt atcaggggtc
gggaccaagg cccaaatgtc tgtgcccttc aacagatttt gggcaccaaa aagaaatact
tcagcacttg taagaactgg tataaaaagt ccatctgtgg acagaaaacg actgttttat
atgaatgttg ccctggttat atgagaatgg aaggaatgaa aggctgccca gcagttttgc
ccattgacca tgtttatggc actctgggca tcgtgggagc caccacaacg cagcgctatt
ctgacgcctc aaaactgagg gaggagatcg agggaaaggg atccttcact tactttgcac
cgagtaatga ggcttgggac aacttggatt ctgatatccg tagaggtttg gagagcaacg
tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca
aggacttaaa aaatggcatg attattcctt caatgtataa caatttgggg cttttcatta
accattatcc taatggggtt gtcactgtta attgtgctcg aatcatccat gggaaccaga
ttgcaacaaa tggtgttgtc catgtcattg accgtgtgct tacacaaatt ggtacctcaa
ttcaagactt cattgaagca gaagatgacc tttcatcttt tagagcagct gccatcacat
cggacatatt ggaggccctt ggaagagacg gtcacttcac actctttgct cccaccaatg
aggcttttga gaaacttcca cgaggtgtcc tagaaaggtt catgggagac aaagtggctt
ccgaagctct tatgaagtac cacatcttaa atactctcca gtgttctgag tctattatgg
gaggagcagt ctttgagacg ctggaaggaa atacaattga gataggatgt gacggtgaca
gtataacagt aaatggaatc aaaatggtga acaaaaagga tattgtgaca aataatggtg
tgatccattt gattgatcag gtcctaattc ctgattctgc caaacaagtt attgagctgg
ctggaaaaca gcaaaccacc ttcacggatc ttgtggccca attaggcttg gcatctgctc
tgaggccaga tggagaatac actttgctgg cacctgtgaa taatgcattt tctgatgata
ctctcagcat ggttcagcgc ctccttaaat taattctgca gaatcacata ttgaaagtaa
aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc
tcagagtctt cgtatatcgt acagctgtct gcattgaaaa ttcatgcatg gagaaaggga
gtaagcaagg gagaaacggt gcgattcaca tattccgcga gatcatcaag ccagcagaga
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aagctgcaga cttgaaagag ctcctgacac aacctggaga ctggacatta tttgtgccaa
ccaatgatgc ttttaaggga atgactagtg aagaaaaaga aattctgata cgggacaaaa
atgctcttca aaacatcatt ctttatcacc tgacaccagg agttttcatt ggaaaaggat
ttgaacctgg tgttactaac attttaaaga ccacacaagg aagcaaaatc tttctgaaag
aagtaaatga tacacttctg gtgaatgaat tgaaatcaaa agaatctgac atcatgacaa
caaatggtgt aattcatgtt gtagataaac tcctctatcc agcagacaca cctgttggaa
atgatcaact gctggaaata cttaataaat taatcaaata catccaaatt aagtttgttc
gtggtagcac cttcaaagaa atccccgtga ctgtctatac aactaaaatt ataaccaaag
ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag
gacccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag
gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaatac accaaaatca
ttgatggagt gcctgtggaa ataactgaaa aagagacacg agaagaacga atcattacag
gtcctgaaat aaaatacact aggatttcta ctggaggtgg agaaacagaa gaaactctga
agaaattgtt acaagaagag gtcaccaagg tcaccaaatt cattgaaggt ggtgatggtc
atttatttga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt
tgcaagccaa caaaaaagtt caaggttcta gaagacgatt aagggaaggt cgttctcagt
gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag
aaaattgtga gagccaagtt gacttcagga actgaaacat cagcacaaag aagcaatcat
caaataattc tgaacacaaa tttaatattt ttttttctga atgagaaaca tgagggaaat
tgtggagtta gcctcctgtg gtaaaggaat tgaagaaaat ataacacctt acacccttt
tcatcttgac attaaaagtt ctggctaact ttggaatcca ttagagaaaa atccttgtca
ccagattcat tacaattcaa atcgaagagt tgtgaactgt tatcccattg aaaagaccga
gccttgtatg tatgttatgg atacataaaa tgcacgcaag ccattatctc tccatgggaa
gctaagttat aaaaataggt gcttggtgta caaaactttt tatatcaaaa ggctttgcac
atttctatat gagtgggttt actggtaaat tatgttattt tttacaacta attttgtact
ctcagaatgt ttgtcatatg cttcttgcaa tgcatatttt ttaatctcaa acgtttcaat
aaaaccattt ttcagatata aagagaatta cttcaaattg agtaattcag aaaaactcaa
gatttaagtt aaaaagtggt ttggacttgg gaa

SEQ ID NO: 38 Homo sapiens periostin, osteoblast specific factor (POSTN) (NP_006466.1)

MIPFLPMFSLLLLLIVNPINANNHYDKILAHSRIRGRDQGPNVCALQQILGTKKKYFSTCKNWYKKSICGQKTTV
LYECCPGYMRMEGMKGCPAVLPIDHVYGTLGIVGATTTQRYSDASKLREEIEGKGSFTYFAPSNEAWDNLDSDIR
RGLESNVNVELLNALHSHMINKRMLTKDLKNGMIIPSMYNNLGLFINHYPNGVVTVNCARIIHGNQIATNGVVHV
IDRVLTQIGTSIQDFIEAEDDLSSFRAAAITSDILEALGRDGHFTLFAPTNEAFEKLPRGVLERFMGDKVASEAL
MKYHILNTLQCSESIMGGAVFETLEGNTIEIGCDGDSITVNGIKMVNKKDIVTNNGVIHLIDQVLIPDSAKQVIE
LAGKQQTTFTDLVAQLGLASALRPDGEYTLLAPVNNAFSDDTLSMVQRLLKLILQNHILKVKVGLNELYNGQILE
TIGGKQLRVFVYRTAVCIENSCMEKGSKQGRNGAIHIFREIIKPAEKSLHEKLKQDKRFSTFLSLLEAADLKELL
TQPGDWTLFVPTNDAFKGMTSEEKEILIRDKNALQNIILYHLTPGVFIGKGFEPGVTNILKTTQGSKIFLKEVND
TLLVNELKSKESDIMTTNGVIHVVDKLLYPADTPVGNDQLLEILNKLIKYIQIKFVRGSTFKEIPVTVYTTKIIT
KVVEPKIKVIEGSLQPIIKTEGPTLTKVKIEGEPEFRLIKEGETITEVIHGEPIIKKYTKIIDGVPVEITEKETR
EERIITGPEIKYTRISTGGGETEETLKKLLQEEVTKVTKFIEGGDGHLFEDEEIKRLLQGDTPVRKLQANKKVQG
SRRRLREGRSQ

SEQ ID NO: 39 Homo sapiens wingless-type MMTV integration site family, member 5A (WNT5A) (NM_003392)

agttgcctgc gcgccctcgc cggaccggcg gctccctagt tgcgccccga ccaggccctg
cccttgctgc cggctcgcgc gcgtccgcgc cccctccatt cctgggcgca tcccagctct
gccccaactc gggagtccag gcccgggcgc cagtgcccgc ttcagctccg gttcactgcg
cccgccggac gcgcgccgga ggactccgca gccctgctcc tgaccgtccc cccaggctta
acccggtcgc tccgctcgga ttcctcggct gcgctcgctc gggtggcgac ttcctccccg
cgccccctcc ccctcgccat gaagaagtcc attggaatat taagcccagg agttgctttg
gggatggctg gaagtgcaat gtcttccaag ttcttcctag tggctttggc catatttttc
tccttcgccc aggttgtaat tgaagccaat tcttggtggt cgctaggtat gaataaccct
gttcagatgt cagaagtata tattatagga gcacagcctc tctgcagcca actggcagga
ctttctcaag gacagaagaa actgtgccac ttgtatcagg accacatgca gtacatcgga
gaaggcgcga agacaggcat caaagaatgc cagtatcaat tccgacatcg aaggtggaac
tgcagcactg tggataacac ctctgttttt ggcagggtga tgcagatagg cagccgcgag
acggccttca catacgcggt gagcgcagca ggggtggtga acgccatgag ccgggcgtgc
cgcgagggcg agctgtccac ctgcggctgc agccgcgccg cgcgccccaa ggacctgccg
cgggactggc tctggggcgg ctgcggcgac aacatcgact atggctaccg ctttgccaag
gagttcgtgg acgcccgcga gcgggagcgc atccacgcca agggctccta cgagagtgct
cgcatcctca tgaacctgca caacaacgag gccggccgca ggacggtgta caacctggct
gatgtggcct gcaagtgcca tggggtgtcc ggctcatgta gcctgaagac atgctggctg
cagctggcag acttccgcaa ggtgggtgat gccctgaagg agaagtacga cagcgcggcg
gccatgcggc tcaacagccg gggcaagttg gtacaggtca acagccgctt caactcgccc
accacacaag acctggtcta catcgacccc agccctgact actgcgtgcg caatgagagc
accggctcgc tgggcacgca gggccgcctg tgcaacaaga cgtcggaggg catggatggc
tgcgagctca tgtgctgcgg ccgtggctac gaccagttca agaccgtgca gacggagcgc
tgccactgca agttccactg gtgctgctac gtcaagtgca agaagtgcac ggagatcgtg
gaccagtttg tgtgcaagta gtgggtgcca cccagcactc agccccgctc ccaggacccg
cttatttata gaaagtacag tgattctggt ttttggtttt tagaaatatt ttttatttct
ccccaagaat tgcaaccgga accatttttt ttcctgttac catctaagaa ctctgtggtt
tattattaat attataatta ttatttggca ataatggggg tgggaaccaa gaaaaatatt
tattttgtgg atctttgaaa aggtaataca agacttcttt tgatagtata gaatgaaggg
gaaataacac ataccctaac ttagctgtgt ggacatggta cacatccaga aggtaaagaa
atacattttc tttttctcaa atatgccatc atatgggatg ggtaggttcc agttgaaaga
gggtggtaga aatctattca caattcagct tctatgacca aaatgagttg taaattctct
ggtgcaagat aaaaggtctt gggaaaacaa aacaaaacaa aacaaacctc ccttccccag
cagggctgct agcttgcttt ctgcattttc aaaatgataa tttacaatgg aaggacaaga
atgtcatatt ctcaaggaaa aaaggtatat cacatgtctc attctcctca aatattccat
ttgcagacag accgtcatat tctaatagct catgaaattt gggcagcagg gaggaaagtc
cccagaaatt aaaaaattta aaactcttat gtcaagatgt tgatttgaag ctgttataag
aattaggatt ccagattgta aaaagatccc caaatgattc tggacactag atttttttgt
ttggggaggt tggcttgaac ataaatgaaa atatcctgtt attttcttag ggatacttgg
ttagtaaatt ataatagtaa aaataataca tgaatcccat tcacaggttc tcagcccaag
caacaaggta attgcgtgcc attcagcact gcaccagagc agacaaccta tttgaggaaa
aacagtgaaa tccaccttcc tcttcacact gagccctctc tgattcctcc gtgttgtgat

gtgatgctgg ccacgtttcc aaacggcagc tccactgggt ccccttggt tgtaggacag
gaaatgaaac attaggagct ctgcttggaa aacagttcac tacttaggga tttttgtttc
ctaaaacttt tattttgagg agcagtagtt ttctatgttt taatgacaga acttggctaa
tggaattcac agaggtgttg cagcgtatca ctgttatgat cctgtgttta gattatccac
tcatgcttct cctattgtac tgcaggtgta ccttaaaact gttcccagtg tacttgaaca
gttgcattta taaggggga aatgtggttt aatggtgcct gatatctcaa agtcttttgt
acataacata tatatatata tacatatata taaatataaa tataaatata tctcattgca
gccagtgatt tagatttaca gtttactctg gggttatttc tctgtctaga gcattgttgt
ccttcactgc agtccagttg ggattattcc aaaagttttt tgagtcttga gcttgggctg
tggccctgct gtgatcatac cttgagcacg acgaagcaac cttgtttctg aggaagcttg
agttctgact cactgaaatg cgtgttgggt tgaagatatc ttttttcttt tctgcctcac
ccctttgtct ccaacctcca tttctgttca ctttgtggag agggcattac ttgttcgtta
tagacatgga cgttaagaga tattcaaaac tcagaagcat cagcaatgtt tctcttttct
tagttcattc tgcagaatgg aaacccatgc ctattagaaa tgacagtact tattaattga
gtccctaagg aatattcagc ccactacata gatagctttt ttttttttt ttttaataag
gacacctctt tccaaacagt gccatcaaat atgttcttat ctcagactta cgttgtttta
aaagtttgga aagatacaca tctttcatac ccccccttagg caggttggct ttcatatcac
ctcagccaac tgtggctctt aatttattgc ataatgatat tcacatcccc tcagttgcag
tgaattgtga gcaaaagatc ttgaaagcaa aaagcactaa ttagtttaaa atgtcacttt
tttggttttt attatacaaa aaccatgaag tacttttttt atttgctaaa tcagattgtt
ccttttttagt gactcatgtt tatgaagaga gttgagttta acaatcctag cttttaaaag
aaactattta atgtaaaata ttctacatgt cattcagata ttatgtatat cttctagcct
ttattctgta cttttaatgt acatatttct gtcttgcgtg atttgtatat ttcactggtt
taaaaaacaa acatcgaaag gcttatgcca aatggaagat agaatataaa ataaaacgtt
acttgtatat tggtaagtgg tttcaattgt ccttcagata attcatgtgg agatttttgg
agaaaccatg acggatagtt taggatgact acatgtcaaa gtaataaaag agtggtgaat
tttaccaaaa ccaagctatt tggaagcttc aaaaggtttc tatatgtaat ggaacaaaag
gggaattctc ttttcctata tatgttcctt acaaaaaaaa aaaaaaaaga aatcaagcag
atggcttaaa gctggttata ggattgctca cattctttta gcattatgca tgtaacttaa
ttgttttaga gcgtgttgct gttgtaacat cccagagaag aatgaaaagg cacatgcttt
tatccgtgac cagattttta gtccaaaaaa atgtattttt ttgtgtgttt accactgcaa
ctattgcacc tctctatttg aatttactgt ggaccatgtg tggtgtctct atgccctttg
aaagcagttt ttataaaaag aaagcccggg tctgcagaga atgaaaactg gttggaaact
aaaggttcat tgtgttaagt gcaattaata caagttattg tgcttttcaa aaatgtacac
ggaaatctgg acagtgctgc acagattgat acattagcct ttgctttttc tctttccgga
taaccttgta acatattgaa acctttttaag gatgccaaga atgcattatt ccacaaaaaa
acagcagacc aacatataga gtgtttaaaa tagcatttct gggcaaattc aaactcttgt
ggttctagga ctcacatctg tttcagtttt tcctcagttg tatattgacc agtgttcttt
attgcaaaaa catatacccg atttagcagt gtcagcgtat tttttcttct catcctggag
cgtattcaag atcttcccaa tacaagaaaa ttaataaaaa atttatatat aggcagcagc
aaaagagcca tgttcaaaat agtcattatg ggctcaaata gaaagaagac ttttaagttt
taatccagtt tatctgttga gttctgtgag ctactgacct cctgagactg gcactgtgta
agttttagtt gcctacccta gctcttttct cgtacaattt tgccaatacc aagtttcaat
ttgtttttac aaaacattat tcaagccact agaattatca aatatgacgc tatagcagag
taaatactct gaataagaga ccggtactag ctaactccaa gagatcgtta gcagcatcag
tccacaaaca cttagtggcc cacaatatat agagagatag aaaaggtagt tataacttga
agcatgtatt taatgcaaat aggcacgaag gcacaggtct aaaatactac attgtcactg
taagctatac ttttaaaata tttatttttt ttaaagtatt ttctagtctt ttctctctct
gtggaatggt gaaagagaga tgccgtgttt tgaaagtaag atgatgaaat gaatttttaa
ttcaagaaac attcagaaac ataggaatta aaacttagag aaatgatcta atttccctgt
tcacacaaac tttacacttt aatctgatga ttggatattt tattttagtg aaacatcatc
ttgttagcta actttaaaaa atggatgtag aatgattaaa ggttggtatg attttttttt
aatgtatcag tttgaaccta gaatattgaa ttaaaatgct gtctcagtat tttaaaagca
aaaaaggaat ggaggaaaat tgcatcttag accatttta tatgcagtgt acaatttgct
gggctagaaa tgagataaag attatttatt tttgttcata tcttgtactt ttctattaaa
atcatttttat gaaatccaaa aaaaaaaaaa aaaaa

SEQ ID NO: 40 Homo sapiens wingless-type MMTV integration site family, member 5A (WNT5A) (NP_003383.2)

MKKSIGILSPGVALGMAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNNPVQMSEVYIIGAQPLCSQLAGL
SQGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNCSTVDNTSVFGRVMQIGSRETAFTYAVSAAGVVNAM
SRACREGELSTCGCSRAARPKDLPRDWLWGGCGDNIDYGYRFAKEFVDARERERIHAKGSYESARILMNLHNNEA
GRRTVYNLADVACKCHGVSGSCSLKTCWLQLADFRKVGDALKEKYDSAAAMRLNSRGKLVQVNSRFNSPTTQDLV
YIDPSPDYCVRNESTGSLGTQGRLCNKTSEGMDGCELMCCGRGYDQFKTVQTERCHCKFHWCCYVKCKKCTEIVD
QFVCK

SEQ ID NO: 41 Homo sapiens prostaglandin D2 synthase 21kDa (brain) (PTGDS) (NM_000954)

gctcctcctg cacacctccc tcgctctccc acaccactgg caccaggccc cggacacccg
ctctgctgca ggagaatggc tactcatcac acgctgtgga tgggactggc cctgctgggg
gtgctgggcg acctgcaggc agcaccggag gcccaggtct ccgtgcagcc caacttccag
caggacaagt tcctggggcg ctggttcagc gcgggcctcg cctccaactc gagctggctc
cgggagaaga aggcggcgtt gtccatgtgc aagtctgtgg tggcccctgc cacggatggt
ggcctcaacc tgacctccac cttcctcagg aaaaaccagt gtgagacccg aaccatgctg
ctgcagcccg cggggtccct cggctcctac agctaccgga gtccccactg gggcagcacc
tactccgtgt cagtggtgga gaccgactac gaccagtacg cgctgctgta cagccagggc
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agggctgagt taaaggagaa attcaccgcc ttctgcaagg cccagggctt cacagaggat
accattgtct tcctgcccca aaccgataag tgcatgacgg aacaatagga ctccccaggg
ctgaagctgg gatcccggcc agccaggtga cccccacgct ctggatgtct ctgctctgtt
ccttccccga gcccctgccc cggctccccg ccaaagcaac cctgcccact caggcttcat
cctgcacaat aaactccgga agcaagtcag taaaaaaaaa aaaaaaaaaa aaaaaaa

SEQ ID NO: 42 Homo sapiens prostaglandin D2 synthase 21kDa (brain) (PTGDS) (NP_000945.3)

MATHHTLWMGLALLGVLGDLQAAPEAQVSVQPNFQQDKFLGRWFSAGLASNSSWLREKKAALSMCKSVVAPATDG
GLNLTSTFLRKNQCETRTMLLQPAGSLGSYSYRSPHWGSTYSVSVVETDYDQYALLYSQGSKGPGEDFRMATLYS
RTQTPRAELKEKFTAFCKAQGFTEDTIVFLPQTDKCMTEQ

SEQ ID NO: 43 Homo sapiens defensin, alpha 3, neutrophil-specific (DEFA3) (NM_005217)

ccttgctata gaagacctgg gacagaggac tgctgtctgc cctctctggt caccctgcct
agctagagga tctgtgaccc cagccatgag gaccctcgcc atccttgctg ccattctcct
ggtggccctg caggcccagg ctgagccact ccaggcaaga gctgatgagg ttgctgcagc
cccggagcag attgcagcgg acatcccaga agtggttgtt tcccttgcat gggacgaaag
cttggctcca aagcatccag gctcaaggaa aaacatggac tgctattgca gaataccagc
gtgcattgca ggagaacgtc gctatggaac ctgcatctac cagggaagac tctgggcatt
ctgctgctga gcttgcagaa aaagaaaaat gagctcaaaa tttgctttga gagctacagg
gaattgctat tactcctgta ccttctgctc aatttccttt cctcatctca aataaatgcc ttgttac

SEQ ID NO: 44 Homo sapiens defensin, alpha 3, neutrophil-specific (DEFA3) (NP_005208.1)

MRTLAILAAILLVALQAQAEPLQARADEVAAAPEQIAADIPEVVVSLAWDESLAPKHPGSRKNMDCYCRIPACIA
GERRYGTCIYQGRLWA

SEQ ID NO: 45 Homo sapiens POU domain, class 1, transcription factor 1 (Pit1, growth hormone factor 1) (POU1F1) (NM_000306)

ctcagagcct tcctgatgta tatatgcagg tagtgagaat tgaatcggcc ctttgagaca
gtaatataat aaaactctga tttggggagc agcggttctc cttatttttc tactctcttg
tgggaatgag ttgccaagct tttacttcgg ctgatacctt tatacctctg aattctgacg
cctctgcaac tctgcctctg ataatgcatc acagtgctgc cgagtgtcta ccagtctcca
accatgccac caatgtgatg tctacagcaa caggacttca ttattctgtt ccttcctgtc
attatggaaa ccagccatca acctatggag tgatggcagg tagtttaacc ccttgtcttt
ataaatttcc tgaccacacc ttgagtcatg gatttcctcc tatacaccag cctcttctgg
cagaggaccc cacagctgct gatttcaagc aggaactcag gcggaaaagt aaattggtgg
aagagccaat agacatggat tctccagaaa tcagagaact tgaaaagttt gccaatgaat

ttaaagtgag acgaattaaa ttaggataca cccagacaaa tgttggggag gccctggcag
ctgtgcatgg ctctgaattc agtcaaacaa caatctgccg atttgaaaat ctgcagctca
gctttaaaaa tgcatgcaaa ctgaaagcaa tattatccaa atggctggag gaagctgagc
aagtaggagc tttgtacaat gaaaaagtgg gagcaaatga aaggaaaaga aaacgaagaa
caactataag cattgctgct aaagatgctc tggagagaca ctttggagaa cagaataaac
cttcttctca agagatcatg aggatggctg aagaactgaa tctggagaaa gaagtagtaa
gagtttggtt ttgcaaccgg aggcagagag aaaaacgggt gaaaacaagt ctgaatcaga
gtttatttc tatttctaag gaacatcttg agtgcagata agatttttct attgtataat
agccttttc tcccgtttca ttcctttctc ttcctcaaca aaaacagaaa ttacttggtt
gacttaaaat cattttatat caatagcttt tacagaagct ttacttttcc actttttttt
aaaaaaaaga aaccaacaat ttaaattata ttgatgttat ttacttaaaa taattattct
cagaagccac attatctatt ttaagccaaa tatattaaca gtaataaaat gatctctctg tc

SEQ ID NO: 46 Homo sapiens POU domain, class 1, transcription factor 1 (Pit1, growth hormone factor 1) (POU1F1) (NP_000297.1)

MSCQAFTSADTFIPLNSDASATLPLIMHHSAAECLPVSNHATNVMSTATGLHYSVPSCHYGNQPSTYGVMAGSLT
PCLYKFPDHTLSHGFPPIHQPLLAEDPTAADFKQELRRKSKLVEEPIDMDSPEIRELEKFANEFKVRRIKLGYTQ
TNVGEALAAVHGSEFSQTTICRFENLQLSFKNACKLKAILSKWLEEAEQVGALYNEKVGANERKRKRRTTISIAA
KDALERHFGEQNKPSSQEIMRMAEELNLEKEVVRVWFCNRRQREKRVKTSLNQSLFSISKEHLECR

SEQ ID NO: 47 Homo sapiens cadherin 13, H-cadherin (heart) (CDH13) (NM_001257)

gggaagttgg ctggctggcg aggcagagcc tctcctcaaa gcctggctcc cacggaaaat
atgctcagtg cagccgcgtg catgaatgaa aacgccgccg ggcgcttcta gtcggacaaa
atgcagccga gaactccgct cgttctgtgc gttctcctgt cccaggtgct gctgctaaca
tctgcagaag atttggactg cactcctgga tttcagcaga aagtgttcca tatcaatcag
ccagctgaat tcattgagga ccagtcaatt ctaaacttga ccttcagtga ctgtaaggga
aacgacaagc tacgctatga ggtctcgagc ccatacttca aggtgaacag cgatggcggc
ttagttgctc tgagaaacat aactgcagtg ggcaaaactc tgttcgtcca tgcacggacc
ccccatgcgg aagatatggc agaactcgtg attgtcgggg ggaaagacat ccagggctcc
ttgcaggata tatttaaatt tgcaagaact tctcctgtcc caagacaaaa gaggtccatt
gtggtatctc ccattttaat tccagagaat cagagacagc ctttcccaag agatgttggc
aaggtagtcg atagtgacag gccagaaagg tccaagttcc ggctcactgg aaagggagtg
gatcaagagc ctaaaggaat tttcagaatc aatgagaaca cagggagcgt ctccgtgaca
cggaccttgg acagagaagt aatcgctgtt tatcaactat ttgtggagac cactgatgtc
aatggcaaaa ctctcgaggg gccggtgcct ctggaagtca ttgtgattga tcagaatgac
aaccgaccga tctttcggga aggcccctac atcggccacg tcatggaagg gtcacccaca
ggcaccacag tgatgcggat gacagccttt gatgcagatg acccagccac cgataatgcc
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atcgatcctg agaaaggaga cattgtcact gttgtgtcac ctgcgctgct ggaccgagag
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gttggattaa caggcacggc cacagccacg atcatgatcg atgacaaaaa tgatcactca
ccaaaattca ccaagaaaga gtttcaagcc acagtcgagg aaggagctgt gggagttatt
gtcaatttga cagttgaaga taaggatgac cccaccacag gtgcatggag ggctgcctac
accatcatca acggaaaccc cgggcagagc tttgaaatcc acaccaaccc tcaaaccaac
gaagggatgc tttctgttgt caaaccattg gactatgaaa tttctgcctt ccacaccctg
ctgatcaaag tggaaaatga agacccactc gtacccgacg tctcctacgg ccccagctcc
acagccaccg tccacatcac tgtcctggat gtcaacgagg gcccagtctt ctacccagac
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gcaggttggc tgaatattaa ccccatcaat gggactgttg acaccacagc tgtgctggac
cgtgagtccc catttgtcga caacagcgtg tacactgctc tcttcctggc aattgacagt
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aatgccccgt tcatttaccc cacagtagct gaagtctgtg atgatgccaa aaacctcagt
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gaaatccaca aacaagctgt tcctgataaa gtctggaaga tctccaagat caacaataca
cacgccctgg taagccttct tcaaaatctg aacaaagcaa actacaacct gcccatcatg
gtgacagatt cagggaaacc acccatgacg aatatcacag atctcagggt acaagtgtgc
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tcagtcctgc tcctcagcct cttcagctta gcttgtctgt gagaactcct gacgtctgaa

gcttgactcc caagtttcca tagcaacagg aaaaaaaaaa atctatccaa atctgaagat
tgcggtttac agctatcgaa cttcacaact aggcctcaat tgttccggtt ttttattttc
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gagagcagag aaagaagtcc tttctcttta ttgagttcga ggactacaac caatttacac
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tgtcccgaat ccacagtcgt actgattcta atggggacac agatcatggt agagaatctc
tccctcctca gtaaatgtac aactgcacct gtcatcatgg aggtcataca tgcatacaaa
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caccaaattt ttctatcaaa taaaactagt gacagcttgt ggctttttat tagagctcgc
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agatagagtt ccatatattg tatttgtttc aatggtaaat ccttttggaa catatagaat
gcagagattt ttttttccat taaaataaat gggtattggt ggttaaaaaa aaaaaaaaaa aa

SEQ ID NO: 48 Homo sapiens cadherin 13, H-cadherin (heart) (CDH13) (NP_001248.1)

MQPRTPLVLCVLLSQVLLLTSAEDLDCTPGFQQKVFHINQPAEFIEDQSILNLTFSDCKGNDKLRYEVSSPYFKV
NSDGGLVALRNITAVGKTLFVHARTPHAEDMAELVIVGGKDIQGSLQDIFKFARTSPVPRQKRSIVVSPILIPEN
QRQPFPRDVGKVVDSDRPERSKFRLTGKGVDQEPKGIFRINENTGSVSVTRTLDREVIAVYQLFVETTDVNGKTL
EGPVPLEVIVIDQNDNRPIFREGPYIGHVMEGSPTGTTVMRMTAFDADDPATDNALLRYNIRQQTPDKPSPNMFY
IDPEKGDIVTVVSPALLDRETLENPKYELIIEAQDMAGLDVGLTGTATATIMIDDKNDHSPKFTKKEFQATVEEG
AVGVIVNLTVEDKDDPTTGAWRAAYTIINGNPGQSFEIHTNPQTNEGMLSVVKPLDYEISAFHTLLIKVENEDPL
VPDVSYGPSSTATVHITVLDVNEGPVFYPDPMMVTRQEDLSVGSVLLTVNATDPDSLQHQTIRYSVYKDPAGWLN
INPINGTVDTTAVLDRESPFVDNSVYTALFLAIDSGNPPATGTGTLLITLEDVNDNAPFIYPTVAEVCDDAKNLS
VVILGASDKDLHPNTDPFKFEIHKQAVPDKVWKISKINNTHALVSLLQNLNKANYNLPIMVTDSGKPPMTNITDL
RVQVCSCRNSKVDCNAAGALRFSLPSVLLLSLFSLACL

SEQ ID NO: 49 Homo sapiens tripartite motif-containing 58 (TRIM58) (NM_015431)

gggagacggt gcgggcggcc gggagcgcag ccctccggga ggcgggtcat ggcctgggcg
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gagccggtca gcgtggactg cggccacagc ttctgcctca ggtgcatctc cgagttctgc
gagaagtcgg acggcgcgca gggcggcgtc tacgcctgtc cgcagtgccg gggccccttc
cggccctcgg gctttcgccc caaccggcag ctggcgggcc tggtggagag cgtgcggcgg
ctggggttgg gcgcggggcc cggggcgcgg cgatgcgcgc ggcacggcga ggacctgagc
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aggacgcacc gcacggcgcc gctgcaggag gccgccggca gctaccaggt aaagctccag
atggctctgg aacttatgag gaaagagttg gaggacgcct tgactcagga ggccaacgtg
gggaaaaaga ctgtcatttg gaaggagaaa gtggaaatgc agaggcagcg cttcagattg
gagtttgaga agcatcgtgg ctttctggcc caggaggagc aacggcagct gaggcggctg
gaggcggagg agcgagcgac gctgcagaga ctgcgggaga gcaagagccg gctggtccag
cagagcaagg ccctgaagga gctggcggat gagctgcagg agaggtgcca gcgcccggcc
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gaagcagaga acatccccat ggaactgaag acagcatgct gcatccctgg gaggagggag
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aggcattact gggaggttct ggtgggagaa ggagcagagt ggggtttagg ggtctgtcaa
gacacactgc caagaaaggg ggaaaccacg ccatctcctg agaatggggt ctgggccctg
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tccaacaaaa aggttaaaag tcattgaagg ctaaccttac tgccttcttt gtatcactgt
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gtggacttca gctcagcaac agcatccctt cccacaggga tcaggtgggt ggcttgagat
acccctcca tggggcacca cccattcagt gagacgggga agccctgggt gggagggaga
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cccttccact cccattctct ctacagcagc tgggctgatt cctttagcac ccaaggatat
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gtcagaatcc tcacagtgaa tccccaggcc ctagaggatg tgaaccccca ggccctagag
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ggccatttcc ccgcctgtgg cttctgcttg acattccctt ttccctgata tccccttgac
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tggaggctct ttgttcccca tacagtacgt gtcgtcgtac tatattgtta ggcttattta
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tctgttgaca atgatacatt caatgtttct caagcacccc caatgctggt ttgtatgtgg 5101
ttatcattca atctgtattt gttgaatgaa taaatgattg actatgtgga gagcaaaa

SEQ ID NO: 58 Homo sapiens tripartite motif-containing 58 (TRIM58) (NP_056246.3)

MAWAPPGERLREDARCPVCLDFLQEPVSVDCGHSFCLRCISEFCEKSDGAQGGVYACPQCRGPFRPSGFRPNRQL
AGLVESVRRLGLGAGPGARRCARHGEDLSRFCEEDEAALCWVCDAGPEHRTHRTAPLQEAAGSYQVKLQMALELM
RKELEDALTQEANVGKKTVIWKEKVEMQRQRFRLEFEKHRGFLAQEEQRQLRRLEAEERATLQRLRESKSRLVQQ
SKALKELADELQERCQRPALGLLEGVRGVLSRSKAVTRLEAENIPMELKTACCIPGRRELLRKFQVDVKLDPATA
HPSLLLTADLRSVQDGEPWRDVPNNPERFDTWPCILGLQSFSSGRHYWEVLVGEGAEWGLGVCQDTLPRKGETTP
SPENGVWALWLLKGNEYMVLASPSVPLLQLESPRCIGIFLDYEAGEISFYNVTDGSYIYTFNQLFSGLLRPYFFI
CDATPLILPPTTIAGSGNWASRDHLDPASDVRDDHL

SEQ ID NO: 59 Homo sapiens Zwilch, kinetochore associated, homolog (Drosophila) (ZWILCH) (NM_017975)

agtcgaggta tcttctcccc aaccactgct cttattttaa ttattgcaga cggaagttga
agactattga catagtaaat agctctgggt ggcttgaaac gaaagtttaa ctttgcggac
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gaacttcaat ctgaagaaac tgccatatct gatttctcta ctggcgaaaa tgttggacca
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gaacaggttt atcgtgtcca aaaactccac catattctag aaatattagt cagttgcatg
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aaggaaagca tatttctctg attgccctta tggagaaata aagataaaat tcaaagaaac
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SEQ ID NO: 60 Homo sapiens Zwilch, kinetochore associated, homolog (Drosophila) (ZWILCH) (NP_060445.3)

MWERLNCAAEDFYSRLLQKFNEEKKGIRKDPFLYEADVQVQLISKGQPNPLKNILNENDIVFIVEKVPLEKEETS
HIEELQSEETAISDFSTGENVGPLALPVGKARQLIGLYTMAHNPNMTHLKINLPVTALPPLWVRCDSSDPEGTCW
LGAELITTNNSITGIVLYVVSCKADKNYSVNLENLKNLHKKRHHLSTVTSKGFAQYELFKSSALDDTITASQTAI
ALDISWSPVDEILQIPPLSSTATLNIKVESGEPRGPLNHLYRELKFLLVLADGLRTGVTEWLEPLEAKSAVELVQ
EFLNDLNKLDGFGDSTKKDTEVETLKHDTAAVDRSVKRLFKVRSDLDFAEQLWCKMSSSVISYQDLVKCFTLIIQ
SLQRGDIQPWLHSGSNSLLSKLIHQSYHGTMDTVSLSGTIPVQMLLEIGLDKLKKDYISFFIGQELASLNHLEYF
IAPSVDIQEQVYRVQKLHHILEILVSCMPFIKSQHELLFSLTQICIKYYKQNPLDEQHIFQLPVRPTAVKNLYQS
EKPQKWRVEIYSGQKKIKTVWQLSDSSPIDHLNFHKPDFSELTLNGSLEERIFFTNMVTCSQVHFK

SEQ ID NO: 61 Homo sapiens pelota homolog (Drosophila) (PELO) (NM_015946)

gatttggccc ggagaacgag atcaccctct caatgaaagg cagatgtccc tttaaggttt
gcttctacag cccgtggact ttagcctaaa cacggacccg cgaagctggc tttatttgtc
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SEQ ID NO: 62 Homo sapiens pelota homolog (Drosophila)(PELO)(NP_057030.3)

MKLVRKNIEKDNAGQVTLVPEEPEDMWHTYNLVQVGDSLRASTIRKVQTESSTGSVGSNRVRTTLTLCVEAIDFD
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LVTPSMTLTRAKVEVNIPRKRKGNCSQHDRALERFYEQVVQAIQRHIHFDVVKCILVASPGFVREQFCDYLFQQA
VKTDNKLLLENRSKFLQVHASSGHKYSLKEALCDPTVASRLSDTKAAGEVKALDDFYKMLQHEPDRAFYGLKQVE
KANEAMAIDTLLISDELFRHQDVATRSRYVRLVDSVKENAGTVRIFSSLHVSGEQLSQLTGVAAILRFPVPELSD
QEGDSSSEED

SEQ ID NO: 63 Homo sapiens zinc finger protein 711 (ZNF711)(NM_021998)

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SEQ ID NO: 64 Homo sapiens zinc finger protein 711 (ZNF711)(NP_068838.3)

MDSGGGSLGLHTPDSRMAHTMIMQDFVAGMAGTAHIDGDHIVVSVPEAVLVSDVVTDDGITLDHGLAAEVVHGPD
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LKCKRCKRGFRQQNELKKHMKTHTGRKIYQCEYCEYSTTDASGFKRHVISIHTKDYPHRCEFCKKGFRRPSEKNQ
HIMRHHKEALM

SEQ ID NO: 65 Homo sapiens intersectin 1 (SH3 domain protein) (ITSN1) (NM_003024)

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ggccaagagc aacaaggagc tgtatggctt ccttttcaac gacttcctcc tgctgactca
gatcacgaag cctttggggt cttctggcac cgacaaagtc ttcagcccca aatcaaacct
gcagtataaa atgtataaaa cacctatttt cctaaatgag gttctagtaa aattacccac
cgacccttct ggagacgagc ccatcttcca catctcccac attgaccgcg tctatactct
ccgagcagaa agcataaatg aaaggactgc ctgggtgcag aaaatcaaag ctgcttctga
actctacata gagactgaga aaaagaagcg cgagaaagcg tacctggtcc gttcccaaag
ggcaacaggc attggaaggt tgatggtgaa cgtggttgaa ggcatcgagt tgaaaccctg
tcggtcacat ggaaagagca acccgtactg tgaggtgacc atgggttccc agtgccacat
caccaagacg atccaggaca ctctgaaccc caagtggaat tccaactgcc agttcttcat
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caaaggtcca gttacgaagt gtcttctgct gcacgaagtc cccacgggag agattgtggt
ccgcttggac ctgcagttgt ttgatgagcc gtaggcagcg ggctcagggt gtgctcagca
gggtcccagc ccacggccac acatgctgtc tggaaattgt attccttttc taagaaacca
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atagccctca acagggtgca gctgggagtc tagccccttc ccgggcttga gggatgggtc
tggttactat aaaatagatt tataaatgca atgtctatat ttttggagaa ctcatgtaac
cctcctgttt cttacatcca ccagtcccca agtagacttc ttggcctaca atgcccagtc
cttggtgtga gtttagaaac aattatgacg gtcctgtcat tgcttcagaa tcccatctct
cctgcaggga aatgctgcct agagctgatc actcggtgag acggtctgat caggccctgg
cttagctctt tgaagagctg gtctatggaa gtttccagca tgtgcaccgt tatagccgtt
ccttcccccc ctaggccttg tattaatata tgtcaatgaa aacacactgg tgtattgttg
cgtggattca gttctgattc ccagcatgct tagaatatgg tcacagaaag tcattatcta
gaaagtcacc cctctgctgg atcagatcac tacaggtcac tggaaaggca actttacaat
gttgggtcac tgggtctcgg ttggcagcca tgttggaaaa atctcttttg gctcggaggc
ctgtgatatt tcatagcagc agtcgttgct ggtgacctgt tctgtgcttg aatgtgctga
atcctgattg ttgtaggaca tttcaacagc tctttttggt acgttcccca aaaagccatg
tcctagatcc ccaaggcgt

SEQ ID NO: 66 Homo sapiens intersectin 1 (SH3 domain protein) (ITSN1) (NP_003015.2)

MAQFPTPFGGSLDIWAITVEERAKHDQQFHSLKPISGFITGDQARNFFFQSGLPQPVLAQIWALADMNNDGRMDQ
VEFSIAMKLIKLKLQGYQLPSALPPVMKQQPVAISSAPAFGMGGIASMPPLTAVAPVPMGSIPVVGMSPTLVSSV
PTAAVPPLANGAPPVIQPLPAFAHPAATLPKSSSFSRSGPGSQLNTKLQKAQSFDVASVPPVAEWAVPQSSRLKY
RQLFNSHDKTMSGHLTGPQARTILMQSSLPQAQLASIWNLSDIDQDGKLTAEEFILAMHLIDVAMSGQPLPPVLP
PEYIPPSFRRVRSGSGISVISSTSVDQRLPEEPVLEDEQQQLEKKLPVTFEDKKRENFERGNLELEKRRQALLEQ
QRKEQERLAQLERAEQERKERERQEQERKRQLELEKQLEKQRELERQREEERRKEIERREAAKRELERQRQLEWE
RNRRQELLNQRNKEQEDIVVLKAKKKTLEFELEALNDKKHQLEGKLQDIRCRLTTQRQEIESTNKSRELRIAEIT
HLQQQLQESQQMLGRLIPEKQILNDQLKQVQQNSLHRDSLVTLKRALEAKELARQHLRDQLDEVEKETRSKLQEI
DIFNNQLKELREIHNKQQLQKQKSMEAERLKQKEQERKIIELEKQKEEAQRRAQERDKQWLEHVQQEDEHQRPRK
LHEEEKLKREESVKKKDGEEKGKQEAQDKLGRLFHQHQEPAKPAVQAPWSTAEKGPLTISAQENVKVVYYRALYP
FESRSHDEITIQPGDIVMVKGEWVDESQTGEPGWLGGELKGKTGWFPANYAEKIPENEVPAPVKPVTDSTSAPAP
KLALRETPAPLAVTSSEPSTTPNNWADFSSTWPTSTNEKPETDNWDAWAAQPSLTVPSAGQLRQRSAFTPATATG
SSPSPVLGQGEKVEGLQAQALYPWRAKKDNHLNFNKNDVITVLEQQDMWWFGEVQGQKGWFPKSYVKLISGPIRK
STSMDSGSSESPASLKRVASPAAKPVVSGEEFIAMYTYESSEQGDLTFQQGDVILVTKKDGDWWTGTVGDKAGVF
PSNYVRLKDSEGSGTAGKTGSLGKKPEIAQVIASYTATGPEQLTLAPGQLILIRKKNPGGWWEGELQARGKKRQI
GWFPANYVKLLSPGTSKITPTEPPKSTALAAVCQVIGMYDYTAQNDDELAFNKGQIINVLNKEDPDWWKGEVNGQ
VGLFPSNYVKLTTDMDPSQQWCSDLHLLDMLTPTERKRQGYIHELIVTEENYVNDLQLVTEIFQKPLMESELLTE
KEVAMIFVNWKELIMCNIKLLKALRVRKKMSGEKMPVKMIGDILSAQLPHMQPYIRFCSRQLNGAALIQQKTDEA

PDFKEFVKRLAMDPRCKGMPLSSFILKPMQRVTRYPLIIKNILENTPENHPDHSHLKHALEKAEELCSQVNEGVR
EKENSDRLEWIQAHVQCEGLSEQLVFNSVTNCLGPRKFLHSGKLYKAKSNKELYGFLFNDFLLLTQITKPLGSSG
TDKVFSPKSNLQYKMYKTPIFLNEVLVKLPTDPSGDEPIFHISHIDRVYTLRAESINERTAWVQKIKAASELYIE
TEKKKREKAYLVRSQRATGIGRLMVNVVEGIELKPCRSHGKSNPYCEVTMGSQCHITKTIQDTLNPKWNSNCQFF
IRDLEQEVLCITVFERDQFSPDDFLGRTEIRVADIKKDQGSKGPVTKCLLLHEVPTGEIVVRLDLQLFDEP

SEQ ID NO: 67 Homo sapiens phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1) (NM_021127)

actggacaaa agcgtggtct ctggcgcggg gatctcagag tttcccgggc actcaccgtg
tgtagttggc atctccgcgc gtccggacac ccgatcccag catccctgcc tgcaggactg
ttcgtgttca gctcgcgtcc tgcagctgtc cgaggtgctc cagttggagg ctgaggttcc
cgggctctgt agctgagtgg gcggcggcac cggcggagat gcctgggaag aaggcgcgca
agaacgctca accgagcccc gcgcgggctc cagcagagct ggaagtcgag tgtgctactc
aactcaggag atttggagac aaactgaact tccggcagaa acttctgaat ctgatatcca
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ggaatgtgaa ggtgcattca tgggtgccct tggaaacgga agatggaata catcaaagtg
aatttctgtt caagttttcc cagattatca ttctttggga tgagagaaca ttataaaacc
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tgttatactc agtgttgatt tcttcggtca ctacacaacg taaaatcatt tgtttctttt
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ggttacttgg ggccagtaaa tcagtagact gaacattcaa tataataaaa gaacatgggg
attttgtata accagggata ataaaaagaa aaaagaagtt aatttttaat tgatgttttt
gaaacttagt agaacaaata ttcagaagta acttgataag atatgaatgt ttctaaagaa
gtttctaaag gttcggaaaa tgctccttgt cacattagtg tgcatcctac aaaaagtgat
ctcttaatgt aaattaagaa tattttcata attggaatat acttttctta aaaaaaagga
acagttagtt ctcatctaga atgaaagttc catatatgca ttggtgaata tatatgtata
cacatactta catacttata tgggtatctg tatagataat ttgtattaga gtattatata
gcttcttagt agggtctcaa gtaagtttca tttttttttat ctgggctata tacagtcctc
aaataaataa tgtcttgatt ttatttcagc aggaataatt ttatttattt tgcctattta
taattaaagt atttttcttt agtttgaaaa tgtgtattaa agttacattt ttgagttaca
agagtcttat aactacttga atttttagtt aaaatgtctt aatgtaggtt gtagtcactt
tagatggaaa attacctcac atctgttttc ttcagtatta cttaagattg tttatttagt
ggtagagagt ttttttttttc agcctagagg cagctatttt accatctggt atttatggtc
taatttgtat ttaaacatat gcacacatat aaaagttgat actgtggcag taaactatta
aaagttttca ctgttcaaaa aaaaaaaaaa aaaa

SEQ ID NO: 68 Homo sapiens phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1) (NP_066950.1)

MPGKKARKNAQPSPARAPAELEVECATQLRRFGDKLNFRQKLLNLISKLFCSGT

SEQ ID NO: 69 Homo sapiens transmembrane protein 47 (TMEM47) (NM_031442)

ggcagagcgc ggcgcggggc cggcggcgaa ggtccggggt ggaatcgacg tcgctgcggc
tgccgacgac ccacacccgg ccggccgcct ccgcagaccc accttggccg cgcggcaggg
ggcgcgcaga gccccgaggg agcgagtccc cgcgcgtggc agctcggcgg cttctccctt
cgggaggtcc ggctcccggc tctccggacc cgcctggcgt cctcgcctgc ggcggggcgg
acgacagcgg cgcccaggaa tggcttcggc gggcagcggc atggaggagg tgcgcgtgtc
ggtgctgacc cccttgaagc tggtcgggct ggtgtgcatc ttcctggcgc tgtgtctgga
cctgggggcg gtgctgagcc cggcctgggt cacagctgac caccagtact acctgtcgtt
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atgacagcaa ccattgtgag aaactagttg gaatgagatt tgcctcaatc tcctattgcc
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ctttggcaat cagcgtctcc ctgggaagag agtcaagact tggagacatg tgcttctcat
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tatcacacgt aaaattaata tttactctag tgaagtggtt tgagcactaa ccttgtacac
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aaaagagagt agcaattagg atgatcattt tgtgtaaaat tcattaaaat agaaggctgc
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atataaatat ctaaatgtct cagtagagga gtagaattca tctggttatc acctggtcct
ctgaagttaa ctgatgggct aaccgatttg tgcacacact taggatggat ttatgttaag
ggaattactt actgactgtt caatggaagg aagtattaat aatagggaat aagtttgcaa
ctaatctcat gctgcaaact tgtgttaatt ctgtttaata tacaaatttg gatagcttaa
ttataaacat atttttatat caaatataca gttctaatat aaaagttata aataattatt
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aggaccacat cgatagtatt taataatttg ttttacctcc caaaacacag ttcttctttc
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gatttcagca actaaacatt ctctgttctg agatctcttt attcctgaat aatgaaagaa
tagtactttg gtgctgacac caatgaggca cttctcttgg tcctagtaga ggatgcagtg
tactgttaaa ccaatatcat cacatctcga gtcttatcaa gttttcattc tctgtcaata
tgacaagctc aaagtgacag aatatgttat aggttgaagc acacatattt gcagtttact
gaaaagtaga tttcttatgt gacttttttc ccttctcagc aaagagccct acactagatt
tctaccatca ctaatatttg gaagtatttc attactaaca atctcagtac aacatgaaaa
ttgttgcttc tcatctaaaa tacaattttg tctatcagaa taaacacaag tgaaattttc
acctacatta acattatgtc tttgcagctt taggtttgtt agatgtgttc ttaagcataa
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agttattccg atttcttgca caattattta gctttttgta agttcaacat gtaaatttta
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gtacctgtat attattaaac atgcaatgaa ctgactggta agtgacgtct aattgtatgg
ctagcaatgt aatttattca gactgtattt ttgtacagag cagtgcactc taacctatgc
ctctgtgtcc tctttaatgc ctaaagctgt gcctagaaat ttcatctgtc ttaaaagtaa
aatatacttc atgctgttta tgctattagt ttctgtactg ctattctata tttattattt
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taagtcatct gggggaaaac ctgtttatca ctccagtgat tttgagtttg cagtttcaca
atcagttctt catttcatga tttttgtagt tgacatgaag tcatctatgt ggaaaaaaat
aaaaataaaa gtgatttcac ggatgtggtt tgaaaaaaaa aaaaaaaa

SEQ ID NO: 70 Homo sapiens transmembrane protein 47 (TMEM47)(NP_113630.1)

MASAGSGMEEVRVSVLTPLKLVGLVCIFLALCLDLGAVLSPAWVTADHQYYLSLWESCRKPASLDIWHCESTLSS
DWQIATLALLLGGAAIILIAFLVGLISICVGSRRRFYRPVAVMLFAAVVLQVCSLVLYPIKFIETVSLKIYHEFN
WGYGLAWGATIFSFGGAILYCLNPKNYEDYY

SEQ ID NO: 71 Homo sapiens interleukin 11 (IL11)(NM_000641)

gctcagggca catgcctccc ctccccaggc cgcggcccag ctgaccctcg gggctccccc
ggcagcggac agggaagggt taaaggcccc cggctccctg ccccctgccc tggggaaccc
ctggccctgt ggggacatga actgtgtttg ccgcctggtc ctggtcgtgc tgagcctgtg
gccagataca gctgtcgccc ctgggccacc acctggcccc cctcgagttt ccccagaccc
tcgggccgag ctggacagca ccgtgctcct gacccgctct ctcctggcgg acacgcggca
gctggctgca cagctgaggg acaaattccc agctgacggg gaccacaacc tggattccct
gcccaccctg gccatgagtg cgggggcact gggagctcta cagctcccag gtgtgctgac
aaggctgcga gcggacctac tgtcctacct gcggcacgtg cagtggctgc gccgggcagg
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gctgctgcgc cggctgcagc tcctgatgtc ccgcctggcc ctgccccagc cacccccgga
cccgccggcg cccccgctgg cgccccccctc ctcagcctgg gggggcatca gggccgccca
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gaagactcgg ctgtgacccg gggcccaaag ccaccaccgt ccttccaaag ccagatctta
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ccccctagtt agagacagtc cttccgtgag gcctgggggg catctgtgcc ttatttatac
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ggactggggt cccggattct tgggtctcca agaagtctgt ccacagactt ctgccctggc
tcttccccat ctaggcctgg gcaggaacat atattattta tttaagcaat tacttttcat
gttggggtgg ggacggaggg gaaagggaag cctgggtttt tgtacaaaaa tgtgagaaac
ctttgtgaga cagagaacag ggaattaaat gtgtcataca tatccacttg agggcgattt
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ccattcaggt ggaggtcccg agtgggcggg gcagcgactg ggagatgggt cggtcaccca
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ttgtttgttt tttgagatgg agtctcgctc tgttgcctag gctggagtgc agtgaggcaa
tctgaggtca ctgcaacctc cacctcccgg gttcaagcaa ttctcctgcc tcagcctccc
gattagctgg gatcacaggt gtgcaccacc atgcccagct aattatttat ttcttttgta
tttttagtag agacagggtt tcaccatgtt ggccaggctg gtttcgaact cctgacctca
ggtgatcctc ctgcctcggc ctcccaaagt gctgggatta caggtgtgag ccaccacacc
tgacccatag gtcttcaata aatatttaat ggaaggttcc acaagtcacc ctgtgatcaa
cagtacccgt atgggacaaa gctgcaaggt caagatggtt cattatggct gtgttcacca
tagcaaactg gaaacaatct agatatccaa cagtgagggt taagcaacat ggtgcatctg
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tgtaatcctg gcactttggg aggacgaagc gagtggatca ctgaagtcca agagttcgag
accggcctgc gagacatggc aaaaccctgt ctcaaaaaag aaagaatgat gtcctgacat
gaaacagcag gctacaaaac cactgcatgc tgtgatccca attttgtgtt tttctttcta
tatatggatt aaaacaaaaa tcctaaaggg aaatacgcca aaatgttgac aatgactgtc
tccaggtcaa aggagagagg tgggattgtg ggtgactttt aatgtgtatg attgtctgta
ttttacagaa tttctgccat gactgtgtat tttgcatgac acattttaaa aataataaac
actattttta gaat

SEQ ID NO: 72 Homo sapiens interleukin 11 (IL11)(NP_000632.1)

MNCVCRLVLVVLSLWPDTAVAPGPPPGPPRVSPDPRAELDSTVLLTRSLLADTRQLAAQLRDKFPADGDHNLDSL
PTLAMSAGALGALQLPGVLTRLRADLLSYLRHVQWLRRAGGSSLKTLEPELGTLQARLDRLLRRLQLLMSRLALP
QPPPDPPAPPLAPPSSAWGGIRAAHAILGGLHLTLDWAVRGLLLLKTRL

SEQ ID NO: 73 Homo sapiens chemokine (C motif) ligand 2 (XCL2)(NM_003175)

agctcagcgg gacctcagcc atgagacttc tcatcctggc cctccttggc atctgctctc
tcactgcata cattgtggaa ggtgtaggga gtgaagtctc acataggagg acctgtgtga
gcctcactac ccagcgactg ccagttagca gaatcaagac ctacaccatc acggaaggct
ccttgagagc agtaattttt attaccaaac gtggcctaaa agtctgtgct gatccacaag
ccacgtgggt gagagacgtg gtcaggagca tggacaggaa atccaacacc agaaataaca
tgatccagac caagccaaca ggaacccagc aatcgaccaa tacagctgtg accctgactg
gctagtagtc tctggcaccc tgtccgtctc cagccagcca gctcatttca ctttacaccc

tcatggactg agattatact caccttttat gaaagcactg catgaataaa attattcctt
tgtattttta cttttaaatg tcttctgtat tcacttatat gttctaatta ataaattatt
tattattaag aa

SEQ ID NO: 74 Homo sapiens chemokine (C motif) ligand 2 (XCL2)(NP_003166.1)

MRLLILALLGICSLTAYIVEGVGSEVSHRRTCVSLTTQRLPVSRIKTYTITEGSLRAVIFITKRGLKVCADPQAT
WVRDVVRSMDRKSNTRNNMIQTKPTGTQQSTNTAVTLTG

SEQ ID NO: 74 Homo sapiens prostaglandin E receptor 4 (subtype EP4) (PTGER4) (NM_000958)

gcgagagcgg agctccaagc ccggcagccc gagaggaaga tgaacagccc caggccagag
cctctggcag agtggacccc gagccgcccc caggtagcca ggagcggcct cagcggcagc
cgcaaactcc agtagccgcc cgtgctgccc gtggctgggg cggagggcag ccagagctgg
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gacgagaccg gcgggcactg caaagctggg actcgtcttt gaaggaaaaa aaatagcgag
taagaaatcc agcaccattc ttcactgacc catcccgctg cacctcttgt ttcccaagtt
tttgaaagct ggcaactctg acctcggtgt ccaaaaatcg acagccactg agaccggctt
tgagaagccg aagatttggc agtttccaga ctgagcagga caaggtgaaa gcaggttgga
ggcgggtcca ggacatctga gggctgaccc tgggggctcg tgaggctgcc accgctgctg
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cccggcggtg atgttcatct tcggggtggt gggcaacctg gtggccatcg tggtgctgtg
caagtcgcgc aaggagcaga aggagacgac cttctacacg ctggtatgtg ggctggctgt
caccgacctg ttgggcactt tgttggtgag cccggtgacc atcgccacgt acatgaaggg
ccaatggccc gggggccagc cgctgtgcga gtacagcacc ttcattctgc tcttcttcag
cctgtccggc ctcagcatca tctgcgccat gagtgtcgag cgctacctgg ccatcaacca
tgcctatttc tacagccact acgtggacaa gcgattggcg ggcctcacgc tctttgcagt
ctatgcgtcc aacgtgctct tttgcgcgct gcccaacatg ggtctcggta gctcgcggct
gcagtaccca gacacctggt gcttcatcga ctggaccacc aacgtgacgg cgcacgccgc
ctactcctac atgtacgcgg gcttcagctc cttcctcatt ctcgccaccg tcctctgcaa
cgtgcttgtg tgcggcgcgc tgctccgcat gcaccgccag ttcatgcgcc gcacctcgct
gggcaccgag cagcaccacg cggccgcggc cgcctcggtt gcctcccggg gccaccccgc
tgcctcccca gccttgccgc gcctcagcga ctttcggcgc cgccggagct tccgccgcat
cgcgggcgcc gagatccaga tggtcatctt actcattgcc acctccctgg tggtgctcat
ctgctccatc ccgctcgtgg tgcgagtatt cgtcaaccag ttatatcagc caagtttgga
gcgagaagtc agtaaaaatc cagatttgca ggccatccga attgcttctg tgaaccccat
cctagacccc tggatatata tcctcctgag aaagacagtg ctcagtaaag caatagagaa
gatcaaatgc ctcttctgcc gcattggcgg gtcccgcagg gagcgctccg gacagcactg
ctcagacagt caaaggacat cttctgccat gtcaggccac tctcgctcct tcatctcccg
ggagctgaag gagatcagca gtacatctca gaccctcctg ccagacctct cactgccaga
cctcagtgaa aatggccttg gaggcaggaa tttgcttcca ggtgtgcctg gcatgggcct
ggcccaggaa gacaccacct cactgaggac tttgcgaata tcagagacct cagactcttc
acagggtcag gactcagaga gtgtcttact ggtggatgag gctggtggga gcggcagggc
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atcagaaaaa tgtatataat aggcaaggaa agaaatacag tactgtttct ggacccttat
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catcctacaa ctcacattag agaacatcct ggcttttgag cacttttcaa acaatcaagt
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ttgtggtcac aacttgatgg ctgcgaagac ctaccctccg tttttctact agataggagg
atggtagaag tttggctgct gtcataacat ccagagcttt gtcgtatttg gcacacagca
gaggcccaga tattagaaag gctctattcc aataaactat gaggactgcc ttatggatga
tttaagtgtc tcactaaagc atgaaatgtg aatttttatt gttgtacata cgatttaagg
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ataaacaagt tcgagtcaaa gttgaaaatt catagtaaga ttgatatcta taaaatagat
ataaattttt aagagaaaga atttagtatt atcaaaggga taaagaaaaa aatactattt
aagatgtgaa aattacagtc caaaatactg ttctttccag gctatgtata aaatacatag
tgaaaattgt ttagtgatat tacatttatt tatccagaaa actgtgattt caggagaacc
taacatgctg gtgaatattt tcaacttttt ccctcactaa ttggtacttt taaaaacata
acataaattt tttgaagtct ttaataaata acccataatt gaagtgtata atataaaaaa

ttttaaaaat ctaagcagct tattgtttct ctgaaagtgt gtgtagtttt actttcctaa
ggaattacca agaatatcct ttaaaattta aaaggatggc aagttgcatc agaaagcttt
attttgagat gtaaaaagat tcccaaacgt ggttacatta gccattcatg tatgtcagaa
gtgcagaatt ggggcactta atggtcacct tgtaacagtt ttgtgtaact cccagtgatg
ctgtacacat atttgaaggg tctttctcaa agaaatatta agcatgtttt gttgctcagt
gtttttgtga attgcttggt tgtaattaaa ttctgagcct gatattgata tggttttaag
aagcagttgt accaagtgaa attatttttgg agattataat aaatatatac attcaaaaaa
aaaaaaaaaa aa

SEQ ID NO: 76 Homo sapiens prostaglandin E receptor 4 (subtype EP4) (PTGER4) (NP_000949.1)

MSTPGVNSSASLSPDRLNSPVTIPAVMFIFGVVGNLVAIVVLCKSRKEQKETTFYTLVCGLAVTDLLGTLLVSPV
TIATYMKGQWPGGQPLCEYSTFILLFFSLSGLSIICAMSVERYLAINHAYFYSHYVDKRLAGLTLFAVYASNVLF
CALPNMGLGSSRLQYPDTWCFIDWTTNVTAHAAYSYMYAGFSSFLILATVLCNVLVCGALLRMHRQFMRRTSLGT
EQHHAAAAASVASRGHPAASPALPRLSDFRRRRSFRRIAGAEIQMVILLIATSLVVLICSIPLVVRVFVNQLYQP
SLEREVSKNPDLQAIRIASVNPILDPWIYILLRKTVLSKAIEKIKCLFCRIGGSRRERSGQHCSDSQRTSSAMSG
HSRSFISRELKEISSTSQTLLPDLSLPDLSENGLGGRNLLPGVPGMGLAQEDTTSLRTLRISETSDSSQGQDSES
VLLVDEAGGSGRAGPAPKGSSLQVTFPSETLNLSEKCI

SEQ ID NO: 77 Homo sapiens caspase 2, apoptosis-related cysteine peptidase (neural precursor cell expressed, developmentally down-regulated 2) (CASP2) (NM_032982)

gggtggcctg gtgtgtgggc gcggcagggc gcaggcgcag gcgcagtgtg cgtccgcgtc
tgaggggagg gatgtggggg aagcgacggc ccccggtttg tttgggctgt gggcggtgcg
cagcggagag cccgggaaaa gcgggaaatg gcggcgccga gcgcggggtc ttggtccacc
ttccagcaca aggagctgat ggccgctgac aggggacgca ggatattggg agtgtgtggc
atgcatcctc atcatcagga aactctaaaa aagaaccgag tggtgctagc caaacagctg
ttgttgagcg aattgttaga acatcttctg gagaaggaca tcatcacctt ggaaatgagg
gagctcatcc aggccaaagt gggcagtttc agccagaatg tggaactcct caacttgctg
cctaagaggg gtccccaagc ttttgatgcc ttctgtgaag cactgaggga gaccaagcaa
ggccacctgg aggatatgtt gctcaccacc ctttctgggc ttcagcatgt actcccaccg
ttgagctgtg actacgactt gagtctccct tttccggtgt gtgagtcctg tcccctttac
aagaagctcc gcctgtcgac agatactgtg gaacactccc tagacaataa agatggtcct
gtctgccttc aggtgaagcc ttgcactcct gaattttatc aaacacactt ccagctggca
tataggttgc agtctcggcc tcgtggccta gcactggtgt tgagcaatgt gcacttcact
ggagagaaag aactggaatt tcgctctgga ggggatgtgg accacagtac tctagtcacc
ctcttcaagc ttttgggcta tgacgtccat gttctatgtg accagactgc acaggaaatg
caagagaaac tgcagaattt tgcacagtta cctgcacacc gagtcacgga ctcctgcatc
gtggcactcc tctcgcatgg tgtggagggc gccatctatg gtgtggatgg gaaactgctc
cagctccaag aggtttttca gctctttgac aacgccaact gcccaagcct acagaacaaa
ccaaaaatgt tcttcatcca ggcctgccgt ggagatgaga ctgatcgtgg ggttgaccaa
caagatggaa agaaccacgc aggatcccct gggtgcgagg agagtgatgc cggtaaagaa
aagttgccga agatgagact gcccacgcgc tcagacatga tatgcggcta tgcctgcctc
aaagggactg ccgccatgcg gaacaccaaa cgaggttcct ggtacatcga ggctcttgct
caagtgtttt ctgagcgggc ttgtgatatg cacgtggccg acatgctggt taaggtgaac
gcacttatca aggatcggga aggttatgct cctggcacag aattccaccg gtgcaaggag
atgtctgaat actgcagcac tctgtgccgc cacctctacc tgttcccagg acaccctccc
acatgatgtc acctccccat catccacgcc aagtggaagc cactggacca caggaggtgt
gatagagcct ttgatcttca ggatgcacgg tttctgttct gcccctcag ggatgtggga
atctcccaga cttgtttcct gtgcccatca tctctgcctt tgagtgtggg actccaggcc
agctcctttt ctgtgaagcc ctttgcctgt agagccagcc ttggttggac ctattgccag
gaatgtttca gctgcagttg aagagcctga caagtgaagt tgtaaacaca gtgtggttat
ggggagaggg catataaatt ccccatattt gtgttcagtt ccagcttttg tagatggcac
tttagtgatt gcttttatta cattagttaa gatgtctgag agaccatctc ctatctttta
tttcattcat atcctccgcc ctttttgtcc tagagtgaga gtttggaagg tgtccaaatt
taatgtagac attatctttt ggctctgaag aagcaaacat gactagagac gcaccttgct
gcagtgtcca gaagcggcct gtgcgttccc ttcagtactg cagcgccacc cagtggaagg
acactcttgg ctcgtttggg ctcaaggcac cgcagcctgt cagccaacat tgccttgcat
ttgtacctta ttgatctttg cccatggaag tctcaaagat ctttcgttgg ttgtttctct
gagctttgtt actgaaatga gcctcgtggg gagcatcaga gaaggccagg aagaatggtg

tgtttcccta gactctgtaa ccacctctct gtctttttcc ttcctgagaa acgtccatct
ctctccctta ctattcccac tttcattcaa tcaacctgca cttcatatct agatttctag
aaaagcttcc tagcttatct ccctgcttca tatctctccc ttctttacct tcatttcatc
ctgttggctg ctgccaccaa atctgtctag aatcctgctt tacaggatca tgtaaatgct
caaagatgta atgtagttct ttgttcctgc tttctctttc agtattaaac tctcctttga
tattatgtgg cttttatttc agtgccatac atgttattgt tttcaaccta gaaaccttta
tccctgctta tctgaaactt cccaacttcc ctgttcttta agacttttt ttttttttt
ttttttttg agacagagtc tcgctctgtc gcccaggctg gagggcagtg gcacgatctc
agctcactgc aagctccaac tcccgggttc acgccattct cctgcctcag ccttccaagt
agctgggact acaggtgccc gccaccgtgc ccggctaatt tttttgtatt tttagtagag
acagggtttc accatgttag ccgggatggt cttgatctcc tgacctcatg atccacccac
ctcagcctcc caaagtgttg ggattacagg cgtgagccac tgcgcccggg caagaccttt
ttttaaaaaa aaaaaaaaaa aaacttccat tctttcttcc tccagtctgt tctcacataa
cagagtagtt ttggttttta attttttttg gttgtttgct gtttttgtt ttttaaggtg
agttctcact atgtttctca gactggtctc gaactcctgg cctcaagcca tcttcccgcc
tcagcctctc aaatagctgg gcttacaggc atgagccacc acacctggcc aggatttggt
tgtttaaata taaatctgat caccccccctg cttagaaccc ttctgctttc tattacccct
catttaaaat gtaaactctt caccttggtt tatgagaact ggttcttgcc ttccccttga
acctcattaa atggtgattt cttgctaagc tccagcccga gtggtctcct ctcagcttct
aattttgtgc tctttcctgc ccttttcctg ggccttctca gctctccacc cccaccactc
ttgactcagg tggtgtcctt cttcctcaag tcttgacaat tcccgggccc ttcagtccct
gagcagtcta cttctgtgtc tgtcaccaca tcttgtcttt tcccctcatt gcatttattg
cagtttatat atatgctact tttacttgtt catttctgtc tcccctacca ggctgtaaat
gagggcagaa accttgtttg ttttattcac catcatgtac caagtgcttg gcacatagtg
ggccttcatt aaatgtttgt tgaataaaag agggaagaag gcaagccaac cttagctaca
atcctacctt ttgataaaat gttccttttg acaatatаca cggattatta tttgtacttt
gtttttccat gtgttttgct tttatccact ggcatttta gctccttgaa gacatatcat
gtgtgagata acttccttca catctcccat ggtccctagc aaaatgctag gcctgtagta
gtcaaggtgc tcaataaata tttgtttggg tggtttgtga gccttgctgc caagtcctgc
ctttgggtcg acatagtatg gaagtatttg agagagagaa cctttccact cccactgcca
ggattttgta ttgccatcgg gtgccaaata aatgctcata tttattaaaa aaaaaaaaaa aaaaa

SEQ ID NO: 78 Homo sapiens caspase 2, apoptosis-related cysteine peptidase (neural precursor cell expressed, developmentally down-regulated 2) (CASP2) (NP_116764.2)

MAAPSAGSWSTFQHKELMAADRGRRILGVCGMHPHHQETLKKNRVVLAKQLLLSELLEHLLEKDIITLEMRELIQ
AKVGSFSQNVELLNLLPKRGPQAFDAFCEALRETKQGHLEDMLLTTLSGLQHVLPPLSCDYDLSLPFPVCESCPL
YKKLRLSTDTVEHSLDNKDGPVCLQVKPCTPEFYQTHFQLAYRLQSRPRGLALVLSNVHFTGEKELEFRSGGDVD
HSTLVTLFKLLGYDVHVLCDQTAQEMQEKLQNFAQLPAHRVTDSCIVALLSHGVEGAIYGVDGKLLQLQEVFQLF
DNANCPSLQNKPKMFFIQACRGDETDRGVDQQDGKNHAGSPGCEESDAGKEKLPKMRLPTRSDMICGYACLKGTA
AMRNTKRGSWYIEALAQVFSERACDMHVADMLVKVNALIKDREGYAPGTEFHRCKEMSEYCSTLCRHLYLFPGHP
PT

SEQ ID NO: 79 Homo sapiens killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1 (KIR2DS1) (NM_014512)

caccggcagc accatgtcgc tcacggtcgt cagcatggcg tgtgttgggt tcttcttgct
gcaggggccc tggccacatg agggagtcca cagaaaacct tccctcctgg cccacccagg
tcgcctggtg aaatcagaag agacagtcat cctgcaatgt tggtcagatg tcatgtttga
acacttcctt ctgcacagag aggggatgtt taacgacact ttgcgcctca ttggagaaca
ccatgatggg gtctccaagg ccaacttctc catcagtcgc atgaagcaag acctggcagg
gacctacaga tgctacggtt ctgttactca ctccccctat cagttgtcag ctcccagtga
ccctctggac atcgtgatca taggtctata tgagaaacct tctctctcag cccagccggg
ccccacggtt ctggcaggag agaatgtgac cttgtcctgc agctcccgga gctcctatga
catgtaccat ctatccaggg aaggggaggc ccatgaacgt aggctccctg cagggaccaa
ggtcaacgga acattccagg ccaactttcc tctgggccct gccacccatg gagggaccta
cagatgcttc ggctctttcc gtgactctcc atacgagtgg tcaaagtcaa gtgacccact
gcttgtttct gtcacaggaa acccttcaaa tagttggcct tcacccactg aaccaagctc
cgaaaccggt aaccccagac acctacatgt tctgattggg acctcagtgg tcaaaatccc
tttcaccatc ctcctcttct ttctccttca tcgctggtgc tccgacaaaa aaaatgctgc
tgtaatggac caagagcctg cagggaacag aacagtgaac agcgaggatt ctgatgaaca

agaccatcag gaggtgtcat acgcataatt ggatcactgt gttttcacac agagaaaaat
cactcgccct tctgagaggc ccaagacacc cccaacagat accagcatgt acatagaact
tccaaatgct gagcccagat ccaaagttgt cttctgtcca cgagcaccac agtcaggcct
tgaggggatc ttctagggag a

SEQ ID NO: 80 Homo sapiens killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1 (KIR2DS1) (NP_055327.1)

MSLTVVSMACVGFFLLQGAWPHEGVHRKPSLLAHPGRLVKSEETVILQCWSDVMFEHFLLHREGMFNDTLRLIGE
HHDGVSKANFSISRMKQDLAGTYRCYGSVTHSPYQLSAPSDPLDIVIIGLYEKPSLSAQPGPTVLAGENVTLSCS
SRSSYDMYHLSREGEAHERRLPAGTKVNGTFQANFPLGPATHGGTYRCFGSFRDSPYEWSKSSDPLLVSVTGNPS
NSWPSPTEPSSETGNPRHLHVLIGTSVVKIPFTILLFFLLHRWCSDKKNAAVMDQEPAGNRTVNSEDSDEQDHQE
VSYA

SEQ ID NO: 81 Homo sapiens mitogen-activated protein kinase kinase kinase kinase 2 (MAP4K2) (NM_004579)

cagagccacg ggcgcccgcc ccgccccgcg ccgccccgcg ccggctccgc agctcgcgcc
cgcccgcctg ccggcccgcc cggcgccggg ccatggcgct gctgcgggat gtgtcgctgc
aggacccgcg ggaccgcttc gagctgctgc agcgcgtggg ggccgggacc tatggcgacg
tctacaaggc ccgcgacacg gtcacgtccg aactggccgc cgtgaagata gtcaagctag
acccagggga cgacatcagc tccctccagc aggaaatcac catcctgcgt gagtgccgcc
accccaatgt ggtggcctac attggcagct acctcaggaa tgaccgcttg tggatctgca
tggagttctg cggaggggge tccctgcagg agatttacca tgccactggg cccctggagg
agcggcagat tgcctacgtc tgccgagagg cactgaaggg gctccaccac ctgcattctc
aggggaagat ccacagagac atcaagggag ccaaccttct cctcactctc cagggagatg
tcaaactggc tgactttggg gtgtcaggcg agctgacagc gtctgtggcc aagaggaggt
ctttcattgg gactccctac tggatggctc ccgaggtggc tgctgtggag cgcaaaggtg
gctacaatga gctatgtgac gtctgggccc tgggcatcac tgccattgag ctgggcgagc
tgcagccccc tctgttccac ctgcacccca tgagggccct gatgctcatg tcgaagagca
gcttccagcc gcccaaactg agagataaga ctcgctggac ccagaatttc caccactttc
tcaaactggc cctgaccaag aatcctaaga agaggccgac agcagagaag ctcctgcagc
acccgttcac gactcagcag ctccctcggg ccctcctcac acagctgctg gacaaagcca
gtgaccctca tctggggacc ccctcccctg aggactgtga gctggagacc tatgacatgt
ttccagacac cattcactcc cgggggcagc acggcccagc cgagaggacc ccctcggaga
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agccgtggga ggaagagtgg acactactgg gaaaggaaga gttgagtggg agcctgctgc
agtcggtcca ggaggccctg gaggaaagga gtctgactat tcggtcagcc tcagaattcc
aggagctgga ctccccagac gataccatgg gaaccatcaa gcgggccccg ttcctagggc
cactccccac tgaccctcca gcagaggagc ctctgtccag tcccccagga accctgcccc
cacctccttc aggccccaac agctccccac tgctgcccac ggcctgggcc accatgaagc
agcgggagga tcctgagagg tcatcctgcc acgggctccc cccaactccc aaggtgcata
tgggcgcctg cttctccaag gtcttcaatg gctgcccccc gcggatccac gctgctgtca
cctggattca ccctgttact cgggaccagt tcctggtggt aggggccgag gaaggcatct
acacactcaa cctgcatgaa ctgcatgagg atacgctgga gaagctgatt tcacatcgct
gctcctggct ctactgcgtg aacaacgtgc tgctgtcact ctcagggaaa tccacgcaca
tctgggccca tgacctccca ggcctgtttg agcagcggag gctacagcaa caggttcccc
tctccatccc caccaaccgc ctcacccagc gcatcatccc caggcgcttt gctctgtcca
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gtgccacctt cctgctggcc gccctgccca ccagcctgct cctgctgcag tggtatgagc
cgctgcagaa gtttctgctg ctgaagaact tctccagccc tctgcccagc ccagctggga
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cgcccgacat cctcatccca cctgagggga tcccaggctc ggcccagcag gtgatccagg
tggacaggga cacaatccta gtcagctttg aacgctgtgt gaggattgtc aacatgcagg
gcgagcccac ggccacactg gcacctgagc tgacctttga tttccccatc gagactgtgg
tgtgcctgca ggacagtgtg ctggccttct ggagccatgg gatgcaaggc cgaagcctgg
ataccaatga ggtgacccag gagatcacag atgaaacaag gatcttccga gtgcttgggg
cccacagaga catcatcctg gagagcattc ccactgacaa cccagaggcg cacagcaacc
tctacatcct cacgggccac cagagcacct actaagagca gcgggcctgt ccaggggctc
cccgccccac cccacgcctt agctgcaggc ccttttgggc aaaggggccc atcctagacc

agaggagccc aggccctggc cctgctgggg ctgaaggtca gaagtaatcc tgagaaatgt
ttcaggcctg gggagggagg ggagcccccg acgcctctgc aataactgga ccaggggggag
ctgctgtcac tcccccatcc ccgaggcagc ccagtcccta gtgcccaagg cagggaccct
gggcctgggc catccattcc attttgttcc acatttcctt tctactcttt ctgccaagag
cctgcccctg catttgtcct gggaaacacg gtatttaaga gagaactata ttggtattaa
agctggtttg ttttaaaaaa aaaa

SEQ ID NO: 82 Homo sapiens mitogen-activated protein kinase kinase kinase kinase 2 (MAP4K2) (NP_004570.2)

MALLRDVSLQDPRDRFELLQRVGAGTYGDVYKARDTVTSELAAVKIVKLDPGDDISSLQQEITILRECRHPNVVA
YIGSYLRNDRLWICMEFCGGGSLQEIYHATGPLEERQIAYVCREALKGLHHLHSQGKIHRDIKGANLLLTLQGDV
KLADFGVSGELTASVAKRRSFIGTPYWMAPEVAAVERKGGYNELCDVWALGITAIELGELQPPLFHLHPMRALML
MSKSSFQPPKLRDKTRWTQNFHHFLKLALTKNPKKRPTAEKLLQHPFTTQQLPRALLTQLLDKASDPHLGTPSPE
DCELETYDMFPDTIHSRGQHGPAERTPSEIQFHQVKFGAPRRKETDPLNEPWEEEWTLLGKEELSGSLLQSVQEA
LEERSLTIRSASEFQELDSPDDTMGTIKRAPFLGPLPTDPPAEEPLSSPPGTLPPPPSGPNSSPLLPTAWATMKQ
REDPERSSCHGLPPTPKVHMGACFSKVFNGCPLRIHAAVTWIHPVTRDQFLVVGAEEGIYTLNLHELHEDTLEKL
ISHRCSWLYCVNNVLLSLSGKSTHIWAHDLPGLFEQRRLQQQVPLSIPTNRLTQRIIPRRFALSTKIPDTKGCLQ
CRVVRNPYTGATFLLAALPTSLLLLQWYEPLQKFLLLKNFSSPLPSPAGMLEPLVLDGKELPQVCVGAEGPEGPG
CRVLFHVLPLEAGLTPDILIPPEGIPGSAQQVIQVDRDTILVSFERCVRIVNMQGEPTATLAPELTFDFPIETVV
CLQDSVLAFWSHGMQGRSLDTNEVTQEITDETRIFRVLGAHRDIILESIPTDNPEAHSNLYILTGHQSTY

SEQ ID NO: 83 Homo sapiens chemokine (C-X-C motif) ligand 5 (CXCL5) (NM_002994)

gtgcagaagg cacgaggaag ccacagtgct ccggatcctc caatcttcgc tcctccaatc
tccgctcctc cacccagttc aggaacccgc gaccgctcgc agcgctctct tgaccactat
gagcctcctg tccagccgcg cggcccgtgt ccccggtcct tcgagctcct tgtgcgcgct
gttggtgctg ctgctgctgc tgacgcagcc agggcccatc gccagcgctg gtcctgccgc
tgctgtgttg agagagctgc gttgcgtttg tttacagacc acgcaaggag ttcatcccaa
aatgatcagt aatctgcaag tgttcgccat aggcccacag tgctccaagg tggaagtggt
agcctccctg aagaacggga aggaaatttg tcttgatcca gaagcccctt ttctaaagaa
agtcatccag aaaattttgg acggtggaaa caaggaaaac tgattaagag aaatgagcac
gcatggaaaa gtttcccagt cttcagcaga gaagttttct ggaggtctct gaacccaggg
aagacaagaa ggaaagattt tgttgttgtt tgtttatttg tttttccagt agttagcttt
cttcctggat tcctcacttt gaagagtgtg aggaaaacct atgtttgccg cttaagcttt
cagctcagct aatgaagtgt ttagcatagt acctctgcta tttgctgtta ttttatctgc
tatgctattg aagttttggc aattgactat agtgtgagcc aggaatcact ggctgttaat
ctttcaaagt gtcttgaatt gtaggtgact attatatttc caagaaatat tccttaagat
attaactgag aaggctgtgg atttaatgtg gaaatgatgt ttcataagaa ttctgttgat
ggaaatacac tgttatcttc acttttataa gaaataggaa atattttaat gtttcttggg
gaatatgtta gagaatttcc ttactcttga ttgtgggata ctatttaatt atttcacttt
agaaagctga gtgtttcaca ccttatctat gtagaatata tttccttatt cagaatttct
aaaagtttaa gttctatgag ggctaatatc ttatcttcct ataattttag acattcttta
tctttttagt atggcaaact gccatcattt acttttaaac tttgatttta tatgctattt
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gaagaagcta gaaaacaggc aaattcctga ctgctagttt atatagaaat gtattctttt
agtttttaaa gtaaaggcaa acttaacaat gacttgtact ctgaaagttt tggaaacgta
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aggccctagc atttctcctt ggatagggga ccagagagag cttggaatgt taaaaacaaa
acaaaacaaa aaaaaacaag gagaagttgt ccaagggatg tcaatttttt atccctctgt
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aattatatat aaggtggcca cgctggggca agttccctcc ccactcacag ctttggcccc
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gggaagatgc ctgtcgggtt tttagcacag ttcatttcac tgggattttg aagcatttct
gtctgaatgt aaagcctgtt ctagtcctgg tgggacacac tggggttggg ggtgggggaa
gatgcggtaa tgaaaccggt tagtcagtgt tgtcttaata tccttgataa tgctgtaaag
tttatttta caaatatttc tgtttaagct atttcacctt tgtttggaaa tccttccctt
ttaaagagaa aatgtgacac ttgtgaaaag gcttgtagga aagctcctcc ctttttttct
ttaaaccttt aaatgacaaa cctaggtaat taatggttgt gaatttctat ttttgctttg
tttttaatga acatttgtct ttcagaatag gattctgtga taatatttaa atggcaaaaa
caaaacataa ttttgtgcaa ttaacaaagc tactgcaaga aaaataaaac atttcttggt

aaaaacgtat gtatttatat attatatatt tatatataat atatattata tatttagcat
tgctgagctt tttagatgcc tattgtgtat cttttaaagg ttttgaccat tttgttatga
gtaattacat atatattaca ttcactatat taaaattgta ctttttttact atgtgtctca
ttggttcata gtctttattt tgtcctttga ataaacatta aaagatttct aaacttcaaa
aaaaaaaaaa aaaaa

SEQ ID NO: 84 Homo sapiens chemokine (C-X-C motif) ligand 5 (CXCL5) (NP_002985.1)

MSLLSSRAARVPGPSSSLCALLVLLLLLTQPGPIASAGPAAAVLRELRCVCLQTTQGVHPKMISNLQVFAIGPQC
SKVEVVASLKNGKEICLDPEAPFLKKVIQKILDGGNKEN

SEQ ID NO: 85 Homo sapiens chemokine (C-X-C motif) ligand 3 (CXCL3) (NM_002090)

gctccgggaa tttccctggc ccggccgctc cgggctttcc agtctcaacc atgcataaaa
agggttcgcc gatcttgggg agccacacag cccgggtcgc aggcacctcc ccgccagctc
tcccgcttct cgcacagctt cccgacgcgt ctgctgagcc ccatggccca cgccacgctc
tccgccgccc ccagcaatcc ccggctcctg cgggtggcgc tgctgctcct gctcctggtg
gccgccagcc ggcgcgcagc aggagcgtcc gtggtcactg aactgcgctg ccagtgcttg
cagacactgc agggaattca cctcaagaac atccaaagtg tgaatgtaag gtcccccgga
ccccactgcg cccaaaccga agtcatagcc acactcaaga atgggaagaa agcttgtctc
aaccccgcat cccccatggt tcagaaaatc atcgaaaaga tactgaacaa ggggagcacc
aactgacagg agagaagtaa gaagcttatc agcgtatcat tgacacttcc tgcagggtgg
tccctgccct taccagagct gaaaatgaaa aagagaacag cagctttcta gggacagctg
gaaaggactt aatgtgtttg actatttctt acgagggttc tacttattta tgtatttatt
tttgaaagct tgtattttaa tattttacat gctgttattt aaagatgtga gtgtgtttca
tcaaacatag ctcagtcctg attatttaat tggaatatga tgggttttaa atgtgtcatt
aaactaatat ttagtgggag accataatgt gtcagccacc ttgataaatg acagggtggg
gaactggagg gtgggggat tgaaatgcaa gcaattagtg gatcactgtt agggtaaggg
aatgtatgta cacatctatt ttttatactt ttttttaaa aaaagaatgt cagttgttat
ttattcaaat tatctcacat tatgtgttca acatttttat gctgaagttt cccttagaca
ttttatgtct tgcttgtagg gcataatgcc ttgtttaatg tccattctgc agcgtttctc
tttcccttgg aaaagagaat ttatcattac tgttacattt gtacaaatga catgataata
aaagttttat gaaaaaaaaa aaaaaa

SEQ ID NO: 86 Homo sapiens chemokine (C-X-C motif) ligand 3 (CXCL3) (NP_002081.2)

MAHATLSAAPSNPRLLRVALLLLLLVAASRRAAGASVVTELRCQCLQTLQGIHLKNIQSVNVRSPGPHCAQTEVI
ATLKNGKKACLNPASPMVQKIIEKILNKGSTN

SEQ ID NO: 87 Homo sapiens chemokine (C-C motif) ligand 13 (CCL13) (NM_005408)

aaaaggccgg cggaacagcc agaggagcag agaggcaaag aaacattgtg aaatctccaa
ctcttaacct tcaacatgaa agtctctgca gtgcttctgt gcctgctgct catgacagca
gctttcaacc cccagggact tgctcagcca gatgcactca acgtcccatc tacttgctgc
ttcacattta gcagtaagaa gatctccttg cagaggctga agagctatgt gatcaccacc
agcaggtgtc cccagaaggc tgtcatcttc agaaccaaac tgggcaagga gatctgtgct
gacccaaagg agaagtgggt ccagaattat atgaaacacc tgggccggaa agctcacacc
ctgaagactt gaactctgct acccctactg aaatcaagct ggagtacgtg aaatgacttt
tccattctcc tctggcctcc tcttctatgc tttggaatac ttctaccata attttcaaat
aggatgcatt cggttttgtg attcaaaatg tactatgtgt taagtaatat tggctattat
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ttgagcaagt aggttgctgt ctctaagccc ccttcccttc cactatgagc tgctggcagt
gggtttgtat tcggttccca ggggttgaga gcatgcctgt gggagtcatg gacatgaagg
gatgctgcaa tgtaggaagg agagctcttt gtgaatgtga ggtgttgcta aatatgttat
tgtggaaaga tgaatgcaat agtaggactg ctgacatttt gcagaaaata cattttattt

aaaatctcct aaaaaaaaaa a

SEQ ID NO: 88 Homo sapiens chemokine (C-C motif) ligand 13 (CCL13) (NP_005399.1)

MKVSAVLLCLLLMTAAFNPQGLAQPDALNVPSTCCFTFSSKKISLQRLKSYVITTSRCPQKAVIFRTKLGKEICA
DPKEKWVQNYMKHLGRKAHTLKT

SEQ ID NO: 89 Homo sapiens alpha-fetoprotein (AFP) (NM_001134)

tccatattgt gcttccacca ctgccaataa caaaataact agcaaccatg aagtgggtgg
aatcaatttt tttaattttc ctactaaatt ttactgaatc cagaacactg catagaaatg
aatatggaat agcttccata ttggattctt accaatgtac tgcagagata agtttagctg
acctggctac catatttttt gcccagtttg ttcaagaagc cacttacaag gaagtaagca
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tgtcctacat atgttctcaa caagacactc tgtcaaacaa aataacagaa tgctgcaaac
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cattctctga tgacaagttc attttccata aggatctgtg ccaagctcag ggtgtagcgc
tgcaaacgat gaagcaagag tttctcatta accttgtgaa gcaaaagcca caaataacag
aggaacaact tgaggctgtc attgcagatt tctcaggcct gttggagaaa tgctgccaag
gccaggaaca ggaagtctgc tttgctgaag agggacaaaa actgatttca aaaactcgtg
ctgctttggg agtttaaatt acttcagggg aagagaagac aaaacgagtc tttcattcgg
tgtgaacttt tctctttaat tttaactgat ttaacacttt ttgtgaatta atgaaatgat
aaagactttt atgtgagatt tccttatcac agaaataaaa tatctccaaa tg

SEQ ID NO: 90 Homo sapiens alpha-fetoprotein (AFP) (NP_005399.1)

MKWVESIFLIFLLNFTESRTLHRNEYGIASILDSYQCTAEISLADLATIFFAQFVQEATYKEVSKMVKDALTAIE
KPTGDEQSSGCLENQLPAFLEELCHEKEILEKYGHSDCCSQSEEGRHNCFLAHKKPTPASIPLFQVPEPVTSCEA
YEEDRETFMNKFIYEIARRHPFLYAPTILLWAARYDKIIPSCCKAENAVECFQTKAATVTKELRESSLLNQHACA
VMKNFGTRTFQAITVTKLSQKFTKVNFTEIQKLVLDVAHVHEHCCRGDVLDCLQDGEKIMSYICSQQDTLSNKIT
ECCKLTTLERGQCIIHAENDEKPEGLSPNLNRFLGDRDFNQFSSGEKNIFLASFVHEYSRRHPQLAVSVILRVAK
GYQELLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAI
TRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPGVGQCCTSSYANRRPCFSSLVVDETYVPPA
FSDDKFIFHKDLCQAQGVALQTMKQEFLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI
SKTRAALGV

SEQ ID NO: 91 Homo sapiens C-type lectin domain 4, member E (CLEC4E) (NM_014358)

atattctaca tctatcggag ctgaacttcc taaaagacaa agtgtttatc tttcaagatt
cattctccct gaatcttacc aacaaaacac tcctgaggag aaagaaagag agggagggag
agaaaaagag agagagagaa acaaaaaacc aaagagagag aaaaaatgaa ttcatctaaa
tcatctgaaa cacaatgcac agagagagga tgcttctctt cccaaatgtt cttatggact
gttgctggga tccccatcct atttctcagt gcctgtttca tcaccagatg tgttgtgaca
tttcgcatct ttcaaacctg tgatgagaaa aagtttcagc tacctgagaa tttcacagag
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taagtagttt taaatgttat aattcatgtt actggctgaa gtgcattttc tctctacgtt
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aacattcatc tccacacttt cctgtctcaa gcccatccat tatttcttaa cttttatttt
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gttgtacaga ttatttcatc acccaggtat taagcccagt gcctaatatt gttttttcg
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tggttttctg ttcccatgtt tgctaaggat aatggtttcc agttctaccg atgttcccac
aaaagacata attttctttt ttaaggctgc ttagtattcc atggtatcta tgtatcacat
tttctctatc caatctattg ttgactcaca tttagattga ttccatgttt ttgctattgt
gaatagtgct gcaatgaaca ttcgtgtgca tgtgtcttta tggtagaaag atttatattt
ctctgagtat gtatccagta atagcccatt catttattgc ataaaattct accaatac

SEQ ID NO: 92 Homo sapiens C-type lectin domain 4, member E (CLEC4E) (NP_055173)

MNSSKSSETQCTERGCFSSQMFLWTVAGIPILFLSACFITRCVVFRIFQTCDEKKFQLPENFTELSCYNYGSGSV
KNCCPLNWEYFQSSCYFFSTDTISWALSLKNCSAMGAHLVVINSQEEQEFLSYKKPKMREFFIGLSDQVVEGQWQ
WVDGTPLTK SLSFWDVGEPNNIATLEDCATMRDSSNPRQNWNDVTCFLNYFRICEMVGINPLNKGKSL

WHAT IS CLAIMED IS:

1. A method of providing a prognosis of multiple sclerosis, Alzheimer's disease, or Parkinson's disease in a subject treated with intravenous immunoglobulin (IVIG), the method comprising the steps of:

(a) contacting a biological sample from the subject treated with IVIG with a reagent that specifically binds to at least one marker selected from the group consisting of the nucleic acid and corresponding protein sequences shown in Table 3a, Table 3b, and Table 4; and

(b) determining whether or not the marker is overexpressed or underexpressed in the sample; thereby providing a prognosis for multiple sclerosis, Alzheimer's disease, or Parkinson's disease in a subject treated with IVIG.

2. The method of claim 1, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

3. The method of claim 1, wherein the reagent is an antibody.

4. The method of claim 3, wherein the antibody is monoclonal.

5. The method of claim 1, wherein the reagent is a nucleic acid.

6. The method of claim 1, wherein the reagent is an oligonucleotide.

7. The method of claim 1, wherein the reagent is an RT PCR primer set.

8. The method of claim 1, wherein the sample is a blood sample.

9. The method of claim 8, wherein the blood sample comprises T cells.

10. The method of claim 1, wherein the sample is cerebrospinal fluid.

11. The method of claim 1, wherein said at least one marker is a chemokine.

12. The method of claim 10, wherein said chemokine is selected from the group consisting of CXCL3, CXCL5, CCL13, and XCL2.

13. A method of identifying a compound that prevents or treats multiple sclerosis, Alzheimer's disease, or Parkinson's disease, the method comprising the steps of:

(a) contacting a compound with a sample comprising a cell that expresses a marker selected from the group consisting of the nucleic acid and corresponding protein sequences shown in Table 3a, Table 3b, Table 3c, Table 3d, and Table 4; and

(b) determining the functional effect of the compound on the marker, thereby identifying a compound that prevents or treats multiple sclerosis, Alzheimer's disease, or Parkinson's disease.

14. The method of claim 13, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

15. The method of claim 13, wherein the functional effect is an increase or decrease in expression of the marker.

16. The method of claim 13, wherein the functional effect is an increase or decrease in activity of the marker.

17. The method of claim 13, wherein the compound is a small molecule.

18. The method of claim 13, wherein the compound is a siRNA.

19. The method of claim 13, wherein the compound is a ribozyme.

20. The method of claim 13, wherein the compound is an antibody.

21. The method of claim 20, wherein the antibody is monoclonal.

22. A method of treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease in a subject, the method comprising the step of administering to said subject an effective amount of an antibody which binds a chemokine selected from the group consisting of CXCL5, CXCL3, and CCL13, wherein said effective amount is sufficient to inactivate chemokine cell signaling, thereby treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease.

23. The method of claim 22, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

24. A method of treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease in a subject, the method comprising the step of administering to said subject an effective amount of an antibody which binds a chemokine receptor selected from the group consisting of receptors for CXCL5, CXCL3, and CCL13, wherein said effective amount is sufficient to inactivate said chemokine receptor, thereby treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease.

25. The method of claim 24, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

26. A method of treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease in a subject, the method comprising the step of administering to said subject an effective amount of an antibody which binds to a XCL2 chemokine receptor, wherein said effective amount is sufficient to activate said XCL2 chemokine receptor, thereby treating or preventing multiple sclerosis, Alzheimer's disease, or Parkinson's disease.

27. The method of claim 26, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS).

Fig 1

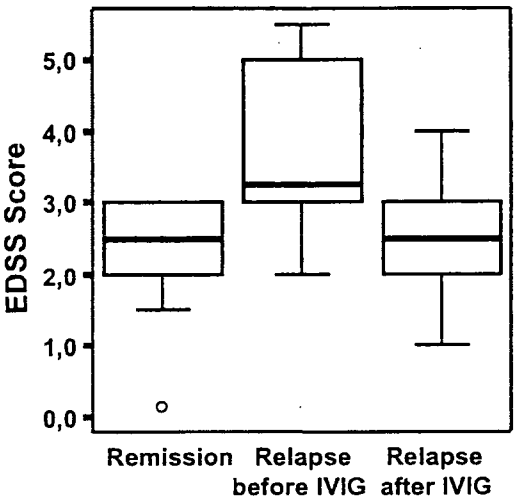

EDSS Score
5,0
4,0
3,0
2,0
1,0
0,0
Remission
Relapse before IVIG
Relapse after IVIG

Fig 2 A-B

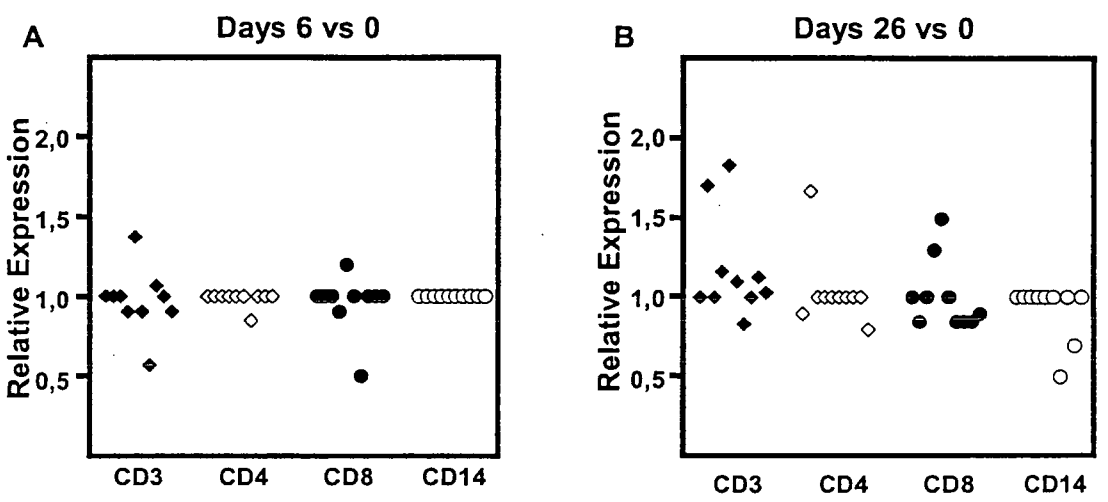
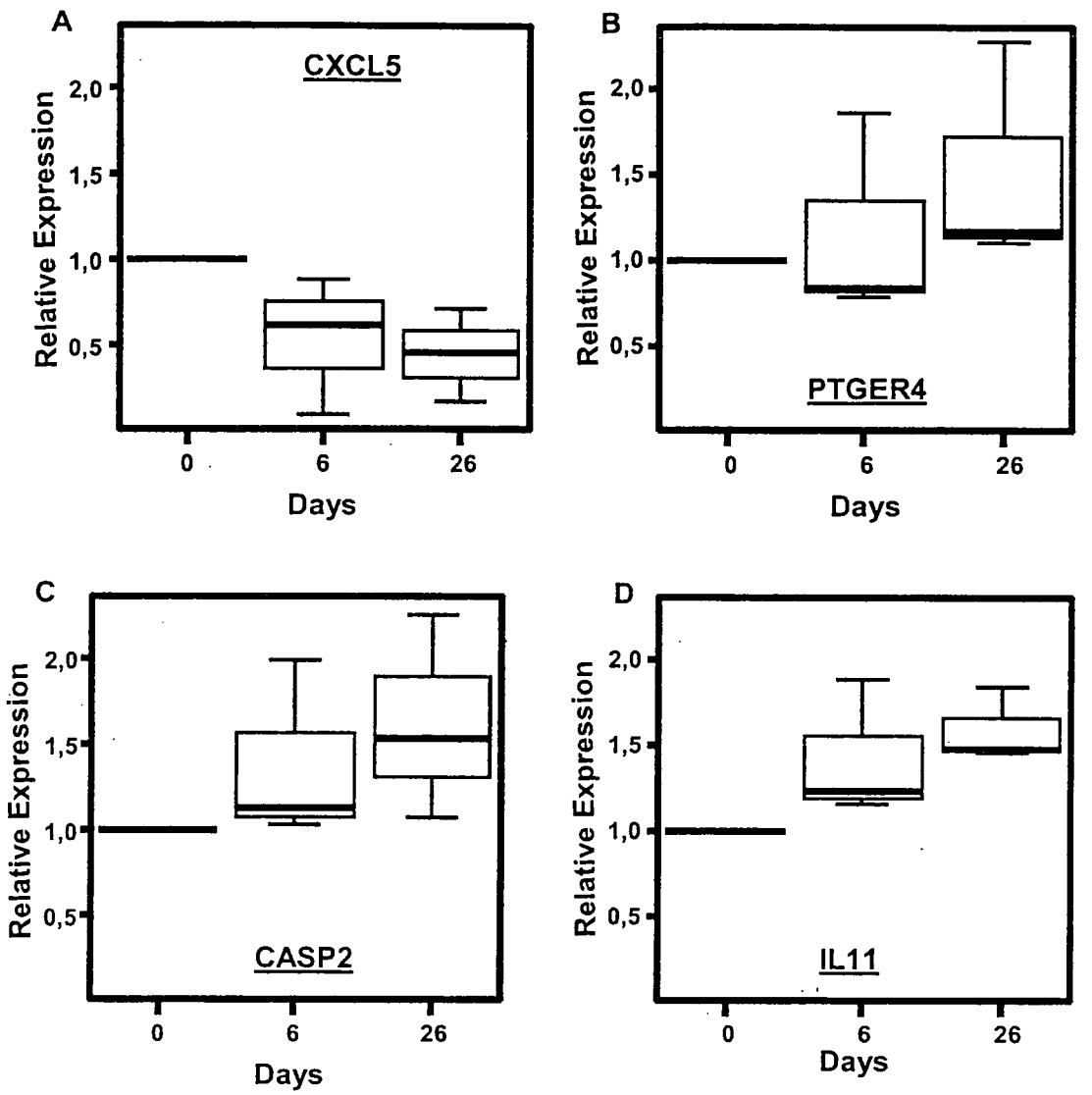

A
Days 6 vs 0
Relative Expression
2,0
1,5
1,0
0,5
CD3
CD4
CD8
CD14
B
Days 26 vs 0
Relative Expression
2,0
1,5
1,0
0,5
CD3
CD4
CD8
CD14

Fig 3 A-D


A
CXCL5
Relative Expression
2,0
1,5
1,0
0,5
0
6
26
Days
B
PTGER4
C
CASP2
D
IL11