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(54) Title: METHODS OF TREATING MULTIPLE SCLEROSIS BY ADMINISTRATION OF ALPHA-FETOPROTEIN IN COMBINATION WITH AN INTEGRIN ANTAGONIST

(57) Abstract: The present invention relates to methods for treating multiple sclerosis by administering therapeutically effective amounts of an alpha-fetoprotein polypeptide (or a biologically active fragment, derivative, or analog thereof) and an integrin antagonist (e.g., natalizumab) to a patient in need thereof. Also disclosed are compositions and kits that comprise therapeutically effective amounts of an alpha-fetoprotein polypeptide (or a biologically active fragment, derivative, or analog thereof) and an integrin antagonist (e.g., natalizumab).



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**METHODS OF TREATING MULTIPLE SCLEROSIS BY ADMINISTRATION
OF ALPHA-FETOPROTEIN IN COMBINATION WITH AN INTEGRIN
ANTAGONIST**

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Field of the Invention

This invention relates to treatment methods using alpha-fetoprotein, including its biologically active fragments, analogs, and derivatives, in conjunction with administration of an integrin antagonist for the treatment of multiple sclerosis.

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Background of the Invention

Multiple Sclerosis (MS) is a neurological disease first described in Holland by a 14th century physician, and which is characterized by irreversible degeneration of the nerves of the central nervous system (CNS). Although the underlying cause is unclear, the neurodegeneration in MS is the direct result of demyelination, or the stripping of myelin, a protein that normally lines the outer layer and insulates the nerves. As the condition progresses, patches of inflammation and scarring develop, interfering with the function of the nerves. Consequently, an MS patient gradually loses sensory and motor functions of the body. About 400,000 to 500,000 people in the U.S. suffer from MS. Usually, a patient is diagnosed with MS between 20 and 40 years of age, but MS has been diagnosed as early as age 15 and as late as age 60. MS is relentless and progressively destructive unless the patient receives medical therapy that is effective in halting or slowing the deterioration. While some individuals manage well in the short term, MS patients invariably become more significantly impaired by the disease over time.

Current therapies for MS are aimed at alleviating the symptoms of the disease and arresting its progress. Drug treatment usually entails the use of disease-modifying agents, such as the interferons (interferon- β -1a, β -1b, and α), glatiramer acetate, or corticosteroids, such as methylprednisolone and prednisone. Chemotherapeutic agents, such as mitoxantrone, methotrexate, azathioprine, and cladribine cyclophosphamide are also used to treat MS.

Thought to be an autoimmune disease, MS is also treated with various immunologic therapies. For example, cyclosporine, an immunosuppressive agent is used to treat MS. In addition, natalizumab (Tysabri[®], Elan Corporation, Inc./Biogen-Idec), a selective adhesion molecule inhibitor introduced in 2005, has also been used
5 for the treatment of MS. Natalizumab, a humanized anti- α 4 integrin antibody, has been shown to block autoimmune encephalomyelitis in a rat and a mouse model (Yednock et al., *Nature* 356:63, 1992; Baron et al., *J. Exp. Med.* 177:57, 1993). Many of the current treatments for MS either lack efficacy, or pose serious risks and side effects. For example, natalizumab can increase the risk of progressive multifocal
10 leukoencephalopathy (PML), an opportunistic viral infection of the brain that typically leads to death or severe disability. Thus, there remains a need for new and effective therapeutic approaches for the treatment of MS. The present invention addresses this and other related needs.

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Summary of the Invention

The present invention features compositions and methods for treating, preventing, or reducing one or more of the symptoms of MS (e.g., tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing problems, paralysis, lack of coordination, cognitive
20 difficulties, fatigue, muscle spasms, dizziness, breathing problems, and seizures) or the progression of MS, in a patient by co-administering alpha-fetoprotein (AFP) and an integrin antagonist. The integrin antagonist can be, e.g., an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule, as is described herein.

In a first aspect, the present invention features a method of treating a patient
25 with MS by administering AFP (or biologically active fragment, derivative, or analog thereof) and an integrin antagonist, each in an amount (e.g., a therapeutically effective amount), to the patient.

In an embodiment, the integrin antagonist is an α 4 integrin antagonist. The integrin antagonist can be, e.g., an antibody, such as natalizumab, a blocking peptide,
30 a nucleic acid inhibitor, or a small molecule inhibitor.

Different administration schedules can be followed in the above method.

For instance, the AFP (or biologically active fragment, derivative, or analog thereof) or the integrin antagonist can be administered one or more times (e.g., 1, 2, 3, 4, 5, or 10 times or more) hourly, daily, weekly, biweekly, or monthly. In addition, the dosage of the AFP (or biologically active fragment, derivative, or analog thereof) per administration may be the same or different.

In other embodiments of the above method, the AFP (or biologically active fragment, derivative, or analog thereof), and the integrin antagonist are administered coextensively or separately. Many variations of administration schemes are possible, for example, both the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist may be administered to the patient during the first treatment phase. Subsequently, the administration of one (e.g., the AFP or the integrin antagonist) may be terminated or the dosage amount may be modified (e.g., increased or decreased) while administration of the other is continued (e.g., at the same dosage level or at a modified level (e.g., increased or decreased)). Alternatively, both the AFP (or biologically active fragment, derivative, or analog thereof) and the integrin antagonist may be administered initially at their maximal or minimal dosages with subsequent dosages of both being reduced or increased, respectively, during the treatment regimen. In addition, the AFP (or biologically active fragment, derivative, or analog thereof) may be administered prior to or following administration of the integrin antagonist.

In an additional embodiment of the method, the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist are administered in the same dosage form or separate dosage forms. In additional embodiments of the method, the AFP (or biologically active fragment, derivative, or analog thereof) is administered at a dosage in the range of 0.1 mg to 400 mg and/or the integrin antagonist is administered at a dosage in the range of 0.1 mg to 500 mg.

In another embodiment of the method, the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist are administered via the same route of administration or via two different routes of administration.

In an embodiment, the method further includes administering a supplemental agent, such as an antagonist of one or more of the following proteins: CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, and IL-6. The supplemental agent can be, e.g., an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor. The CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 antagonist can be administered co-extensively with AFP (or a biologically active fragment, derivative, or analog thereof) and without an integrin antagonist; with an integrin antagonist and without AFP; or all three can be administered in combination.

In a second aspect, the invention features a composition that includes an AFP (or a biologically active fragment, derivative, or analog thereof) and an integrin antagonist, each in an amount (e.g., a therapeutically effective amount) to treat, prevent, or reduce one or more of the symptoms of or the progression of, MS in a patient in need thereof.

In a related embodiment, the composition further includes an amount (e.g., a therapeutically effective amount) of an antagonist of one or more of the following proteins: CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, and IL-6.

In additional embodiments of the composition, the AFP (or a biologically active fragment, derivative, or analog thereof) is in a dose in the range of 0.1 mg to 400 mg and/or the integrin antagonist is in a dose in the range of 0.1 mg to 500 mg. The composition of the invention may be administered to a patient with MS according to the first aspect of the invention.

A third aspect of the invention features a kit that includes 1) an AFP, or a biologically active fragment, derivative, or analog thereof, and an integrin antagonist (e.g., natalizumab), each in an amount (e.g., a therapeutically effective amount) to treat, prevent, or reduce one or more of the symptoms of or the progression of, MS in

a patient in need thereof, and 2) instructions for administration of the AFP and the integrin antagonist to the patient.

In additional embodiments of the kit, the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist of the kit are present in the same composition or are present in the kit in separate compositions; the separate compositions can be admixed prior to administration to a patient or they can be administered separately to the patient. In other embodiments, the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist of the kit are formulated for the same route of administration or for two different routes of administration.

In several embodiments of all the aspects of the invention, the AFP (or a biologically active fragment, derivative, or analog thereof) is recombinant human AFP having an amino acid sequence that is substantially identical (e.g., at least 60% identical, preferably at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical, or even 100% identical) to SEQ ID NO: 1. In other embodiments of all aspects of the invention, the AFP (or a biologically active fragment, derivative, or analog thereof) is non-glycosylated. In yet other embodiments of all aspects of the invention, the AFP may be formulated at a dosage in the range of 0.5 mg to 400 mg; the integrin antagonist may be formulated at a dosage in the range of 0.5 mg to 500 mg.

In other embodiments of all aspects of the invention, the integrin antagonist is an antibody (e.g., natalizumab), a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor. In yet other embodiments, the integrin antagonist is an $\alpha 4$ integrin antagonist.

The AFP (or biologically active fragment, derivative, or analog thereof) and integrin antagonist can be formulated for or administered by one or more of a variety of routes of administration, including, but not limited to, intravenous, intramuscular, oral, by inhalation, parenteral, intraperitoneal, intraarterial, transdermal, sublingual, nasal, through use of suppositories, transbuccal, liposomal, adiposal, intraocular, subcutaneous, intrathecal, topical, or through local administration.

In additional embodiments of all aspects of the invention, the co-administration of the AFP (or a biologically active fragment, derivative, or analog thereof) and the integrin antagonist exhibits a therapeutic effect that is greater than that observed when the AFP (or biologically active fragment, derivative, or analog thereof) and the integrin antagonist are administered alone. In additional
5 embodiments of all aspects of the invention, the AFP, the integrin antagonist, or both can be administered at a lower dosage than that normally required for achieving a therapeutic effect when either are administered alone (e.g., the AFP or the integrin antagonist can be administered at a dosage that is at least 10%, 15%, 20%, 25%, 30%,
10 35%, 40%, 45%, 50%, 60%, or 90% lower). In other embodiments of all aspects of the invention, co-administration of an AFP (or biologically active fragment, derivative, or analog thereof) and an integrin antagonist reduces the toxicity of the integrin antagonist (e.g., by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70% or more) relative to the toxicity of the integrin antagonist when
15 administered at the same concentration in the absence of the AFP. In yet other embodiments of all aspects of the invention, the integrin antagonist can be administered in combination with the AFP at a dosage that is higher (e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 85%, 90%, 95%, 100% or more) than the normal dosage of an integrin antagonist,
20 when administered for treating MS, without the toxicity normally expected or observed at the increased dose of the integrin antagonist when it is administered alone.

Definitions

In this application, when therapeutic agents (e.g., an AFP and an integrin
25 antagonist) are “administered coextensively,” the administration time periods of the agents may completely overlap or at least in part overlap. When the therapeutic agents are “administered separately,” the therapeutic agents are administered in time periods that do not overlap. In certain embodiments of separate administration, the therapeutic agents are administered in time periods that do not overlap, but are within
30 the bioactive period for each respective agent, i.e., an earlier administered agent retains at least a substantial portion of its biological activity in the patient at the time when the latter administered agent is delivered. In other cases of separate

administration, the agents are administered outside of their respective bioactive periods.

As used herein, the term “alpha-fetoprotein” or “AFP” refers to a polypeptide having an amino acid sequence that is substantially identical to the mature human AFP (SEQ ID NO: 1) or to a polypeptide that is encoded by a nucleic acid sequence that is substantially identical to the nucleic acid sequence that encodes human AFP (NCBI Accession No. NM_001134; SEQ ID NO: 2). Mature human AFP is a protein of 591 amino acids (see, SEQ ID NO:1), resulting from cleavage of a precursor of 609 amino acids (GenBank Accession No. NP_001125) to remove an 18-amino acid signal sequence. An AFP of this invention has an amino acid sequence that is substantially identical to SEQ ID NO: 1. The AFP is not limited to the full-length sequence; it also includes biologically active fragments of AFP. An AFP of the invention also includes any recombinant human AFP (whether or not having the same post-translational modifications as the naturally occurring version) and biologically active variants of human AFP (e.g., a non-glycosylated form of AFP; see, e.g., U.S. Patent No. 7,208,576, incorporated by reference herein).

An AFP of this invention may contain modifications of the amino acid sequence of SEQ ID NO: 1, including substitution (e.g., conservative substitution), deletion, or addition of one or more amino acid residues. For instance, a recombinant human AFP is described in U.S. Patent No. 7,208,576, incorporated herein by reference, which contains an asparagine to glutamine substitution at position 233 of SEQ ID NO: 1. The term “alpha-fetoprotein” also encompasses derivatives or analogs of AFP, such as those described herein.

An AFP of this invention exhibits one or more of the biological activities of the native human AFP, including, for example, the ability to bind to human leukocytes, the ability to suppress autoimmune reactions, and the ability to reduce the production of inflammatory cytokines. The leukocyte binding assay used for testing AFP activity is described herein and in, e.g., Parker et al., *Protein Express. Purification* 38:177-183, 2004. The autoimmune suppression activity for an AFP of this invention can be demonstrated by assaying the ability of the AFP to suppress human autologous mixed lymphocyte reactions (AMLR) or by assaying the ability of the AFP to suppress experimental autoimmune encephalomyelitis (EAE) in a mouse

model using the methods described herein. The ability to reduce production of inflammatory cytokines can be assayed using the splenocyte assay described herein. A functional AFP of the invention demonstrates at least 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, or 100% of the biological activity of the native human.

5 A biologically active fragment of AFP, for use in the compositions and methods of the invention, can be identified using one or more assays described herein (e.g., AMLR assays, AFP-binding to monocyte assays, experiments using the EAE mouse model, and splenocyte assays). A typical biologically active AFP fragment contains at least 5 contiguous amino acids of SEQ ID NO: 1, or at least 8 contiguous
10 amino acids, preferably at least 10, 20, or 50 contiguous amino acids, more preferably at least 100 contiguous amino acids, and most preferably at least 200, 300, 400, or more contiguous amino acids in length. For instance, U.S. Patent No. 6,818,741 (herein incorporated by reference) discloses an 8-amino acid fragment of human AFP (amino acids 471-478; EMTPVNPG; SEQ ID NO: 3) as well as other related AFP
15 fragments. An active AFP fragment of this invention may further contain amino acid substitutions, deletions, or additions at a limited number of positions, so long as the AFP fragment has at least 90% identity to its corresponding sequence within SEQ ID NO: 1. For sequence comparison purposes in this application, the corresponding sequence of SEQ ID NO: 1 is deemed to have the same number of amino acids as a
20 given AFP fragment. For instance, a 34-mer AFP peptide corresponding to the 446-479 segment of SEQ ID NO: 1 (LSEDKLLACGEGAADIIIHGLCIRHEMTPVNPGV; SEQ ID NO: 4) may contain up to 3 amino acids altered from the 446-479 segment of SEQ ID NO: 1. One such example of sequence deviation in biologically active AFP fragments is found in U.S.
25 Patent No. 5,707,963 (herein incorporated by reference), which discloses a 34-amino acid fragment of human AFP (SEQ ID NO: 4) with flexibility at two amino acid residues (amino acid 9 and 22 of SEQ ID NO: 4). Some other examples of AFP fragments include Domain I (amino acids 2-198 of mature human AFP; SEQ ID NO: 5), Domain II (amino acids 199-390 of mature human AFP; SEQ ID NO: 6), Domain
30 III (amino acids 391-591 of mature human AFP; SEQ ID NO: 7), Domain I+II (amino acids 2-390 of mature human AFP; SEQ ID NO: 8), Domain II+III (amino acids 199-591 of mature human AFP; SEQ ID NO: 9), and human AFP Fragment I (amino acids 267-591 of mature human AFP; SEQ ID NO: 10).

In this application, 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, and methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones (e.g., peptide mimetics, such as an AFP peptoid), but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics are chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that are capable of functioning in a manner that is similar to a naturally occurring amino acid. An AFP of the invention can include naturally occurring or synthetic amino acids or amino acid mimetics.

As to amino acid sequences, one of skill will recognize that individual substitutions, deletions, or additions to a polypeptide sequence that alter, add, or delete a single amino acid or a small percentage of amino acids in the sequence constitute a “conservatively modified variant,” when the alterations result in the substitution of one or more amino acids with other, chemically similar amino acids. 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.

The term “antibody” herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bi-specific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity. The term also incorporates antibody fragments (e.g., Fab, Fab', Fv fragments, diabodies, linear antibodies, and single chain antibody molecules). The term antibody also includes monoclonal antibodies that are chimeric, primatized, or humanized, and antibody mimics.

By “antibody mimic” is meant a protein or compound that can specifically bind to a target protein (e.g., $\alpha 4$ integrin). Examples include molecules comprising non-immunoglobulin protein scaffolds for the variable regions of antibodies.

Antibody mimics may include proteins (e.g., Adnectins), RNA molecules, unnatural oligomers (e.g., protease inhibitors, benzodiazepines, purine derivatives, and β -turn mimics).

By the term “biologically active” is meant having one or more activities known to be associated with a naturally occurring or synthetic peptide, polypeptide, protein, antibody, compound, small molecule, or fragment, derivative, or analog thereof (e.g., an AFP or fragment, derivative, or analog thereof, or an integrin antagonist).

By “blocking peptide” is meant a peptide that antagonizes the activity of a target protein by binding to the target protein and preventing its interaction with other proteins or receptors or by binding to the receptor of a target protein and blocking the interaction between the receptor and the target protein. In an embodiment, a blocking peptide is one that antagonizes the activity of $\alpha 4$ integrin. Examples of blocking peptides are described herein.

By “CD11/CD18” is meant a family of three heterodimeric glycoproteins with one of three α subunits (i.e., CD11a, CD11b, and CD11c) that include a sequence substantially identical to SEQ ID NO: 25 (NCBI Accession No. P20701; Larson et al., *J. Cell. Biol.* 108:703-712, 1989), SEQ ID NO: 26 (NCBI Accession No. P11215; Corbi et al., *J. Biol. Chem.* 263: 12403-12411, 1988), or SEQ ID NO: 27 (NCBI Accession No. P20702; Corbi et al., *EMBO J.* 6:4023-4028, 1987), or having an mRNA nucleic acid sequence that includes a nucleic acid sequence substantially identical to SEQ ID NO: 29 (NCBI Accession No. NM_02209; Nishida et al., *Immunity* 25:583-594, 2006), SEQ ID NO: 30 (NCBI Accession No. NM_000632; Arnaout et al., *Proc. Natl. Acad. Sci. U.S.A.* 85:2776-2780, 1988), or SEQ ID NO: 31 (NCBI Accession No. NM_000887; Corbi et al., 1987, *supra*); and having a β subunit (CD18) which includes an amino acid sequence substantially identical to SEQ ID NO: 28 (NCBI Accession No. P05107; Kishimoto et al., *Cell* 48:681-690, 1987), or having a nucleic acid sequence that includes an mRNA nucleic acid sequence substantially identical to SEQ ID NO: 32 (NCBI Accession No. Y00057; Law et al., *EMBO J.* 6:915-919, 1987).

By "CD80" is meant a polypeptide that includes an amino acid sequence substantially identical to SEQ ID NO: 13 (NCBI Accession No. P33681; Freeman et al., *J. Immunol.* 143:2714-2722, 1989) or having an mRNA nucleic acid sequence comprising a nucleic acid sequence substantially identical to SEQ ID NO: 14 (NCBI
5 Accession No. NM_005191; Freeman et al., *supra*). CD80 is also referred to in the art as "B-lymphocyte activation antigen," or "B7-1."

By "dosage form" is meant the physical form of a dose of an agent of the invention (e.g., an APF and integrin antagonist). Non-limiting examples of dosage forms include a tablet, capsule, gel, cream, paste, liquid, suspension or emulsion, and
10 spray. The dosage form can be chosen based on the intended route of administration. Alternatively, the route of administration may be dictated by the dosage form of an agent. A dosage form according to the present invention includes those that may be administered intravenously, intramuscularly, orally, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, transbuccally, liposomally,
15 adiposally, intraocularly, subcutaneously, intrathecally, topically, or through local administration.

By "hyaluronate receptor" is meant a polypeptide that includes an amino acid sequence substantially identical to SEQ ID NO: 19 (NCBI Accession No. P16070; Sreaton et al., *Proc. Natl. Acad. Sci. U.S.A.* 89:12160-12164, 1992) or
20 having an mRNA nucleic acid sequence that includes a nucleic acid sequence substantially identical to SEQ ID NO: 20 (NCBI Accession No. AJ251595; Gunthert, *Curr. Top. Microbiol. Immunol.* 184:47-63, 1993). Hyaluronate receptor is also referred to in the art as "CD44," "phagocytic glycoprotein-1" or "PGP-1," "lymphocyte antigen-24" or "Ly-24," or "extracellular matrix receptor III" or "ECMR
25 III."

As used here, "integrin antagonist" refers to an agent that suppresses or inhibits the biological activity of an integrin molecule, such as the $\alpha 4$ subunit of an integrin molecule. The agent may act directly or indirectly on the $\alpha 4$ integrin subunit (NCBI Accession No. P13612; SEQ ID NO: 11; Takada et al., *EMBO J.* 8:1361-1368,
30 1989; or SEQ ID NO: 34) by inhibiting the activity or expression of the $\alpha 4$ integrin subunit, or may act on the target to which the intact integrin containing an $\alpha 4$ subunit binds. For example, an antibody or blocking peptide that binds to vascular cell adhesion molecule-1 (VCAM-1), thus preventing the binding of $\alpha 4\beta 1$ integrin to

VCAM-1 is considered an integrin antagonist for purposes of the present invention. Non-limiting exemplary integrin antagonists suitable for use with the present invention may include proteins, blocking peptides, antibodies, such as natalizumab, small molecule inhibitors, and nucleic acid inhibitors. Examples of nucleic acid inhibitors used as integrin antagonists are those that include a sequence which is complimentary to a sequence substantially identical to all or part of the mRNA sequence of human $\alpha 4$ integrin (NCBI Accession No. NM_000885; SEQ ID NO: 12; Takada et al. *supra*; or SEQ ID NO: 35). For example, a sequence that is complementary to nucleotides 1-25 of SEQ ID NO: 12 or SEQ ID NO: 35.

Examples of $\alpha 4$ integrin antagonists include, but are not limited to, natalizumab (Elan/Biogen Idec; see, e.g., U.S. Patent Nos. 5,840,299; 6,033,665; 6,602,503; 5,168,062; 5,385,839; and 5,730,978), oMEPUPA-V (Biogen; U.S. Patent No. 6,495,525; incorporated by reference herein), CDP-323 (Celltech); firategrast (SB-68399; GlaxoSmithKline); TR-9109 (Pfizer); ISIS-107248 (Antisense Therapeutics); R-1295 (Roche); and TBC-4746 (Schering-Plough).

Additional non-limiting examples of $\alpha 4$ integrin antagonists include the small molecules described in U.S. Patent Nos. 5,821,231; 5,869,448; 5,936,065; 6,265,572; 6,288,267; 6,365,619; 6,423,728; 6,426,348; 6,458,844; 6,479,666; 6,482,849; 6,596,752; 6,667,331; 6,668,527; 6,685,617; 6,903,128; and 7,015,216 (each herein incorporated by reference); in U.S. Patent Application Publication Nos. 2002/0049236; 2003/0004196; 2003/0018016; 2003/0078249; 2003/0083267; 2003/0100585; 2004/0039040; 2004/0053907; 2004/0087574; 2004/0102496; 2004/0132809; 2004/0229858; 2006/0014966; 2006/0030553; 2006/0166866; 2006/0166961; 2006/0241132; 2007/0054909; and 2007/0232601 (each herein incorporated by reference); in European Patent Nos. EP 0842943; EP 0842944; EP 0842945; EP 0903353; and EP 0918059; and in PCT Publication Nos. WO 95/15973; WO 96/06108; WO 96/40781; WO 98/04247; WO 98/04913; WO 98/42656; WO 98/53814; WO 98/53817; WO 98/53818; WO 98/54207; WO 98/58902; WO 99/06390; WO 99/06431; WO 99/06432; WO 99/06433; WO 99/06434; WO 99/06435; WO 99/06436; WO 99/06437; WO 99/10312; WO 99/10313; WO 99/20272; WO 99/23063; WO 99/24398; WO 99/25685; WO 99/26615;

WO 99/26921; WO 99/26922; WO 99/26923; WO 99/35163; WO 99/36393; WO 99/37605; WO 99/37618; WO 99/43642; WO 01/42215; and WO 02/28830; all of which are incorporated by reference herein.

Additional examples of $\alpha 4$ integrin antagonists include the phenylalanine derivatives described in: U.S. Patent Nos. 6,197,794; 6,229,011; 6,329,372; 6,388,084; 6,348,463; 6,362,204; 6,380,387; 6,445,550; 6,806,365; 6,835,738; 6,855,706; 6,872,719; 6,878,718; 6,911,451; 6,916,933; 7,105,520; 7,153,963; 7,160,874; 7,193,108; 7,250,516; and 7,291,645 (each herein incorporated by reference). Additional amino acid derivatives that are $\alpha 4$ integrin antagonists include those described in, e.g., U.S. Patent Application Publication Nos. 2004/0229859 and 2006/0211630 (herein incorporated by reference), and PCT Publication Nos. WO 01/36376; WO 01/47868; and WO 01/70670; all of which are incorporated by reference herein.

Other examples of $\alpha 4$ integrin antagonists include the peptides, and the peptide and semi-peptide compounds described in, e.g., PCT Publication Nos. WO 94/15958; WO 95/15973; WO 96/00581; WO 96/06108; WO 96/22966 (Leu-Asp-Val tripeptide; Biogen, Inc.); WO 97/02289; WO 97/03094; and WO 97/49731. An additional example of an $\alpha 4$ integrin antagonist is the pegylated molecule described in U.S. Patent Application Publication No. 2007/066533 (herein incorporated by reference).

Examples of antibodies that are $\alpha 4$ integrin antagonists include those described in, e.g., PCT Publication Nos. WO 93/13798; WO 93/15764; WO 94/16094; and WO 95/19790. Additional examples of $\alpha 4$ integrin antagonists are described herein.

By "leukocyte function antigen-1" or "LFA-1" is meant a polypeptide that includes an α subunit having an amino acid sequence substantially identical to SEQ ID NO: 21 (NCBI Accession No. P20701; Larsen et al., *J. Cell. Biol.* 108:703-712, 1989) and a β subunit having an amino acid sequence substantially identical to SEQ ID NO: 22 (NCBI Accession No. P05107; Kishimoto et al., *Cell* 48:681-690, 1987); or having an mRNA nucleic acid sequence that includes a nucleic acid sequence substantially identical to SEQ ID NO: 23 (NCBI Accession No. Y00796; Larsen et

al., *supra*) or SEQ ID NO: 24 (NCBI Accession No. Y00057; Law et al., *EMBO J.* 6:915-919, 1987).

By “nucleic acid inhibitor” is meant any nucleic acid sequence (DNA or RNA) or peptide-nucleic acid sequence that contains a sequence complimentary to a nucleic acid sequence that is substantially identical to all or part of the mRNA of a targeted protein (e.g., for $\alpha 4$ integrin, a sequence complimentary to SEQ ID NO: 12 or SEQ ID NO: 35; for CD80, a sequence complimentary to SEQ ID NO: 14; for P-selectin, a sequence complimentary to SEQ ID NO: 16; for sphingosine-1-phosphate receptor-1, a sequence complimentary to SEQ ID NO: 18; for hyaluronate receptor, a sequence complimentary to SEQ ID NO: 20; for LFA-1, a sequence complimentary to SEQ ID NOS: 23 or 24; and for CD11/CD18, a sequence complimentary to SEQ ID NOS: 29, 30, 31, or 32), which, when administered to a cell or subject, results in decreased activity or expression of the target protein (e.g., $\alpha 4$ integrin, CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6.) relative to a cell or subject not administered the nucleic acid inhibitor. Examples of nucleic acid inhibitors include RNAi, antisense RNA, siRNA, miRNA, and peptide-nucleic acids. One example of a nucleic acid inhibitor is a nucleic acid sequence that results in a decrease in the activity or expression of $\alpha 4$ integrin.

Examples of antisense nucleic acid molecules include RNA or DNA molecules having a sequence that is complementary to the mRNA nucleic acid sequences of target proteins; the sequence of an antisense nucleic acid molecule of the invention has a length of at least 10, 20, 25, 30, 40, 50, 60, 70, 80, 90, or 100, or 100 or more nucleotides. Other examples of antisense nucleic acid molecules are interfering RNA or RNAi molecules (e.g., small interfering RNAs or siRNAs). RNAi molecules contain sequences that are complementary to the mRNA nucleic acid sequences of target proteins (as described above), and may include heterologous sequences which facilitate hairpin formation. RNAi molecules may be at least 10, 20, 25, 30, 40, 50, or even greater than 50 nucleotides in length; preferably the RNAi molecule is 21 or 25 nucleotides in length. Typically, RNAi molecules have at least 25 nucleotides and are complementary to any 25 nucleotides of the target protein mRNA sequence (e.g., the mRNA sequence of $\alpha 4$ integrin set forth in SEQ ID NO:

12 or SEQ ID NO: 35). Additional examples of RNAi molecules are those that are complementary to nucleotides 1-25, 50-75, 50-100, 50-150, 50-1000, or 50-2000 of SEQ ID NO: 12 or SEQ ID NO: 35.

By "P-selectin" is meant a polypeptide having an amino acid sequence substantially identical to SEQ ID NO: 15 (NCBI Accession No. NP_002966; Johnston et al., *Cell* 56:1033-1044, 1989) or having an mRNA nucleic acid sequence that includes a nucleic acid sequence substantially identical to SEQ ID NO: 16 (NCBI Accession No. NM_003005; Johnston et al., *supra*). P-selectin is also referred to in the art as "CD62P," "Granule Membrane Protein-140" or "GMP-140," and "Platelet
5
10 Activation-Dependent Granule to External Membrane Protein" or "PADGEM."

By "small molecule inhibitor" is meant any small molecule which is identified as an antagonist of a target protein (e.g., α 4 integrin, CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or
15 IL-6) using screening or biological assays (e.g., ligand binding assays, protein or receptor activity assays, and other assays as known in the art). The compound may be identified by screening commercially available chemical or small molecule libraries.

By "sphingosine-1-phosphate receptor-1" or "S1P1" is meant a polypeptide having an amino acid sequence substantially identical to SEQ ID NO: 17 (NCBI
20 Accession No. P21453; Hla and Maciag, *J. Biol. Chem.* 265:9308-9313, 1990) or having an mRNA nucleic acid sequence that includes a nucleic acid sequence substantially identical to SEQ ID NO: 18 (NCBI Accession No. BC018650; Strausberg et al., *supra*). Sphingosine-1-phosphate receptor-1 is also referred to in the art as "endothelial differentiation, sphingolipid G-protein coupled receptor-1" or
25 "Edg1."

The term "substantial identity" or "substantially identical," when used in the context of comparing a polynucleotide or polypeptide sequence to a reference sequence, refers to the fact that the polynucleotide or polypeptide sequence is the same as the reference sequence or has a specified percentage of nucleotides or amino
30 acid residues that are the same at the corresponding locations within the reference sequence when the two sequences are optimally aligned. For instance, an amino acid sequence that is "substantially identical" to a reference sequence has at least about

60% identity, preferably at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity, or higher percentage identity (up to 100%) to a reference sequence (e.g., the mature human AFP amino acid sequence as set forth in SEQ ID NO: 1, the human AFP mRNA nucleic acid sequence set forth in
5 SEQ ID NO: 2, or a pre-determined segment of SEQ ID NOS: 1 or 2), when compared and aligned for maximum correspondence over the full length of the reference sequence as measured using BLAST or BLAST 2.0 sequence comparison algorithms with default parameters, or by manual alignment and visual inspection (see, e.g., NCBI web site).

10 A “therapeutically effective amount” of a therapeutic agent (e.g., an AFP or an integrin antagonist) is an amount of the agent that is sufficient to treat or reduce one or more symptoms of MS (e.g., tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing
15 problems, paralysis, lack of coordination, cognitive difficulties, fatigue, muscle spasms, dizziness, breathing problems, or seizures) or the severity of one or more symptoms of MS (e.g., by at least about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, or 80% relative to an untreated control patient). The treatment of MS or reduction in one or more of the symptoms of MS (or their severity) can be determined
20 by using one of several methods known in the art (see, e.g., the Expanded Disability Status Scale (EDSS), Kurtzke, *Neurology* 33:1444-1452, 1983; and the Multiple Sclerosis Severity Score (MSSS), Roxburgh et al., *Neurology* 64:1144-1151, 2005). Such amount may vary depending on the effect to be achieved. For instance, a “therapeutically effective amount” of an integrin antagonist for treating MS when
25 used in combination with AFP (or a biologically fragment thereof) may be different from the “therapeutically effective amount” of an integrin antagonist when used alone for treating MS. In different embodiments, the therapeutic effect is to reduce the symptoms (e.g., muscle weakness and demyelination of nerves) or progression of MS in a patient.

By “treating” is meant the reduction (e.g., by at least 10%, 15%, 20%, 25%,
30 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or even 100%) in the progression, severity, or frequency of one or more symptoms of MS (e.g., tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing problems, paralysis, lack of coordination, cognitive

difficulties (e.g., decreased memory and concentration), fatigue, muscle spasms, dizziness, breathing problems, and seizures) or the prevention or decrease (e.g., by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or even 100%) in the progression of MS in a human patient (e.g.,
5 demyelination of nerves and the frequency or severity of one or more symptoms of MS).

Brief Description of the Figures

Figure 1 shows the amino acid sequence of mature human AFP (SEQ ID NO: 1) and the mRNA nucleic acid sequence of human AFP (SEQ ID NO: 2). N indicates the asparagine 233 glycosylation site in the mature human AFP amino acid sequence.

Figure 2 shows the amino acid sequences of biologically active fragments of AFP including amino acids 2-198 (Domain I; SEQ ID NO: 5), amino acids 199-390
15 (Domain II; SEQ ID NO: 6), amino acids 391-591 (Domain III; SEQ ID NO: 7), amino acids 2-390 (Domains I+II; SEQ ID NO: 8), amino acids 199-591 (Domains II+III; SEQ ID NO: 9), and amino acids 261-591 of mature human AFP (Human AFP Fragment 1; SEQ ID NO: 10).

Figure 3 shows two different amino acid sequences for $\alpha 4$ integrin protein
20 (SEQ ID NOS: 11 and 34) and two different nucleic acid sequences for $\alpha 4$ integrin mRNA (SEQ ID NOS: 12 and 35).

Figure 4 shows the amino acid sequence (SEQ ID NO: 13) and the nucleic acid sequence (SEQ ID NO: 14) of CD80 protein and mRNA, respectively.

Figure 5 shows the amino acid sequence (SEQ ID NO: 15) and the nucleic
25 acid sequence (SEQ ID NO: 16) of P-selectin protein and mRNA, respectively.

Figure 6 shows the amino acid sequence (SEQ ID NO: 17) and the nucleic acid sequence (SEQ ID NO: 18) of sphingosine-1-phosphate receptor-1 protein and mRNA, respectively.

Figure 7 shows the amino acid sequence (SEQ ID NO: 19) and the nucleic acid sequence (SEQ ID NO: 20) of hyaluronate receptor protein and mRNA, respectively.

Figure 8 shows the amino acid sequence (SEQ ID NO: 21) and the nucleic acid sequence (SEQ ID NO: 23) of LFA-1 α subunit protein and mRNA, respectively; and the amino acid sequence (SEQ ID NO: 22) and the nucleic acid sequence (SEQ ID NO: 24) of LFA-1 β subunit protein and mRNA, respectively.

Figure 9 shows the amino acid sequences of CD11a (SEQ ID NO: 25), CD11b (SEQ ID NO: 26), CD11c (SEQ ID NO: 27), and CD18 (SEQ ID NO: 28); and the nucleic acid sequences of CD11a (SEQ ID NO: 29), CD11b (SEQ ID NO: 30), CD11c (SEQ ID NO: 31), and CD18 (SEQ ID NO: 32) mRNA.

Detailed Description

The invention features a combination therapy for treating MS that involves the co-administration of an integrin antagonist and an AFP (or a biologically active fragment thereof), each in a therapeutically effective amount, to an MS patient in need thereof.

The invention also features a pharmaceutical composition that includes both an integrin antagonist and an AFP (or a biologically active fragment thereof), each in a therapeutically effective amount for treating, preventing, or reducing one or more of the symptoms of or the progression of, MS. Such a composition optionally contains one or more pharmaceutically acceptable excipients and is formulated to be administered intravenously, intramuscularly, orally, by inhalation, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, through use of suppositories, transbuccally, liposomally, adiposally, intraocularly, subcutaneously, intrathecally, topically, or through local administration.

The invention also features a kit for treating, preventing, or reducing one or more of the symptoms of or the progression of, MS, which includes a therapeutically effective amount of an integrin antagonist and AFP (or a biologically active fragment thereof), along with proper instructions for using the kit.

The integrin antagonist may be an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor. Examples of integrin antagonists are described herein. The AFP can be full length AFP, a biologically active fragment, derivative, or analog thereof, or a mutein thereof having one or more amino acid
5 substitutions, deletions, or additions. Examples of AFP agents of the invention are described herein. The AFP and the integrin antagonist may be formulated for or administered in a single dosage form or they may be formulated or administered in different dosage forms. The AFP and integrin antagonist of the invention can be administered coextensively or separately. In addition, the AFP or integrin antagonist
10 may be administered one or more times hourly, daily, weekly, biweekly, or monthly.

An antagonist to CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 may also be administered in the methods and compositions of the invention.

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Diagnosis and Monitoring of Multiple Sclerosis

MS can be diagnosed by observing one or more symptoms in a patient. Symptoms of MS may be single or multiple and may range from mild to severe in intensity and short to long in duration. Complete or partial remission from symptoms
20 occurs early in about 70% of MS patients. Visual disturbances often are the first symptoms of MS, but they usually subside. A patient may notice blurred or double vision, red-green distortion, or sudden blindness. Muscle weakness leading to difficulties with coordination and balance commonly is noticed early. Muscle spasms, fatigue, numbness, and prickling pain are common symptoms. There may be
25 a loss of sensation, speech impediment, tremors, dizziness, or occasionally hearing loss. Fifty percent of patients experience mental changes such as decreased concentration, attention deficits, some degree of memory loss, or impairment in judgment. Other symptoms may include depression, manic depression, paranoia, or an uncontrollable urge to laugh and weep called laughing-weeping syndrome. As the
30 disease worsens, patients may experience sexual dysfunction or reduced bowel and bladder control. Heat appears to intensify MS symptoms for about 60% of patients, and relief is found with cold baths or swimming. Pregnancy seems to reduce the number of attacks.

There is no single test for MS. Physicians, particularly neurologists, can take into consideration detailed medical histories and can perform complete physical and neurological examinations in order to diagnose MS. Testing for MS can include, e.g., magnetic resonance imaging (MRI) with intravenous gadolinium or magnetic resonance scanning (MRS), both of which help to identify, describe, and date lesions in the brain (i.e., plaques) that occur in MS patients. Another electro-physiological test, evoked potentials, examines the impulses traveling through the nerves to determine if the impulses are moving normally or too slowly; slower than normal movement of impulses through the nerves is indicative of MS. Finally, examination of the cerebro-spinal fluid that surrounds the spinal cord may be used to identify abnormal chemicals or cells floating in the brain or spinal cord that suggest the presence of MS. Collectively, these three tests strengthen the diagnosis of MS. MS can also be diagnosed by identifying one or more of the following symptoms in a patient: tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing problems, paralysis, lack of coordination, cognitive difficulties (e.g., decreased memory and concentration), fatigue, muscle spasms, dizziness, breathing problems, and seizures.

All of the methodologies described above are also useful for monitoring the progression of MS in patients, as well as for monitoring the resolution of MS following treatment using the compositions and methods of the invention (e.g., the resolution or decrease in the severity or frequency of one or more symptoms of MS), such that the effectiveness of the treatment received by the patient can be assessed. In addition, a patient can be assessed for an improvement in MS following treatment (e.g., an improvement in one or more symptoms of MS (e.g., a decrease in the occurrence, length, or severity of one or more of the symptoms of MS), or for an improvement in motor neural function) using one of several methods known in the art (see, e.g., the Expanded Disability Status Scale (EDSS), Kurtzke, *Neurology* 33:1444-1452, 1983; and the Multiple Sclerosis Severity Score (MSSS), Roxburgh et al., *Neurology* 64:1144-1151, 2005).

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Methods of Treatment of MS by Administration of the Compositions of the Present Invention

The present invention features methods of treating MS in a patient by co-administering a therapeutically effective amount of an AFP (or biologically active
5 fragment thereof) and an integrin antagonist; the compositions of the invention may, but need not, also include additional therapeutic agents, such as those described below. The compositions of the invention can be administered to a patient to treat, prevent, ameliorate, inhibit the progression of, or reduce the severity of one or more symptoms of MS in a human patient. The AFP (or biologically active fragment
10 thereof) and an integrin antagonist may be administered coextensively or separately, in a single dose or in multiple doses. The AFP (or biologically active fragment thereof) and integrin antagonist may be formulated for the same route of administration or formulated for different routes of administration.

Examples of the symptoms of MS that can be treated using the compositions
15 of the invention include: tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing problems, paralysis, lack of coordination, cognitive difficulties (e.g., decreased memory and concentration), fatigue, muscle spasms, dizziness, breathing problems, and seizures. These symptoms of MS, and their resolution during treatment, may be measured by a
20 physician during a physical examination or by using one or more of the tests described above.

A physician may adjust the dose (e.g., increase or decrease the dose) of the AFP or of the integrin antagonist administered to the patient based on the severity of, occurrence of, or progression of MS in the patient. For example, a physician can
25 increase the dose of the AFP or of the integrin antagonist if necessary to alleviate one or more symptoms of MS in a patient. Alternatively, a physician can decrease the dose of the AFP or of the integrin antagonist based on an improvement in one or more symptoms of MS in the patient or to avoid toxicity associated with, e.g., the administration of an integrin antagonist.

30 The combination therapies of the present invention, which include, e.g., an AFP and an integrin antagonist, preferably exhibit a greater therapeutic effect (e.g., improved efficacy or reduced toxicity at higher doses) than that observed when either agent is administered alone.

Compositions of the Present Invention

The present invention provides compositions including an AFP (or a biologically active fragment, derivative, or analog thereof) and an integrin antagonist (e.g., an $\alpha 4$ integrin antagonist) for the treatment of MS. The compositions of the invention may be formulated for any route of administration (e.g., the formulations described herein) and may be administered in a single dose or in multiple doses to a subject in need thereof. The compositions of the invention may also include supplemental agents, e.g., a CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 antagonist. The supplemental agents can be antibodies, blocking peptides, nucleic acid inhibitors, or small molecule inhibitors that antagonist CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6.

AFPs for Use in the Compositions and Methods of the Invention

An alpha-fetoprotein for use in the compositions and methods of the present invention are described below. For the purposes of the present invention, both naturally occurring human AFP and recombinantly produced AFP polypeptides or biologically active fragments thereof can be used. Naturally occurring human AFP can be obtained by, e.g., purification from umbilical cord blood or umbilical cord serum. Recombinant AFP polypeptide or biologically active fragment thereof can be obtained, e.g., by using a prokaryotic or eukaryotic expression system, such as those described in, e.g., U.S. Patent No. 5,384,250 and U.S. Patent Application Publication No. 20040098755 (each of which is herein incorporated by reference). These methods include the purification of AFP from a biological fluid of transgenic mammal that has been engineered to express AFP into the biological fluid, as well as other methods known in the art. These AFPs can be used in the present invention notwithstanding the fact that the use of these different expression systems (e.g., production in a prokaryotic host cell, a eukaryotic host cell, or a transgenic animal or plant) may result in a recombinant AFP or fragment thereof having different post-translational modifications than that in the wild-type AFP (e.g., a different number of

attached sugar residues (e.g., at least 1, 2, 3, 4, 5, 6, 7, or 10 sugar molecules), a different type of glycosylation (e.g., O-linked glycosylation or N-linked glycosylation, or the lack thereof), a different type of sugar residues (e.g., mannose, galactose, N-acetyl-galactosamine, N-acetyl-glucosamine, glucuronate, sialic acid, or xylose, or different combinations thereof), or different amino acids glycosylated). For instance, naturally occurring human AFP is a variably glycosylated protein (e.g., glycosylation at asparagine 233 of SEQ ID NO: 1). In contrast, the recombinant AFP or fragment may be unglycosylated when produced by a prokaryotic host cell or may be somewhat differently glycosylated when produced by a eukaryotic host cell.

10 Alternatively, a recombinant AFP can be genetically modified to eliminate glycosylation (e.g., by removing a glycosylation site, for instance replacing asparagine 233 of SEQ ID NO: 1 with any amino acid other than asparagine), regardless of the expression system in which it is produced. Human AFP is available through various commercial suppliers, including Fitzgerald Industries International

15 (Concord, MA), Cell Sciences (Canton, MA), and Biodesign International (Saco, ME).

Furthermore, it is possible to employ well-known chemical synthesis methods to synthesize an AFP polypeptide or fragment, particularly when the AFP fragment is a peptide of a relatively short length, e.g., with less than 50 or 100 amino acids.

20

Any AFP polypeptide or fragment thereof, regardless of its origin or status of post-translational modification, can be used in the present invention if the polypeptide or fragment has the same or substantially the same biological activity (e.g., at least about 40%, desirably at least about 50%, 60%, 70%, and more desirably at least about 80%, 90%, 100%, or 100% or more of the biological activity) of native human AFP (e.g., as determined based on the ability of the AFP to bind to human leukocytes, to suppress human autologous mixed lymphocyte reactions (AMLR), to suppress EAE in a mouse model, or to inhibit release of inflammatory cytokines in a splenocyte assay).

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Similarly, fragments of the human AFP can also be used in the compositions and methods of the present invention, so long as the fragments retain the same or substantially the same biological activity of naturally occurring human AFP (as

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determined using one or more of the assays for AFP biological activity described below). Fragments of human AFP can be generated by methods known to those skilled in the art, e.g., proteolytic cleavage or recombinant expression, or may result from normal protein processing (e.g., removal from a nascent polypeptide of amino acids that are not required for biological activity). Fragments of human AFP can also be produced recombinantly using the techniques described above. Chemical methods can also be useful for synthesizing active AFP fragments.

Examples of human AFP fragments suitable for use in practicing the present invention are shown in Figure 2 and include Domain I (amino acids 2-198 of mature human AFP; SEQ ID NO: 5), Domain II (amino acids 199-390 of mature human AFP; SEQ ID NO: 6), Domain III (amino acids 391-591 of mature human AFP; SEQ ID NO: 7), Domain I+II (amino acids 2-390 of mature human AFP; SEQ ID NO: 8), Domain II+III (amino acids 199-591 of mature human AFP; SEQ ID NO: 9), and AFP Fragment I (amino acids 267-591 of mature human AFP; SEQ ID NO: 10). Other examples of known AFP fragments are described herein or can be found in, e.g., U.S. Patent No. 5,707,963 and U.S. Patent No. 6,818,741, herein incorporated by reference.

Also encompassed within the claimed invention is the use of functional derivatives or analogs of full-length native human AFP or fragments thereof. As described in earlier sections, such derivatives or analogs can differ from the full-length native human AFP or portions thereof by amino acid sequence differences (e.g., additions, deletions, conservative or non-conservative substitutions), or by modifications (e.g., post-translational modifications) that do not affect sequence, or by both. The derivatives/analogs of the invention will generally exhibit at least 90%, more preferably at least 95%, or even 99% amino acid identity with all or part of the native human AFP amino acid sequence (SEQ ID NO: 1).

An AFP derivative/analog may differ from a naturally occurring human AFP due to post-translational modifications (which do not normally alter primary sequence), which include *in vivo*, or *in vitro* chemical derivatization of polypeptides, e.g., acetylation, carboxylation, or pegylation; such modifications may occur during polypeptide synthesis or processing, or following treatment with isolated modifying enzymes. Also included are cyclized peptide molecules and analogs that contain

residues other than L-amino acids, e.g., D-amino acids, non-naturally occurring, or synthetic amino acids, e.g., β or γ amino acids, or L-amino acids with non-natural side chains (see, e.g., Noren *et al.*, *Science* 244:182, 1989). Methods for site-specific incorporation of non-natural amino acids into the protein backbone of proteins is described, e.g., in Ellman *et al.*, *Science* 255:197, 1992. Also included are chemically synthesized polypeptides or peptides with modified peptide bonds (e.g., non-peptide bonds as described in U.S. Patent No. 4,897,445 and U.S. Patent No. 5,059,653; herein incorporated by reference) or modified side chains to obtain the desired pharmaceutical properties as described herein. Useful AFP, AFP fragments, AFP derivatives, and AFP analogs having the same or substantially the same biological activity (e.g., at least about 40%, desirably at least about 50%, 60%, 70%, and more desirably at least about 80%, 90%, 100%, or 100% or more of the biological activity) of wild-type AFP can be identified using art-recognized methods, such as those described below.

Some preferred functional AFP derivatives contain one or more conservative substitutions, in which certain amino acid residues are substituted by other residues having similar chemical structures (e.g., alanine for glycine, arginine for lysine, etc.). The derivatives/analogues mentioned above may include allelic variants, inter-species variants, and genetic variants, both natural and induced (for example, resulting from random mutagenesis by, e.g., site-specific mutagenesis according to methods described in scientific literature such as Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual*, 3rd ed., 2001; Kriegler, *Gene Transfer and Expression: A Laboratory Manual*, 1990; and Ausubel *et al.*, eds., *Current Protocols in Molecular Biology*, 1994.

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AFP Activity Assays

As stated above, AFP polypeptides or AFP fragments suitable for use in the compositions and methods of the present invention may include various derivatives, analogs, or fragments of the naturally occurring human AFP, so long as the polypeptides or fragments retain the same or substantially the same biological activity of mature human AFP. The biological activity of an AFP of the present invention can be demonstrated by using, e.g., one or more of the following assays.

A first assay for testing a candidate AFP for biological activity entails measuring the ability of the AFP to specifically bind to human leukocytes (e.g., peripheral monocytes). A binding assay suitable for this purpose is described in, e.g., Parker et al., *Protein Express. Purification* 38:177-183, 2004. Briefly, a competitive
5 assay format is used to test a candidate AFP for its ability to specifically bind to U937 cells, a human monocytic cell line. The cells are maintained in RPMI media with 10% fetal bovine serum. Prior to the binding assay, the cells are washed twice with serum-free media and adjusted to 2.5×10^6 cells/ml in phosphate-buffered saline (PBS). Native human AFP (SEQ ID NO: 1) or non-glycosylated human AFP (see,
10 e.g., SEQ ID NO: 36, where, e.g., residue 233 is glutamine) is labeled with a detectable label, e.g., fluorescein, in a proper reaction followed by removal of the unattached labeling material, for instance, by gel filtration. In the case of labeling human AFP with fluorescein, the protein is mixed with a solution of fluorescein-5-isothiocyanate in dimethyl sulfoxide for 1 hour in the dark, followed by gel filtration
15 to remove unbound dye. Labeled human AFP is stored in 20% glycerol at -20°C until use.

For the binding assay, a certain number of U937 cells (e.g., 40 μl of cell suspension at 2.5×10^6 cells/ml concentration) are mixed with a pre-determined amount of labeled human AFP (e.g., at a final concentration of 0.5 μM) and with
20 unlabeled human AFP or an unlabeled candidate AFP, each at a set of final concentrations (e.g., 20, 10, 5, 2.5, 1.25, and 0.625 μM) to determine the IC_{50} values for both human AFP and the candidate AFP. At the conclusion of the binding process, the cells are then washed with PBS and suspended in fresh PBS so that the labeled AFP remaining on U937 cells can be measured, e.g., by flow cytometry.

25 A second assay for testing a candidate AFP for biological activity entails measuring the ability of the AFP to suppress autoimmune reactions, either in AMLR or in a mouse model of EAE. Methods are known in the art for testing AMLR and its inhibition. For instance, U.S. Patent Nos. 5,965,528 and 6,288,034 (each of which is herein incorporated by reference) describe the AMLR system as follows: isolation of
30 human peripheral blood mononuclear cells (PBMC), their fractionation into non-T-cell populations, and the AMLR, performed according to standard procedures. Briefly, responder T-cells are isolated by passing 1.5×10^8 PMBC over a commercial anti-Ig affinity column (US Biotek Laboratories, Seattle, WA) and 2×10^5 responder

cells are subsequently cultured with 2×10^5 autologous ^{137}Cs -irradiated (2500 rads) non-T stimulator cells from a single donor. The medium employed consists of RPMI-1640 supplemented with 20 mM HEPES (Invitrogen), 5×10^{-5} M 2-mercaptoethanol (BDH, Montreal, QC), 4 mM L-glutamine (Invitrogen), 100 U/ml penicillin
5 (Invitrogen), and 100 $\mu\text{g/ml}$ streptomycin sulfate, with the addition of 10% fresh human serum autologous to the responder T-cell donor for the AMLR. Varying concentrations of purified recombinant human AFP, human serum albumin, anti-human AFP monoclonal antibody clone #164 (125 $\mu\text{g/ml}$ final concentration in culture) (Leinco Technologies, St. Louis, MO) are added at the initiation of cultures.
10 AMLR cultures are incubated for 4 to 7 days, at 37 °C in 95% air and 5% CO_2 . At the indicated intervals, DNA synthesis is assayed by a 6 hour pulse with 1 μCi of ^3H -thymidine (specific activity 56 to 80 Ci/mmol; ICN Radioisotopes, Cambridge, MA). The cultures are harvested on a multiple sample harvester (Skatron, Sterling, VA), and the incorporation of ^3H -TdR is measured in a Packard 2500 TR liquid scintillation
15 counter. Results are expressed as mean cpm \pm the standard error of the mean of triplicate or quadruplicate cultures.

The immunosuppressive activity of a candidate AFP within the scope of the present invention can be assessed by its ability to suppress human autologous mixed lymphocyte reactions (AMLR). Generally, the candidate AFP is tested for its ability
20 to inhibit the proliferative response of autoreactive lymphocytes stimulated by autologous non-T-cells, by measuring lymphocyte autoprolieration throughout a time course of 4 to 7 days. Suppression of AMLR in a dose-dependent manner is demonstrated by results from dose-response studies performed at the peak of T-cell autoprolieration where an AFP is added at the initiation of cultures. Furthermore,
25 parallel viability studies can be used to establish that the inhibitory activity of an AFP polypeptide or fragment on human autoreactive T-cells is not due to non-specific cytotoxic effects.

A third assay for testing a candidate AFP for biological activity involves the use of a myelin oligodendrocyte glycoprotein (MOG) mouse model of experimental
30 autoimmune encephalomyelitis (EAE) (see, e.g., Fritz et al., *J. Immunol.* 130:1024, 1983; Naiki et al., *Int. J. Immunopharmacol.* 13:235, 1991; and Goverman, *Lab. Anim. Sci.*, 46:482, 1996). In this *in vivo* assay, genetically susceptible strains of mice are subcutaneously immunized with MOG emulsified in Complete Freund's Adjuvant

(CFA), which leads to the development of EAE in the animals. A candidate AFP is administered to a selected group of mice on a daily basis, beginning prior to, at the same time, or subsequent to the start of the administration of MOG to the animals. The symptoms of EAE in these animals are monitored and compared to those in a control group (e.g., those receiving only saline injections) over a certain time period, 5 e.g., 30 days. Severity of EAE in each animal is given a score between 1-5 based on defined clinical symptoms; the average score of animals in a group indicates the disease state of the group. A biologically active AFP will reduce the severity of EAE in animals receiving MOG compared to controls (e.g., at least a 50% reduction in the 10 severity of disease after 30 days of treatment).

A fourth assay that can be used to test a candidate AFP for biological activity examines the ability of the candidate AFP to inhibit or reduce the release of inflammatory cytokines from mitogen-stimulated *in vitro* splenocyte cultures obtained from naïve mice (e.g., as described in Hooper and Evans, *J. Reprod. Immunol.* 16: 83-15 961, 1989; and Kruisbeek, in *Current Protocols in Immunology*, Vol. 1, Section 3.1.1-3.1.5, 2000). Splenocytes are stimulated with phytohemagglutinin (PHA), concavalin A (ConA), or lipopolysaccharide (LPS) in the presence of increasing concentrations of an AFP for 24 hours. Human serum albumin is used as a negative control for the assays. A 10 point dose response study has shown that biologically active AFP 20 inhibits or substantially inhibits the secretion of PHA induced IFN- γ in a reproducible manner.

Integrin Antagonists for Use in the Compositions and Methods of the Invention

An integrin antagonist for use in the methods of this invention is an agent 25 that decreases (e.g., by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80% or more) the biological activity or expression (transcription or translation) of $\alpha 4$ integrin. Integrin antagonists can include antibodies, blocking peptides, nucleic acid inhibitors, or small molecule inhibitors. As understood in the field of biological science, integrins are integral membrane proteins present in the 30 plasma membrane of cells, that, *inter alia*, play a role in signal transduction and in the attachment of a cell to the extracellular matrix (ECM). There are many types of integrins, and many cells have multiple types on their surface.

Structurally, integrins are non-covalent heterodimeric complexes consisting of an α subunit and a β subunit. See, Hemeler, *Ann. Rev. Immunol.* 8:365, 1990. About 18 α and 8 β subunits have been characterized, with additional variants formed due to differential splicing. Through the different combinations of α and β subunits,
5 at least 24 unique integrins can be generated.

The $\alpha 4\beta 1$ integrin, or very late antigen-4 (VLA-4), is constitutively expressed by all leukocytes (e.g., monocytes, lymphocytes, basophils, eosinophils, mast cells, macrophages, and neutrophils). The binding of VLA-4 to one of its ligands has a number of known cell adhesion and activation functions. See, for
10 example, Hemeler, *supra*; Walsh et al., *Clin. and Exp. Allergy*, 25:1128, 1995; and Hutala et al., *J. Cell Biol.* 129:867, 1995. In particular, VLA-4 interacts with the cytokine inducible endothelial cell surface protein known as vascular cell adhesion molecule-1 (VCAM-1), and the alternatively spliced forms of the extracellular matrix protein fibronectin containing the CS-1 domain (Ruegg et al. *J Cell Biol.* 177:179,
15 1991) and the extracellular matrix protein osteopontin (Bayless et al., *J. Cell Sci.* 111:1165-1174, 1988).

The expression of an $\alpha 4$ integrin may be measured using art-known methods including Western blot, ELISA, fluorescence-assisted cell sorting (FACS), proteomics, RT-PCR, Northern blot, and gene chip technology. The biological
20 activity of $\alpha 4$ integrin may be measured in cellular based assays, including, but not limited to: JAK3 activation and phosphorylation, STAT6 activation and phosphorylation, and STAT6-responsive reporter plasmid assays (e.g., assays using a promoter which is activated by STAT6, e.g., IGE, MHC class II, and CD23). Additional assays for integrin antagonists are described below.

25 Examples of integrin antagonists are described in: U.S. Patent Nos. 5,821,231; 5,869,448; 5,936,065; 6,197,794; 6,229,011; 6,265,572; 6,288,267; 6,329,372; 6,348,463; 6,362,204; 6,365,619; 6,380,387; 6,388,084; 6,423,728; 6,426,348; 6,445,550; 6,458,844; 6,479,666; 6,482,849; 6,596,752; 6,667,331; 6,668,527; 6,685,617; 6,806,365; 6,835,738; 6,855,706; 6,872,719; 6,878,718;
30 6,903,128; 6,911,451; 6,916,933; 7,015,216; 7,105,520; 7,153,963; 7,160,874; 7,193,108; 7,250,516; and 7,291,645 (each herein incorporated by reference); in U.S. Patent Application Publication Nos. 2002/0049236; 2003/0004196; 2003/0018016;

2003/0078249; 2003/0083267; 2003/0100585; 2004/0039040; 2004/0053907;
2004/0087574; 2004/0102496; 2004/0132809; 2004/0229858; 2004/0229859;
2006/0014966; 2006/0030553; 2006/0166866; 2006/0166961; 2006/0211630;
2006/0241132; 2007/0054909; and 2007/066533 (each herein incorporated by
5 reference); in European Patent Nos. EP 0842943; EP 0842944; EP 0842945; EP
0903353; and EP 0918059; in PCT Publication Nos. WO 93/13798; WO 93/15764;
WO 94/15958; WO 94/16094; WO 95/15973; WO 95/19790; WO 96/00581; WO
96/06108; WO 96/22966; WO 96/40781; WO 97/02289; WO 97/03094; WO
97/49731; WO 98/04913; WO 98/04247; WO 98/42656; WO 98/53814; WO
10 98/53817; WO 98/53818; WO 98/54207; WO 98/58902; WO 99/06390; WO
99/06431; WO 99/06432; WO 99/06433; WO 99/06434; WO 99/06435; WO
99/06436; WO 99/06437; WO 99/10312; WO 99/10313; WO 99/20272; WO
99/23063; WO 99/24398; WO 99/25685; WO 99/26615; WO 99/26921; WO
99/26922; WO 99/26923; WO 99/35163; WO 99/36393; WO 99/37605; WO
15 99/37618; WO 99/43642; WO 01/42215; WO 01/47868; WO 01/70670; and WO
02/28830. Examples of antibodies, blocking peptides, nucleic acid inhibitors, and
small molecule inhibitors that can be used as integrin antagonists are described below.

Antibodies

20 An integrin antagonist can be an antibody. Examples of antibodies include
monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bi-
specific antibodies) formed from at least two intact antibodies, and antibody
fragments so long as they function as an integrin antagonist. Other kinds of antibody
included in the invention are antibody fragments (e.g., Fab, Fab', Fv fragments,
25 diabodies, linear antibodies, and single chain antibody molecules). Additional
examples of antibodies include monoclonal antibodies that are chimeric, primatized,
or humanized. The term antibody herein used also encompasses proteins or
molecules which contain the amino acid sequence of the variable region of an
immunoglobulin gene (e.g., an antibody mimic). Methods for the production of the
30 various antibodies described above are known in the art.

Studies using a specific monoclonal antibody antagonist of $\alpha 4$ integrin have
demonstrated that inhibitors of VLA-4 cell adhesion can inhibit or reduce the severity
of numerous pathological conditions, including inflammatory, respiratory, and

autoimmune conditions (Chisholm et al., *Eur. J. Immunol.* 23:682, 1993; Richards et al., *Am. J. Resp. Cell Mol. Biol.* 15:172, 1996; Fryer et al., *J. Clin. Invest.* 99:2036, 1997; Soiluhanninen et al., *J. Neuroimmunol.* 72:95, 1997). These pathological processes can also be inhibited with agents other than antibodies, as evidenced in
5 animal model studies using synthetic CS-1 peptide or small molecule peptide inhibitors of VLA-4 (Ferguson et al., *Proc. Natl. Acad. Sci.*, 88:8072, 1991; Wahl et al., *J. Clin. Invest.* 94:655, 1994; Molossi et al., *J. Clin. Invest.* 95:2601, 1995; Abraham et al., *J. Resp. Crit. Care. Med.* 156:696, 1997; and Jackson et al., *J. Med. Chem.* 40:3359, 1997).

10 An exemplary antibody that binds and blocks the biological activity of $\alpha 4$ integrin is natalizumab, a recombinant humanized IgG4k monoclonal antibody produced in murine myeloma cells (reviewed in Rudick and Sandrock, *Expert Rev. Neurother.* 4:571-580, 2004). Natalizumab contains human antibody framework regions and the complementarity-determining regions of a murine antibody that binds
15 to $\alpha 4$ -integrin.

Other compounds have been developed that can target and bind to $\alpha 4$ integrin in a manner similar to antibodies. Certain of these "antibody mimics" use non-immunoglobulin protein scaffolds as alternative protein frameworks for the variable regions of antibodies. For example, Ladner et al. (U.S. Patent No. 5,260,203,
20 herein incorporated by reference) describe single polypeptide chain binding molecules with binding specificity similar to that of the aggregated, but molecularly separate, light and heavy chain variable region of antibodies. The single-chain binding molecule contains the antigen binding sites of both the heavy and light variable regions of an antibody connected by a peptide linker and will fold into a structure
25 similar to that of the two peptide antibody. The single-chain binding molecule displays several advantages over conventional antibodies, including, smaller size, greater stability, and are more easily modified.

The technique of Lipovsek et al. (U.S. Patent Nos: 6,818,418 and 7,115,396, herein incorporated by reference) can also be used to create integrin antagonists.
30 Lipovsek et al. (U.S. Patent Nos: 6,818,418 and 7,115,396) discloses an antibody mimic featuring a fibronectin or fibronectin-like protein scaffold and at least one variable loop. Known as Adnectins, these fibronectin-based antibody mimics exhibit

many of the same characteristics of natural or engineered antibodies, including high affinity and specificity for any targeted ligand.

The structure of these fibronectin-based antibody mimics is similar to the structure of the variable region of the IgG heavy chain. Therefore, these mimics
5 display antigen binding properties similar in nature and affinity to those of native antibodies. Further, these fibronectin-based antibody mimics exhibit certain benefits over antibodies and antibody fragments. For example, these antibody mimics do not rely on disulfide bonds for native fold stability, and are, therefore, stable under conditions which would normally break down antibodies. In addition, since the
10 structure of these fibronectin-based antibody mimics is similar to that of the IgG heavy chain, a process for loop randomization and shuffling may be employed *in vitro* that is similar to the process of affinity maturation of antibodies *in vivo*.

Beste et al. (*Proc. Natl. Acad. Sci. U.S.A.* 96:1898-1903, 1999) also discloses techniques that can be used to create integrin antagonists. Beste et al.
15 (*supra*) discloses an antibody mimic based on a lipocalin scaffold (i.e., an Anticalin[®]). Lipocalins are composed of a β -barrel with four hypervariable loops at the terminus of the protein. Beste et al. (*supra*) subjected the loops to random mutagenesis and selected for binding with, for example, fluorescein. Three variants exhibited specific binding with fluorescein, with one variant showing binding similar to that of an anti-
20 fluorescein antibody. Further analysis revealed that all of the randomized positions are variable, indicating that Anticalin[®] would be suitable for use as an alternative to antibodies. Anticalins[®] are small, single chain peptides, typically between 160 and 180 residues, which provide several advantages over antibodies, including decreased cost of production, increased stability in storage, and decreased immunological
25 reaction. Thus, the structural framework of Anticalins[®] can be used to produce an integrin antagonist according to the present invention.

Hamilton et al. (U.S. Patent No. 5,770,380, herein incorporated by reference) discloses a method of making synthetic antibody mimics that may be used as integrin antagonists. Hamilton et al. (*supra*) describes a method of making a
30 synthetic antibody mimic using the rigid, non-peptide organic scaffold of calixarene, attached with multiple variable peptide loops used as binding sites. The peptide loops all project from the same side of the calixarene, with respect to each other.

Because of this geometric confirmation, all of the loops are available for binding, increasing the binding affinity to a ligand. However, in comparison to other antibody mimics, the calixarene-based antibody mimic does not consist exclusively of a peptide, and therefore, it is less vulnerable to attack by protease enzymes. Neither
5 does the scaffold consist purely of a peptide, DNA, or RNA, meaning this antibody mimic is relatively stable in extreme environmental conditions and has a long life span. Further, since the calixarene-based antibody mimic is relatively small, it is less likely to produce an immunogenic response.

Another class of antibody mimics that may be used to produce an integrin
10 antagonists is disclosed in Murali et al., *Cell. Mol. Biol.* 49:209-216, 2003. Murali et al. (*supra*) discloses a methodology for reducing antibodies into smaller peptidomimetics, which may also be useful as an alternative to antibodies in the practice of the present invention.

In addition to non-immunoglobulin protein frameworks, antibody properties
15 have also been mimicked in compounds that include RNA molecules and unnatural oligomers (e.g., protease inhibitors, benzodiazepines, purine derivatives, and beta-turn mimics), each of which may be used in the preparation of integrin antagonist suitable for use with the present invention.

20 *Blocking Peptides*

Other exemplary integrin antagonists suitable for use with the present invention are blocking peptides that bind to and antagonize the activity of VLA-4 on leukocytes. The VLA-4 binding domain in the CS-1 region of fibronectin comprises the octapeptide: Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr, as well as the overlapping
25 pentapeptides Glu-Ile-Leu-Asp-Val and Leu-Asp-Val-Pro-Ser. Thus, the minimal amino acid sequence required for inhibition would be Leu-Asp-Val (LDV). In fact, the LDV minimal tripeptide sequence has been shown to be equally effective as the full length CS-1 fragment in binding the activated form of VLA-4 (Wayner et al., *J. Cell Biol.* 116:489, 1992). Another exemplary integrin antagonist suitable for use in
30 the present invention are Arg-Gly-Asp (RGD) based cyclic peptides capable of inhibiting both $\alpha 4\beta 1$ and $\alpha 5\beta 1$ integrins from binding to fibronectin, as disclosed in Nowlin et al., *J. Biol. Chem.* 268:20352, 1993; and PCT/US91/04862. The tri- and

tetra-peptide sequences IDA and REDV are suitable for use as blocking peptides in the present invention, as they have been shown to regulate fibronectin binding to VLA-4, while the pentapeptide QIDSP regulates binding of VLA-4 to VCAM-1 and is also suitable for use with the present invention (Humphries et al., *Ciba Found. Symp.* 189:177, 1995). Additional VLA-4 and VLA-5 blocking peptides that have been shown to inhibit a hypersensitivity response include GRDGSP and EILDV.

Ku et al. (*Proc. Natl. Acad. Sci. U.S.A.* 92:6552-6556, 1995) describes a method of creating peptide antagonists that may function as integrin antagonists. Ku et al. (*supra*) discloses a peptide antagonist based on cytochrome b562. In this method, Ku et al. generated a library in which two of the loops of cytochrome b562 were randomized and selected for binding against bovine serum albumin (BSA). The individual mutants were found to bind selectively with BSA similar to anti-BSA antibodies. Similar mutants can be constructed to selectively bind the $\alpha 4$ integrin subunit.

15

Nucleic Acid Inhibitors

In some embodiments, the integrin antagonist is a nucleic acid inhibitor. For example, ribozymes, antisense RNA and/or interfering RNA (RNAi) molecules can be used to target $\alpha 4$ integrin subunit.

In some embodiments, RNAi molecules are used to target the $\alpha 4$ integrin subunit. In mammalian cells, the introduction of dsRNAs (e.g., dsRNAs having at least 10, 20, 30, 40, 50, or 50 or more nucleotides in length; and desirably having 21 nucleotides in length) often initiates a potent antiviral response, which is exemplified by nonspecific inhibition of protein synthesis and RNA degradation. The phenomenon of RNA interference is described and discussed, for example, in Bass, *Nature* 411:428-29, 2001; Elbahir et al., *Nature* 411:494-98, 2001; and Fire et al., *Nature* 391:806-11, 1998; wherein methods of making interfering RNA also are discussed. RNAi molecules targeting the $\alpha 4$ integrin may include all or part of a nucleic acid sequence the complement of which is substantially identical to the mRNA sequence of $\alpha 4$ integrin (SEQ ID NO: 12 or SEQ ID NO: 35). The nucleic acid sequence preferably has at least 10, 20, 30, 40, 50, or even 50 or more

nucleotides in length (e.g., 21 or 25 nucleotides in length). The RNAi molecules can be made by methods known in the art. Exemplary RNAi molecules according to the invention could have up to 29 bps, 25 bps, 22 bps, 21 bps, 20 bps, 15 bps, 10 bps, 5 bps or any integer thereabout or therebetween. The RNAi molecule may have a
5 sequence which is complementary to any sequence within SEQ ID NO: 12 or SEQ ID NO: 35 (e.g., a sequence that is complementary to nucleotides 1-25, 50-75, 50-100, 50-150, 50-1000, or 50-2000 of SEQ ID NO: 12 or SEQ ID NO: 35).

The RNAi can also comprise two complementary molecules, or can be constructed such that a single transcript has both the sense and complementary
10 antisense sequences from the target sequence (e.g., SEQ ID NO: 12 or SEQ ID NO: 35) so that the RNAi molecule is capable of forming a hairpin.

Methods for designing double stranded RNA to inhibit gene expression in a target cell are known (e.g., US Patent No. 6,506,559; Elbashir et al., *Methods* 26:199-213, 2002; Chalk et al., *Biochem. Biophys Res. Comm* 319:264-274, 2004; Cui et al.,
15 *Comp. Method Prog. Biomed.* 75:67-73, 2004; and Wang et al., *Bioinformatics* 20:1818-1820, 2004). For example, the design of RNAi molecules (including hairpins) typically follows known thermodynamic rules (see, e.g., Schwarz et al., *Cell* 115:199-208, 2003; Reynolds et al., *Nature Biotechnol.* 22:326-30, 2004; and Khvorova et al., *Cell* 115:209-16, 2003). Many computer programs are available for
20 selecting regions of the $\alpha 4$ integrin sequence that are suitable target sites. These include programs available through commercial sources such as Ambion, Dharmacon, Promega, Invitrogen, Ziagen, and GenScript as well as noncommercial sources, such as EMBOSS, The Wistar Institute, Whitehead Institute, and others.

For example, design can be based on the following considerations.
25 Typically shorter sequences, i.e., less than about 30 nucleotides are selected. The coding region of the mRNA is usually targeted. The search for an appropriate target sequence optionally begins 50-100 nucleotides downstream of the start codon, as untranslated region binding proteins and/or translation initiation complexes may interfere with the binding of the siRNP endonuclease complex. Some algorithms,
30 e.g., based on the work of Elbashir et al., *supra*, search for a 23-nt sequence motif AA(N₁₉)TT (N, any nucleotide) and select hits with approximately 50% G/C-content (30% to 70% G/C-content can also be used for selection). If no suitable sequences are

found, the search is extended using the motif NA(N21). The sequence of the sense RNAi corresponds to (N19)TT or N21 (position 3 to 23 of the 23-nt motif), respectively. In the latter case, the 3' end of the sense siRNA is converted to TT.

5 Other algorithms preferentially select RNAi molecules corresponding to the target motif NAR(N17)YNN, where R is purine (A, G) and Y is pyrimidine (C, U). The respective 21-nt sense and antisense RNAi therefore begin with a purine nucleotide and can also be expressed from polymerase III expression vectors without a change in targeting site; expression of RNAs from polymerase III promoters is only efficient when the first transcribed nucleotide is a purine.

10 Other nucleic acids, e.g., ribozymes or antisense, can also be designed based on known principles. For example, Sfold (see, for example, Ding et al., *Nucleic Acids Res.* 32 Web Server issue:W135-W141; Ding and Lawrence, *Nucl. Acids Res.* 31: 7280-7301, 2003; and Ding and Lawrence, *Nucl. Acids Res.* 20:1034-1046, 2001) provides programs relating to designing ribozymes and antisense, as well as RNAi
15 molecules. Examples of antisense RNA molecules that target $\alpha 4$ integrin include a nucleic acid sequence that is complementary to a nucleic acid sequence that is substantially identical to all or part of the mRNA sequence of $\alpha 4$ integrin (SEQ ID NO: 12 or SEQ ID NO: 35), may consist of at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, or even 100 or more nucleotides; and, in particular, may be complementary to
20 nucleotides 1-25, 50-75, 50-100, 50-150, 50-1000, or 50-2000 of SEQ ID NO: 12 or SEQ ID NO: 35.

An additional class of nucleic acid inhibitors are peptide-nucleic acids. Peptide-nucleic acids are molecules which include a nucleic acid sequence that is complimentary to a sequence substantially identical to all or a part of the mRNA
25 nucleic acid sequence of a target protein (e.g., an $\alpha 4$ integrin). Peptide-nucleic acids that are effective as integrin antagonists, have a nucleic acid sequence that is complimentary to a sequence substantially identical to all or a part of the mRNA of $\alpha 4$ integrin (SEQ ID NO: 12 or SEQ ID NO: 35), contain at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, or even greater than 100 nucleotides; and promote a decrease in
30 $\alpha 4$ integrin activity or expression. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos.: 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by

reference. Further teaching of PNA compounds can be found in Nielsen et al., *Science*, 254, 1497 (1991).

Small Molecule Inhibitors

5 Another class of integrin antagonists suitable for use with the present invention include small molecule inhibitors. Non-limiting exemplary small molecule inhibitors suitable for use with the present invention include: the CS-1 peptidomimetics disclosed in PCT Publication Nos: WO 96/15973 and WO 96/06108; U.S. Patent Nos: 5,821,231; 5,936,065, and 5,869,448 (each herein incorporated by
10 reference); the semi-peptidic inhibitors disclosed in PCT International Pub. No. WO 97/03094; the VLA-4 inhibitors disclosed in PCT International Pub. No. WO 96/22966, which uses the LDV tripeptide as a core group; cyclic peptides from 5 to 13 residues modeled after a portion of the CS1 peptide and containing a free acid and the closely related compounds disclosed in PCT International Publication Nos: WO
15 96/00581, WO 97/49731, and WO 96/20216; and the cyclic tetrapeptide dimers, which comprise cyclic dimeric peptides in which a peptide 1 and peptide 2 independently represent a tetrapeptide juxtaposed in parallel or antiparallel orientation by means of two linking moieties as disclosed in PCT International Pub. No. WO 97/02289.

20 Another class of integrin antagonists suitable for use with the present invention include the sulfonylated-Pro-Phe compounds as disclosed in U.S. Patent No. 6,489,300 (herein incorporated by reference); sulfonylated dipeptide compounds disclosed in PCT International Publication No. WO 99/06437; dipeptide compounds disclosed in PCT International Publication Nos: WO 99/06432, WO 99/06433, and
25 WO 99/06435; the tyrosine derivatives disclosed in PCT International Publication No. WO 98/54207; and the phenylalanine derivatives disclosed in U.S. Patent No. 6,174,794 (herein incorporated by reference) and PCT International Publication Nos: WO 99/37618, WO 99/35163, and WO 99/43642; the substituted phenylalanine compounds disclosed in PCT International Publication No. WO 99/06431; the 4-
30 amino-phenylalanine type compounds disclosed in PCT International Publication No. WO 99/06434; the N-aroylphenylalanine derivatives and closely related compounds disclosed in PCT International Publication Nos: WO 99/10312 and WO 99/10313;

and the cyclic amino acids disclosed in PCT International Publication No. WO 99/26615 and the closely related compounds using β -amino acids disclosed in WO 98/153814, WO 99/26921, and WO 99/33789 are suitable for use in the present invention.

5 Another exemplary class of small molecule integrin antagonists include the 5-ring heterocycles and related compounds disclosed in European Patent Application Nos: EP 842 943, EP 842 944 and EP 842 945; and the heterocyclic amide compounds as disclosed in PCT International Publication No. WO 98/53814.

10 Additional small molecule inhibitors for use as integrin antagonist in the present invention are disclosed in, e.g., U.S. Patent Publication Nos: 2003/0130349 and 2002/0049236 (herein incorporated by reference), and PCT International Publication Nos: WO 98/04247, WO 98/04913, WO 99/37605, WO 99/36393, WO 99/24398, WO 98/42656, and WO 96/01544. In addition, the substituted anilides as disclosed in PCT International Publication No. WO 99/23063; the carbamoyloxy
15 compounds disclosed in PCT International Publication No. 99/06390; the benzyl compounds disclosed in PCT International Publication No. WO 99/06436; the imidazolidine derivatives and substituted imidazoline derivatives disclosed in European Patent Application Nos: EP 903 353 and EP 918 059; the biarylalkanoic acids disclosed in WO 98/53817; the sulfonamide compounds as disclosed in WO
20 98/53818 and the closely related azapeptide acids as disclosed in WO 99/20272; the 4-substituted-4-piperidine carboxamide derivatives disclosed in PCT International Publication No. WO 99/25685; the substituted pyrrole derivatives disclosed in PCT International Publication No WO 99/26922; and the para-aminomethylaryl
25 carboxamide derivatives disclosed in WO 99/26923 are also suitable for use with the present invention.

 Another class of integrin antagonists suitable for use with the present invention include the conjugates comprising more than one integrin antagonist covalently attached to a polymer as described in U.S. Patent Publication No. 2006/0013799 (herein incorporated by reference).

30 Further small molecule inhibitors can be identified using screening or biological assays (e.g., ligand binding assays, protein or receptor activity assays, and other assays as known in the art and described herein). For example, an integrin

antagonist may be identified by screening commercially available chemical or small molecule libraries.

Additional antibodies, blocking peptides, nucleic acid inhibitors, or small molecules shown to be potent inhibitors of $\alpha 4$ mediated integrin adhesion to VCAM-1, CS-1, or osteopontin, using the assays disclosed herein are suitable for use with the methods of the invention for the treatment of patients with multiple sclerosis as described herein.

Functional Assays for Integrin Antagonists

A variety of assays are available to establish the antagonistic activity of an integrin antagonist for use in the compositions and methods of the present invention. Non-limiting exemplary assays include the Jurkat-endothelial cell adhesion assay and the Jurkat-CS-1 assay as disclosed in U.S. Patent Publication No. 2003/0130349 (herein incorporated by reference), and the EAE model disclosed in greater detail in Example 2. PCT International Publication No. WO 98/53817 further discloses an assay for determining antagonism of $\alpha 4\beta 7$ dependent binding to VCAM-Ig fusion protein.

The Jurkat-endothelial cell adhesion assay measures the adhesive interactions of a T-cell line (Jurkat), which express the $\alpha 4\beta 1$ integrin, to endothelial monolayers in the presence of test compounds to identify integrin antagonists suitable for use with the present invention. Briefly, the test compounds are added in increasing concentration to the T-cells, and then the T-cell/compound mixture is added to interleukin-1 stimulated endothelial cell monolayers. The plates are incubated, washed, and the number of attached T-cells is quantitated. The assay directly demonstrates the cell adhesion inhibitory or modulatory activity of integrin antagonists at various concentrations for use with the present invention.

The Jurkat-CS-1 assay, described in U.S. Patent Publication No. 2003/0130349 is a modification of the previously published method of Cardarelli et al. (*J. Biol. Chem.* 269:18668-18673, 1994; and *Proc. Natl. Acad. Sci. U.S.A.* 83:2647-2651, 1986). Briefly, a CS-1 peptide, CLHPGEILDVPST, and the scrambled control peptide CLHGPIELVSDPT are immobilized onto microplates using a heterobifunctional crosslinker (e.g., 3-(2-pyridyldithio)propionic acid

N-hydroxysuccinimide ester (SPDP) as described by Pierschbacher et al., *Proc. Nat. Acad. Sci. U.S.A.* 80:1224-1227, 1983). Briefly, the procedure involves coating the microtiter plates with horse-serum albumin (HSA) for 2 hours, washing the plates, and derivitizing with 10 µg/ml SPDP for 1 hour. After washing the derivitized plates, a recently dissolved 100 µg/ml cysteine containing CS-1 or control peptide solution is added and allowed to crosslink to the plates overnight at 4 °C. The unbound peptide is removed by washing and the unreacted sites are blocked with a 2.5 mg/ml solution of bovine-serum albumin (BSA). A known number of Jurkat cells in a defined volume (e.g., 100 µl of cells at 2.5×10^6 cells/ml) are mixed with a desired concentration of the integrin antagonist and added to the peptide-coated dishes and incubated for 1 hour at 37 °C. Following incubation, the plates are washed and attached cells are fixed with 3% paraformaldehyde in PBS and stained with toluidine blue overnight at room temperature. Cell attachment is quantitated via optical density at 590 nm using a vertical pathway spectrophotometer.

Preferred integrin antagonists are those which have low IC50 values in the Jurkat endothelial cell assay or the CS-1 assay, or at least moderate activity in both assays. Typically, an integrin antagonist suitable for use with the present invention has activity at less than 50 µM in the CS-1 assay or at less than 500 µM in the endothelial assay.

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Supplemental Therapeutic Agents for Use in the Combination Therapies of the Invention

In addition to an AFP (or a biologically active fragment, derivative, or analog thereof) and an integrin antagonist, the combination therapies of the invention can also include the administration of an antagonist (e.g., an antibody, blocking peptide, nucleic acid inhibitor, or small molecule) to CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6.

For example, the compositions of the invention may include, or the methods of the invention may involve the administration of, a CD80 antagonist as a supplemental therapeutic agent. CD80 provides a co-stimulatory signal to the T-cell receptor (Lanier et al., *J. Immunol.* 154:97-105, 1995). Myeloid dendritic cells from MS

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patients have increased CD80 expression (Karni et al., *J. Immunol.* 177:4196-4202, 2006); therefore, CD80 is an attractive target for treatment of MS.

The compositions of the invention may also include, and the methods of the invention may also involve the administration of, an antagonist of P-selectin. P-selectin is a protein which plays a role in recruitment of leukocytes to the site of injury and is also a target for MS therapy.

In addition, compositions of the invention may also include, and the methods of the invention may also involve the administration of, a sphingosine-1-phosphate-receptor-1 (S1P1) antagonist. S1P1 plays a role in thymocyte and lymphocyte maturation. An inhibitor of S1P1 has been shown to deprive thymocytes and lymphocytes of the signal to egress from lymphoid organs (Brinkman et al., *Am. J. Transplant.* 4:1019-1025, 2004). Therefore, an inhibitor of S1P1 can be included in the AFP/integrin antagonist treatment regimen described herein.

A hyaluronate receptor (CD44) antagonist can also be included in the compositions of the invention or administered with an AFP and integrin antagonist in the methods of the invention. Hyaluronate receptor is a protein which plays a role in leukocyte extravasation in inflammatory central nervous system disease (Brennan et al., *Immunology* 98:427-435, 1999). Hyaluronate receptor is also highly expressed in the T cells of MS patients (Soilu-Hanninen et al., *J. Neuroimmunol.* 166:189-192, 2005). Therefore, an antagonist of hyaluronate receptor can also be included in the combination therapies of the invention.

In another example, the compositions and methods of the invention may include a leukocyte function antigen-1 (LFA-1) antagonist. LFA-1 is expressed on lymphocytes and plays a major role in the activation and trafficking of T-lymphocytes to the site of inflammation. LFA-1 has also been considered as a therapeutic target for MS (Avolio et al., *J. Neurol. Sci.* 186:65-73, 2001; Lujan et al., *Mult. Sclerosis* 4:239-242, 1998); therefore, an antagonist of LFA-1 may also be included in the combination therapies of the invention.

An antagonist of CD11/CD18 may also be used in conjunction with the compositions and methods of the present invention. CD11/CD18 is a heterodimeric integrin receptor which consists of one of three α subunits (CD11a, CD11b, or CD11c) and one β subunit (CD18). The CD11/CD18 receptor is involved in crucial

leukocyte adhesion functions, including chemotaxis, phagocytosis, adhesion to the endothelium, aggregation, and cell-mediated cytotoxicity. One humanized monoclonal antibody to CD11/CD18 is already in phase I MS clinical trials (Bowen et al., *Clin. Pharmacol. Ther.* 64:339-346, 1998).

5 Additionally, the compositions and methods of the invention may include CD20 antagonist. CD20 is a B-lymphocyte surface molecule which plays a role in the development and differentiation of B-cells into plasma cell. Monoclonal antibodies to CD20 include rituxumab, ibritumomab tiuxetan, and tositumomab. Rituximab (Rituxan[®], by Genentech) is currently being studied in a multi-center phase II/III trial
10 involving primary-progressive MS, and a phase II trial in secondary-progressive MS. A case report for the use of rituximab on MS was reported in Stuve et al. (*Arch Neurol.* 2005; 62:1620-1623). Therefore, an antagonist of CD20 can also be included in the combination therapies of the invention.

 In another example, the compositions and methods of the invention may
15 include a CD86 antagonist. CD86 (cluster of differentiation 86) is a protein that provides a costimulatory signal necessary for T cell activation and survival. CD86 principal mode of action is by binding to CD28. CD86 and CD80 provide the necessary stimuli to prime T cells against antigens presented by antigen-presenting cells. The CD86 pathway is currently being evaluated as a potential target for the
20 treatment of MS. Therefore, an antagonist of CD86 can also be used in conjunction with the combination therapies of the invention.

 The compositions and methods of the invention may also include an
antagonist of ICOS ligand. ICOS ligand is a membrane-protein that is expressed on
activated monocytes and dendritic cells. ICOS ligand functions as a costimulatory
25 signal for T-cell proliferation and cytokine secretion and induces B-cell proliferation and differentiation into plasma cells. ICOS ligand may play an important role in mediating local tissue response to inflammatory conditions and may modulate the secondary immune response by co-stimulating memory T-cell function. Therefore, an
antagonist to ICOS ligand can also be used in conjunction with the combination
30 therapies of the invention.

The compositions and methods of the invention may also include an CCR2 (chemokine (C-C motif) receptor 2) antagonist. CCR2 is a chemokine receptor that mediates recruitment of both infiltrating macrophages and resident microglia to specific sites of central nervous system inflammation. ChemoCentryx has initiated a Phase 1 for the use of CCX915, a small molecule antagonist of CCR2, in the treatment of MS. Humanized anti-CCR2 antibodies are described in U.S. Patent No. 6,406,865, herein incorporated by reference. Therefore, an antagonist to CCR2 can also be used in conjunction with the combination therapies of the invention.

Additionally, the compositions and methods of the invention may include a CXCR3 antagonist. CXCR3 is a chemokine receptor that is expressed on activated T lymphocytes and NK cells. CXCR3 regulates leukocyte trafficking and the binding of chemokines to CXCR3 induces various cellular responses, most notably integrin activation, cytoskeletal changes and chemotactic migration. CXCR3-ligand interaction attracts Th1 cells and promotes Th1 cell maturation. CXCR3 has been implicated for a role in the development of MS. Several antagonists of CXCR3 are known in the art, including, small molecules (e.g., those described in WO 06/088837) and humanized antibodies (e.g., those described in WO 05/030793). Therefore, an antagonist to CXCR3 can also be used in conjunction with the combination therapies of the invention.

Finally, the compositions and methods of the invention may also include a CCR5 antagonist. CCR5 is a chemokine receptor expressed on T cells, macrophages, dendritic cells and microglia. CCR5 may play a role in inflammatory responses to infection. A role for CCR5 in the pathogenesis of MS has been suggested (Trebst et al., *Am. J. Pathol.* 159:1701-1710, 2001). Several antagonists to CCR5 are known in the art, including small molecule inhibitors (see, e.g., EP 1 539 695) and humanized antibodies (see, e.g., U.S. Patent No. 7,122,185, herein incorporated by reference). Therefore, an antagonist to CCR5 can also be used in conjunction with the combination therapies of the invention.

30 **Pharmaceutical Compositions**

The present invention also relates to a pharmaceutical composition that contains a therapeutically effective amount of an AFP and/or an integrin antagonist. The active ingredients, AFP and an integrin antagonist, may be present in the same

pharmaceutical composition (a single dosage form) or separate pharmaceutical compositions (separate dosage forms) to be administered coextensively or separately. In addition, the composition can include one or more different AFPs or integrin antagonists. The compositions can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the compositions for proper formulation. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed., 1985. For a brief review of methods for drug delivery, see, Langer, *Science* 249: 1527-1533, 1990.

10 The pharmaceutical compositions can be formulated for parenteral, intranasal, topical, oral, or local administration, such as by a transdermal means, for prophylactic and/or therapeutic treatment. Commonly, the pharmaceutical compositions are administered parenterally (e.g., by intravenous, intramuscular, or subcutaneous injection), by oral ingestion, or by topical application at areas affected by MS. Thus, the invention features compositions for parenteral administration that include an AFP and/or an integrin antagonist dissolved or suspended in an acceptable carrier, preferably an aqueous carrier, e.g., water, buffered water, saline, PBS, and the like. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, detergents, and the like. The invention also features compositions for oral delivery, which may contain inert ingredients such as binders or fillers for the formulation of a tablet, a capsule, and the like. Furthermore, this invention features compositions for local administration, which may contain inert ingredients such as solvents or emulsifiers for the formulation of a cream, an ointment, and the like. In different embodiments of the invention, the AFP and the integrin antagonist may be administered in the same or separate compositions for administration via the same or two different routes of administration.

 Compositions of the invention may be sterilized by conventional sterilization techniques or they may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and

8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of an AFP and/or an integrin antagonist, such as in a sealed package of tablets or capsules (e.g., a blister pack). The composition in solid form can also be packaged
5 in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

The compositions of the invention containing an effective amount of an AFP and/or an integrin antagonist can be administered for prophylactic and/or therapeutic treatments. In prophylactic applications, compositions of the invention containing an
10 AFP and/or an integrin antagonist are administered to a patient susceptible to or otherwise at risk of developing MS. Such an amount is defined to be a “prophylactically effective dose.” In this use, the precise amounts again depend on the patient’s state of health, but generally range from about 0.5 mg to about 400 mg of an AFP per dose (e.g., 10 mg, 50 mg, 100 mg, 200 mg, 300 mg, or 400 mg per dose)
15 and from about 0.1 mg to about 500 mg of an integrin antagonist per dose (e.g., 10 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg per dose). A dose of the AFP and/or integrin antagonist can be administered prophylactically to a patient one or more times per hour, day, week, month, or year (e.g., 2, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per hour, day, week, month, or year). More commonly, a single dose per
20 week of an AFP and/or an integrin antagoist is administered to a patient.

In therapeutic applications, compositions of the invention can be administered to a patient already suffering from MS in an amount sufficient to cure or at least partially arrest one or more of the symptoms of the disease and their complications. An amount adequate to accomplish this purpose is defined as a
25 “therapeutically effective dose.” Amounts effective for this use may depend on the severity of the disease or condition and the general state of the patient, but may range from about 0.5 mg to about 400 mg of an AFP per dose (e.g., 10 mg, 50 mg, 100 mg, 200 mg, 300 mg, or 400 mg per dose) and from about 0.1 mg to about 500 mg of an integrin antagonist per dose (e.g., 10 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, or
30 500 mg per dose).

In several embodiments, the patient may receive an AFP (with or without an integrin antagonist) in the range of about 0.5 to about 400 mg per dose one or more

times per week (e.g., 2, 3, 4, 5, 6, or 7 or more times per week), preferably about 5 mg to about 300 mg per dose one or more times per week, and even more preferably about 5 mg to about 200 mg per dose one or more times per week. The patient may also receive a biweekly dose of an AFP in the range of about 50 mg to about 800 mg or a monthly dose of an AFP in the range of about 50 mg to about 1,200 mg.

In other embodiments, an AFP may be administered to a patient in a typical dosage range of about 0.5 mg to about 400 mg per dose per week, about 1.0 mg to about 300 mg per dose per week, about 5 mg to about 200 mg per dose per week, about 10 mg to about 100 mg per dose per week, about 20 mg to about 80 mg per dose per week, about 100 mg to about 300 mg per dose per week, or about 100 mg to about 200 mg per dose per week. An AFP may be administered in the range of about 0.5 mg to about 100 mg per dose every other day, preferably about 5 mg to about 75 mg per dose every other day, more preferably about 10 mg to about 50 mg per dose every other day, and even more preferably 20 mg to about 40 mg per dose every other day. An AFP may also be administered in the range of about 0.5 mg to about 100 mg per dose three times per week, preferably about 5 mg to about 75 mg per dose three times per week, more preferably about 10 mg to about 50 mg per dose three times per week, and even more preferably about 20 mg to about 40 mg per dose three times per week.

In several embodiments, the patient may receive an integrin antagonist (with or without an AFP) in the range of about 0.1 to about 500 mg per dose per one or more times per week (e.g., 2, 3, 4, 5, 6, or 7 or more times per week), preferably about 0.1 mg to about 400 mg per dose one or more times per week, or about 0.1 mg to about 300 mg per dose one or more times per week, more preferably about 1 mg to about 200 mg per dose one or more times per week, or most preferably about 5 mg to about 100 mg per dose one or more times per week. The patient may also receive a biweekly, triweekly, or monthly dose of an integrin antagonist in the range of about 0.1 mg to about 1.5 g, preferably a dose in the range of about 1 mg to about 1,000 mg, more preferably a dose in the range of about 5 mg to about 800 mg. Preferably, the dose of an integrin antagonist (e.g., natalizumab) is about 300 mg per dose every four weeks.

In some embodiments where the integrin antagonist administered is natalizumab, the patient receives a typical dosage in the range of about 15 μ g to about 150 mg per dose per week, preferably about 1 mg to about 120 mg per dose per week, more preferably about 2 mg to about 100 mg per dose per week, and even more preferably about 5 mg to 80 mg per dose per week. In another embodiment, natalizumab is administered in the range of about 200 mg to 400 mg per dose every four weeks. The patient may also receive an AFP polypeptide in the range of about 0.5 mg to about 200 mg per dose per week, preferably about 5 mg to about 100 mg per dose per week, more preferably about 10 mg to about 80 mg per dose per week, and even more preferably about 20 mg to about 70 mg per dose per week.

A dose of the AFP and/or integrin antagonist can be administered therapeutically to a patient one or more times per hour, day, week, month, or year (e.g., 2, 4, 5, 6, 7, 8, 9, 10, 11, or 12 times per hour, day, week, month, or year). More commonly, a single dose per week of an AFP and/or an integrin antagonist is administered to a patient.

In non-limiting embodiments of the methods of the present invention, an AFP and an integrin antagonist are administered to a patient: continuously for 1, 2, 3, or 4 hours; 1, 2, 3, or 4 times a day; every other day or every third, fourth, fifth, or sixth day; 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times a week; biweekly; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 times a month; bimonthly; 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times every six months; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 times a year; or biannually. The AFP (or biologically active fragment thereof) and the integrin antagonist may be administered at different frequencies during a therapeutic regime (i.e., administered at a higher frequency in the later stages of MS (e.g., administered once a week in the initial stages of MS and administered three times a week a later stage of MS) or administered at a higher frequency in the early stages of MS (e.g., administered three times a week during the initial stages of MS and administered once a week at a later stage of MS)). In additional embodiments, the AFP and the integrin antagonist may be administered to a patient at the same frequency or at a different frequency.

The amount of integrin antagonist and AFP polypeptide required to achieve the desired therapeutic effect depends on a number of factors, such as the specific integrin antagonist(s) chosen, the mode of administration, and clinical condition of the recipient. A skilled artisan will be able to determine the appropriate dosages of
5 integrin antagonist and AFP (or biologically active fragment thereof) to achieve the desired results.

The coadministration of an AFP and an integrin antagonist according to the methods of this invention refers to the use of the two active ingredients in the same general time period or using the same general administration method. It is not always
10 necessary, however, to administer both at the exact same time. For instance, if an AFP and an integrin antagonist are administered to a patient suffering from MS in two separate pharmaceutical compositions, the two compositions need not be delivered to the patient during the same time period or even during two partially overlapping time periods. In some cases, the administration of the second agent (e.g., an AFP) may
15 begin shortly after completion of the administration period for the first agent (e.g., an integrin antagonist, such as natalizumab), or *vice versa*. The time gap between the two administration periods may vary from one or more hours, days, weeks, or months. In some cases, one therapeutic agent (e.g., an AFP) may be administered first with the second (e.g., an integrin antagonist, such as natalizumab) in a separate time period,
20 and subsequently administered without the second in a following period. A typical schedule of this type may require a higher dosage of the first therapeutic agent in the first, co-administration period, and a lower dosage in the second period, and *vice versa*. The same applies for the second agent.

Single or multiple administrations of the compositions of the present
25 invention that include an effective amount of an AFP and/or an integrin antagonist can be carried out with the dose levels and the pattern being selected by the treating physician. The dose and administration schedule can be determined and adjusted based on the severity of MS in a patient, which may be monitored throughout the course of treatment according to the methods commonly practiced by clinicians or
30 those described herein.

In addition to an AFP and/or an integrin antagonist, the composition may also include an antagonist to CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6. The antagonist to
5 CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 may be an antibody, a binding peptide, a nucleic acid inhibitor, or a small molecule inhibitor; which can be identified according to the same methods described above with regard to an integrin antagonist.

10 The patient may receive an antagonist to CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 in the range of about 0.1 to about 500 mg per dose per one or more times per hour, day, week, or month (e.g., 2, 3, 4, 5, 6, or 7 times per hour, day, week, or month), about
15 0.1 to about 400 mg per dose one or more times per week, about 0.1 to about 300 mg per dose one or more times per week, about 1 to about 200 mg per dose one or more times per week, or about 5 to about 100 mg per dose one or more times per week. The patient may also receive a biweekly, triweekly, or monthly dose of an antagonist to CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-
20 1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 in the range of about 0.1 mg to about 1.5 g, preferably a dose in the range of about 1 mg to about 1,000 mg, more preferably a dose in the range of about 5 mg to about 800 mg.

Kits of the Invention

25 The invention also features kits for treating or reducing the symptoms of, or severity of, MS according to the combination treatment method of the present invention. The kits typically include a pharmaceutical composition containing an AFP and a pharmaceutical composition containing an integrin antagonist, each in a therapeutically effective amount for treating MS. In one example, effective amounts
30 of an AFP and an integrin antagonist can be present in a single pharmaceutical composition. Optionally, the pharmaceutical composition(s) may contain one or more pharmaceutically acceptable excipients.

Preferably, the kits include multiple packages of the single-dose pharmaceutical composition(s) containing an effective amount of an AFP and/or an integrin antagonist. Optionally, instruments or devices necessary for administering the pharmaceutical composition(s) may be included in the kits. For instance, a kit of this invention may provide one or more prefilled syringes containing an effective amount of an AFP and one or more prefilled syringes containing an effective amount of an integrin antagonist. Alternatively, the kit may provide one or more prefilled syringes containing an effective amount of an AFP and tablets containing a dosage of an integrin antagonist. Furthermore, the kits may also include additional components such as instructions or administration schedules for a patient suffering from MS to use the pharmaceutical composition(s) containing an AFP and/or an integrin antagonist.

In addition to an AFP and/or an integrin antagonist, the kit may also include an antagonist of CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6. The antagonist of CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, LFA-1, CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 may be an antibody, a binding peptide, a nucleic acid inhibitor, or a small molecule inhibitor.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, methods, and kits of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

The following examples are meant to illustrate the invention and should not be construed as limiting.

EXAMPLES

The following two examples are provided by way of illustration only and not by way of limitation. Those skilled in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

Example 1

Functional Test of a Recombinant AFP Using MOG-EAE Mouse Model

Efficacy experiments of a recombinant version of human AFP (recombinant human AFP, rhAFP, produced according to U.S. Patent Application Publication No. 20040098755) were performed in a mouse model in which experimental autoimmune encephalomyelitis (EAE) is induced by immunization of susceptible strains of mice with myelin antigen or peptides (myelin oligodendrocyte protein [MOG] or proteolipid protein [PLP]). This assay system is useful for determining the functionality of an AFP of this invention.

Purpose of Study: The purpose of these studies was to test compounds intended as therapeutics for MS, an autoimmune disease directly associated with the major histocompatibility complex (MHC) class II molecule HLA-DR2. The mouse experimental autoimmune encephalomyelitis (EAE) model was chosen for its relevance to human MS.

EAE Model Description and Features: Experimental Allergic Encephalomyelitis (EAE) is a demyelinating disease of the central nervous system. It serves as the animal model MS (Goverman, *Lab. Anim. Sci.* 46:482, 1996; and Paterson, *Clin. Immunol. Rev.* 1:581, 1981). EAE can assume an acute, chronic, or relapsing-remitting disease course that is dependent upon the method of induction and type of animal used. Disease induction results in escalating degrees of ascending animal paralysis. The resulting paralysis is debilitating, but not painful, and most animals will show some degree of recovery even from advanced stages of EAE. Paralysis usually begins with a weakened tail, gradually followed by hind limb weakness progressing to paralysis, and less frequently front limb paralysis. EAE disease progression can be monitored with a scoring system that starts with the normal condition and ends when the mice become moribund. Since the severity of the disease varies from animal to animal there is no way to reliably predict whether an animal will recover. As a result, close monitoring is needed in this animal model.

EAE can be induced with components of the central nervous system (Levine and Sowinski, *J. Immunol.* 110:139, 1973; and Fritz et al., *J. Immunol.* 130:1024, 1983) or peptides (Tuohy et al., *J. Immunol.* 140:1868, 1988; McFarlin et al., *Science* 179:478, 1973; and Linington et al., *Eur. J. Immunol.* 23:1364, 1993) and also via T

cell transfer from one animal to another animal (Yamamura et al., *J. Neurol. Sci.* 76:269, 1986). Complete Freund's adjuvant (CFA) must be used with the proteins or peptides to effectively trigger the autoimmune response. CFA is often used in combination with pertussis toxin (Lee, *Proc. Soc. Exp. Biol. Med.* 89:263, 1955; and
5 Kamradt et al., *J. Immunol.* 147:3296, 1991) to increase the efficiency of immunization. It is not possible to administer analgesics to lessen any pain that may be associated with the CFA injections, as most analgesics affect the immune response that is an essential component of the model (Billiau, *J. Leukoc. Biol.* 70:849, 2001; and Naiki et al., *Int. J. Immunopharmacol.* 13:235, 1991).

10 Experimental Design and Methods

Induction of experimental MS-like disease syndrome: 50 female mice (C57BL6) between 6 and 8 weeks of age, were immunized subcutaneously on day 0 (left paralumbar region) and day 7 (right paralumbar region) with an emulsion (125 µg per mouse) of myelin oligodendrocyte glycoprotein (mMOG-35-55 peptide) in
15 CFA containing heat-killed *Mycobacterium tuberculosis* H37RA. In addition, mice were given pertussis toxin (Ptx) intraperitoneally on days 0 and 2 post-immunization.

Disease monitoring: The initial signs of disease (weakened tail or paralysis) were observed beginning ~10 days after the first immunization. Actively immunized mice were assessed daily through day 30 for clinical signs of EAE
20 according to an established scale:

- | | |
|----|-----------------------------------------------------------|
| 0 | No disease |
| 1 | Tail weakness |
| 2 | One or two weak hind limbs, sufficient to impair righting |
| 3 | One of two hind limb paralysis |
| 25 | 4 One or two front limb paralysis |
| 5 | Moribund or dead |

The 50 mice were randomized into 5 groups of 10 mice each. One group of 10 animals received a saline injection to serve as an untreated EAE disease control.
30 Four compounds were evaluated in the remaining 4 groups.

Mice were injected with 100 μ l of test rhAFP or control material IP daily. These compounds are: 1-500 μ g rhAFP or 1-500 μ g human serum albumin (control). Furthermore, depleting antibodies to specific leukocyte subsets (e.g., CD4⁺ cells) are employed as additional control(s) in some studies.

- 5 Mice were used in this study to assess the effect of rhAFP on disease progression in an experimental model of MS (EAE). Without treatment it was expected that many of the animals would develop signs and symptoms of EAE, namely progressive encephalopathy and paralysis.

10 In addition to daily monitoring of the animals for disease progression over a 30-day time course, animals were sacrificed at the end of the study and central nervous system tissues (brain and spinal cord) were harvested for immunohistochemical analysis of infiltrating, disease-causing cells (i.e., CD4⁺ T cells).

15 Additionally, six to ten-day short-term studies were employed to assess the effect(s) of rhAFP administration on the induction phase of disease. In these shorter studies, draining lymph node cells were harvested for FACs analysis of immunologic cell subsets including but not limited to: T cells, CD4⁺ cells, regulatory T cells, and their activation markers. A fraction of harvested cells from each treatment group were assessed for *in vitro* proliferative response to a panel of stimuli to assess Ag-specific recall response to the immunizing antigen (Ag), MOG35-55, and Ag-nonspecific responses to a panel of mitogens (Concanavalin A, PHA, and LPS).
20 Supernatants from cultures set-up in the same fashion are analyzed for cytokines (e.g., IL-2, IL-4, or IFN γ).

Example 2

25 **Effect of AFP and an integrin antagonist in MOG-EAE Mouse Model**

The synergistic effect of recombinant human AFP and an integrin antagonist (e.g., an antibody, such as a surrogate anti-mouse antibody (e.g., an anti-VLA-4 antibody or a rat anti-mouse antibody, such as PS/2)) for treating EAE is tested in a study utilizing the MOG-EAE or PLP-EAE mouse model for MS.

The general experimental design is identical to Example 1. Briefly, 70 female mice (C57BL6) between 6 and 8 weeks of age are immunized subcutaneously on day 0 (left paralumbar region) and day 7 (right paralumbar region) with an emulsion (125 µg per mouse) of myelin oligodendrocyte glycoprotein (mMOG-35-55 peptide) in CFA containing heat-killed *Mycobacterium tuberculosis* H37RA.

The 70 mice are randomized into 7 groups of 10 mice each. One group of 10 animals receives a saline injection to serve as an untreated EAE disease control. Six different formulations are evaluated in the remaining 6 groups. The mice of group 1 receive a placebo; group 2 receives rhAFP at 10 µg/day; group 3 receives rhAFP at 100 µg/day; group 4 receives the integrin antagonist at 10 µg/day; group 5 receives the integrin antagonist at 100 µg/day; group 6 receives both rhAFP and the integrin antagonist at 10 µg/day and 10 µg/day, respectively; and group 7 receives both rhAFP and the integrin antagonist at 100 µg/day and 100 µg/day, respectively. The experimental design can alternatively include modifying (e.g., increasing or decreasing) the dosages of one or both of the rhAFP and the integrin antagonist during the administration period. For example, the mice could initially be administered a constant dose of rhAFP and an escalating dose (e.g., 0.1, 1.0, 10, 20, 50, or 100 µg/mouse given every other day) of the integrin antagonist (e.g., a mouse anti-α4 mAb) to determine if rhAFP enables the administration of a suboptimal dose of the integrin antagonist. As an alternative, the mice could initially be administered a constant dose of the integrin antagonist and an escalating dose of rhAFP.

The administration is by daily injections (interperitoneally or subcutaneously) from day 0 until the end of experiment at between days 40 and 60. All groups are scored daily for disease symptoms according to the scale as described in Example 1 for the duration of the study.

All mice are euthanized between days 40 and 60, and various organs and blood (e.g., spleen, knees, and hind and fore paws) are harvested for immunohistochemistry and immunological analysis.

Other Embodiments

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

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference in their entirety.

What is claimed is:

Claims

1. A method of treating a patient with multiple sclerosis comprising administering to said patient alpha-fetoprotein (AFP) or a biologically active fragment thereof and an integrin antagonist.
2. The method of claim 1, wherein said AFP or biologically active fragment thereof is recombinant human AFP.
3. The method of claim 1, wherein said AFP or biologically active fragment thereof is non-glycosylated.
4. The method of claim 1, wherein said integrin antagonist is an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor.
5. The method of claim 4, wherein said antibody is an anti- α 4 integrin antibody.
6. The method of claim 5, wherein said anti- α 4 integrin antibody is natalizumab.
7. The method of claim 1, wherein said method further comprises administering an antagonist of one or more of the following proteins: CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, and IL-6.
8. The method of claim 7, wherein said antagonist of CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, or IL-6 is an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor.

9. The method of claim 1, wherein said AFP or biologically active fragment thereof, or said integrin antagonist is administered intravenously, intramuscularly, orally, by inhalation, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, through use of suppositories, transbuccally, liposomally, adiposally, intraocularly, subcutaneously, intrathecally, topically, or through local administration.

10. The method of claim 1, wherein said AFP or biologically active fragment thereof, or said integrin antagonist is administered one or more times hourly, daily, weekly, biweekly, or monthly.

11. The method of claim 1, wherein said AFP or biologically active fragment thereof, and said integrin antagonist are administered coextensively or separately.

12. The method of claim 1, wherein said AFP or biologically active fragment thereof, and said integrin antagonist are administered in separate dosage forms.

13. The method of claim 1, wherein said AFP or biologically active fragment thereof and said integrin antagonist are administered in the same dosage form.

14. The method of claim 1, wherein said AFP or biologically active fragment thereof and said integrin antagonist are administered via two different routes of administration.

15. The method of claim 1, wherein said AFP or biologically active fragment thereof and said integrin antagonist are administered via the same route of administration.

16. The method of claim 1, wherein said AFP or biologically active fragment thereof is administered in the range of 0.5 mg to 400 mg per dose.

17. The method of claim 1, wherein said integrin antagonist is administered in the range of 0.1 mg to 500 mg per dose.

18. The method of claim 1, wherein said AFP or biologically active fragment thereof is administered prior to said integrin antagonist.

19. The method of claim 1, wherein said AFP or biologically active fragment thereof is administered after said integrin antagonist.

20. The method of claim 1, wherein said administering results in a loss of or reduction in severity of one or more symptoms of multiple sclerosis.

21. The method of claim 20, wherein said one or more symptoms of multiple sclerosis are selected from the group consisting of tingling, numbness, tremors, loss of balance, weakness in one or more limbs, blurred or double vision, slurred speech, swallowing problems, paralysis, lack of coordination, cognitive difficulties, fatigue, muscle spasms, dizziness, breathing problems, and seizures.

22. A composition comprising an AFP or a biologically active fragment thereof and an integrin antagonist.

23. The composition of claim 22, wherein said composition further comprises an antagonist to one or more of the following proteins: CD80, P-selectin, sphingosine-1-phosphate receptor-1, hyaluronate receptor, leukocyte function antigen-1 (LFA-1), CD11/CD18, CD20, CD86, ICOS ligand, CCR2, CXCR3, CCR5, CD40, CD154, CD28, IL-23, IL-17, and IL-6.

24. The composition of claim 22, wherein said AFP or biologically active fragment thereof is recombinant human AFP.

25. The composition of claim 22, wherein said AFP or biologically active fragment thereof is non-glycosylated.

26. The composition of claim 22, wherein said integrin antagonist is an antibody, a blocking peptide, a nucleic acid inhibitor, or a small molecule inhibitor.

27. The composition of claim 22, wherein said integrin antagonist is natalizumab.

28. The composition of claim 22, wherein said composition is formulated for intravenous, intramuscular, oral, parenteral, intraperitoneal, intraarterial, transdermal, sublingual, nasal, transbuccal, liposomal, adiposal, intraocular, subcutaneous, intrathecal, topical, or through suppository, inhalation, or local administration.

29. The composition of claim 22, wherein said AFP or biologically active fragment thereof is in a dose of between 0.5 mg and 400 mg and said integrin antagonist is in a dose of between 0.1 mg to 500 mg.

30. A kit comprising an AFP or a biologically active fragment thereof and an integrin antagonist, and instructions for administration to said patient.

31. The kit of claim 30, wherein said AFP or biologically active fragment thereof is recombinant human AFP.

32. The kit of claim 30, wherein said APF or biologically active fragment thereof is non-glycosylated.

33. The kit of claim 30, wherein said integrin antagonist is natalizumab

34. The kit of claim 30, wherein said AFP or biologically active fragment thereof or said integrin antagonist is formulated for intravenous, intramuscular, oral, parenteral, intraperitoneal, intraarterial, transdermal, sublingual, nasal, transbuccal, liposomal, adiposal, intraocular, subcutaneous, intrathecal, topical, or through suppository, inhalation, or local administration.

35. The kit of claim 30, wherein said AFP or biologically active fragment thereof and said integrin antagonist are present in the same composition.

36. The kit of claim 30, wherein said AFP or biologically active fragment thereof and said integrin antagonist are formulated in separate compositions.

37. The kit of claim 30, wherein said AFP or biologically active fragment thereof and said integrin antagonist are formulated for two different routes of administration.

38. The kit of claim 30, wherein said AFP or biologically active fragment thereof and said integrin antagonist are formulated for the same route of administration.

FIGURE 1

Mature Human AFP (SEQ ID NO: 1)

N indicates the asparagine 233 glycosylation site

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1  RTLHRNEYGI  ASILDSYQCT  AEISLADLAT  IFFAQFVQEA
41  TYKEVSKMVK  DALTAIEKPT  GDEQSSGCLE  NQLPAFLEEL
81  CHEKEILEKY  GHSDCCSQSE  EGRHNCFLAH  KKPTPAS IPL
121 FQVPEPVTSC  EAYEEDRETF  MNKFIYEIAR  RHPFLYAPTI
161 LLWAARYDKI  IPSCCKAENA  VECFQTKAAT  VTKE LRESSL
201 LNQHACAVMK  NFGTRTFQAI  TVTKLSQKFT  KVNFT EIQKL
241 VLDVAHVHEH  CCRGDVLDCL  QDGEKIMSYI  CSQQDTLSNK
281 ITECCKLTTL  ERGQCIHAE  NDEKPEGLSP  NLNRFLGDRD
321 FNQFSSGEKN  IFLASFVHEY  SRRHPQLAVS  VILRVAKGYQ
361 ELLEKCFQTE  NPLECQDKGE  EELQKYIQES  QALAKRSCGL
401 FQKLGEYYLQ  NAFLVAYTKK  APQLTSSELM  AITRKMAATA
441 ATCCQLSEDK  LLACGEGAAD  IIIGHL CIRH  EMTPVNPGVG
481 QCCTSSYANR  RPCFSSLVVD  ETYVPPAFSD  DKFIFHKDLC
521 QAQGVALQTM  KQEFLINLVK  QKPQITEEQL  EAVIADFSGL
561 LEKCCQGQEQ  EVCFAEEGQK  LISKTR AALG  V

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Human AFP mRNA (SEQ ID NO: 2)

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1  tccatattgt  gcttcacca  ctgccaataa  caaaataact
41  agcaaccatg  aagtgggtgg  aatcaat ttt  tttaat tttc
81  ctactaaatt  ttactgaatc  cagaacactg  catagaaatg
121 aatatggaat  agcttccata  ttggattcct  accaatgtac
161 tgcagagata  agtttagctg  acctggctac  catat ttttt
201 gccagtttg  ttcaagaagc  cacttacaag  gaagtaagca
241 aaatggtgaa  agatgcattg  actgcaattg  agaaaccac
281 tggagatgaa  cagtcttcag  ggtgtttaga  aaaccagcta
321 cctgcctttc  tggagaact  ttgccatgag  aaagaaattt
361 tggagaagta  cggacattca  gactgctgca  gccaaagtga
401 agaggaaga  cataactgtt  ttcttgca  caaaaagccc
441 actccagcat  cgatcccact  tttccaagtt  ccagaacctg
481 tcacaagctg  tgaagcatat  gaagaagaca  gggagacatt
521 catgaacaaa  ttcatttatg  agatagcaag  aaggcatccc
561 ttctgtatg  cacctacaat  tcttctttgg  gctgctcgct
601 atgacaaaat  aattccatct  tgctgcaaag  ctgaaaatgc
641 agttgaatgc  ttccaaacaa  aggcagcaac  agttacaaaa
681 gaattaagag  aaagcagctt  gttaaatcaa  catgcatgtg
721 cagtaatgaa  aaat tttggg  acccgaactt  tccaagccat
761 aactgttact  aaactgagtc  agaagtttac  caaagttaat
801 tttactgaaa  tccagaaact  agtcctggat  gtggcccatg
841 tacatgagca  ctgttgca  ggagatgtgc  tggattgtct
881 gcaggatggg  gaaaaaatca  tgtcctacat  atgttctcaa
921 caagacactc  tgtcaaacaa  aataacagaa  tgctgcaaac
961 tgaccacgct  ggaacgtgg  caatgtataa  ttc atgcaga
1001 aaatgatgaa  aaacctgaag  gtctatctcc  aaatctaaac
1041 aggttttttag  gagatagaga  ttttaaccaa  ttttcttcag

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CONTINUED

1081 gggaaaaaaa tatcttcttg gcaagttttg ttcatagaata
1121 ttcaagaaga catcctcagc ttgctgtctc agtaattcta
1161 agagttgcta aaggatacca ggagttattg gagaagtgtt
1201 tccagactga aaaccctctt gaatgccaag ataaaggaga
1241 agaagaatta cagaaataca tccaggagag ccaagcattg
1281 gcaaagcgaa gctgcggcct cttccagaaa ctaggagaat
1321 attacttaca aaatgctgtt ctgcttgctt acacaaagaa
1361 agccccccag ctgacctcgt cggagctgat ggccatcacc
1401 agaaaaatgg cagccacagc agccacttgt tgccaactca
1441 gtgaggacaa actattggcc tgtggcgagg gaggcgctga
1481 cattattatc ggacacttat gtatcagaca tgaaatgact
1521 ccagtaaacc ctggtggttg ccagtgtctc acttcttcat
1561 atgccaacag gaggccatgc ttcagcagct tgggtggtgga
1601 tgaaacatat gtccctcctg cattctctga tgacaagttc
1641 attttccata aggatctgtg ccaagctcag ggtgtagcgc
1681 tgcaaacgat gaagcaagag tttctcatta accttgtgaa
1721 gcaaaaagcca caaataacag aggaacaact tgaggctgtc
1761 attgcagatt tctcaggcct gttggagaaa tgctgccaag
1801 gccaggaaca ggaagtctgc tttgctgaag agggacaaaa
1841 actgatttca aaaactcgtg ctgctttggg agtttaaatt
1881 acttcagggg aagagaagac aaaacgagtc tttcattcgg
1921 tgtgaacttt tctctttaat tttaactgat ttaacacttt
1961 ttgtgaatta atgaaatgat aaagactttt atgtgagatt
2001 tccttatcac agaaataaaa tatctccaaa tg

FIGURE 2

Domain I (SEQ ID NO: 5)

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1 TLHRNEYGIA SILDSYQCTA EISLADLATI FFAQFVQEAT
41 YKEVSKMVKD ALTAIEKPTG DEQSSGLEN QLPAFLEELC
81 HEKEILEKYG HSDCCSQSEE GRHNCFLAHK KPTPASIPLF
121 QVPEPVTSC EAYEEDRETFM NKFIYEIARR HPFLYAPTIL
161 LWAARYDKII PSCCKAENAV ECFQTKAATV TKELRES

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Domain II (SEQ ID NO: 6)

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1 SLLNQHACAV MKNFGTRTFQ AITVTKLSQK FTKVNFTEIQ
41 KLVLDVAHVH EHCCRGDVL DCLQDGEKIMS YICSQQDTLS
81 NKITECCKLT TLERGQCIIH AENDEKPEGL SPNLNRFLGD
121 RDFNQFSSGE KNIFLASFVH EYSRRHPQLA VSVILRVAKG
161 YQELLEKCFQ TENPLECQDK GEEELQKYIQ ES

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Domain III (SEQ ID NO: 7)

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1 QALAKRSCGL FQKLGEYYLQ NAFLVAYTKK APQLTSSELM
41 AITRKMAATA ATCCQLSEDK LLACGEGAAD IIIGHL CIRH
81 EMTVPVNGVG QCCTSSYANR RPCFSSLVVD ETYVPPAFSD
121 DKFIFHKDLC QAQVALQTM KQEFLLINLVK QKQPITEEQ
161 EAVIADFSGL LEKCCQGQEQ EVCFAEEGQK LISKTRAAALG
201 V

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Domains I and II (SEQ ID NO: 8)

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1 TLHRNEYGIA SILDSYQCTA EISLADLATI FFAQFVQEAT
41 YKEVSKMVKD ALTAIEKPTG DEQSSGLEN QLPAFLEELC
81 HEKEILEKYG HSDCCSQSEE GRHNCFLAHK KPTPASIPLF
121 QVPEPVTSC EAYEEDRETFM NKFIYEIARR HPFLYAPTIL
161 LWAARYDKII PSCCKAENAV ECFQTKAATV TKELRESSLL
201 NQHACAVMKN FGTRTFQAIT VTKLSQKFTK VNFTEIQKLV
241 LDVAHVHEHC CRGDVLDCLQ DGEKIMSYIC SQQDTLSNKI
281 TECCKLT TLE RGQCIIHAEN DEKPEGLSPN LNRFLGDRDF
321 NQFSSGEKNI FLASFVHEYS RRHPQLAVSV ILRVAKGYQE
361 LLEKCFQ TEN PLE CQDKGEE ELQKYIQES

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Domains II and III (SEQ ID NO: 9)

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1 SLLNQHACAV MKNFGTRTFQ AITVTKLSQK FTKVNFTEIQ
41 KLVLDVAHVH EHCCRGDVL DCLQDGEKIMS YICSQQDTLS
81 NKITECCKLT TLERGQCIIH AENDEKPEGL SPNLNRFLGD
121 RDFNQFSSGE KNIFLASFVH EYSRRHPQLA VSVILRVAKG
161 YQELLEKCFQ TENPLECQDK GEEELQKYIQ ESQALAKRSC
201 GLFQKLGEYY LQNAFLVAYT KKAPQLTSSE LMAITRKMAA
241 TAATCCQLSE DKLLACGEGA ADIIIGHL CI RHEMTVPVNG
281 VGQCCTSSYA NRRPCFSSLV VD ETYVPPAF SDDKFIFHKD

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CONTINUED

321 LCQAQGVALQ TMKQEFLLNL VKQKPOITEE QLEAVIADFS
361 GLLEKCCQGQ EQEVCFAEEG QKLISKTRAA LGV

Human AFP Fragment 1 (SEQ ID NO: 10)

1 QDGEKIMSYI CSQQDTLSNK ITECCKLTTL ERGQCIHAE
41 NDEKPEGLSP NLNRFLGDRD FNQFSSGEKN IFLASFVHEY
81 SRRHPQLAVS VILRVAKGYQ ELLEKCFQTE NPLECQDKGE
121 EELQKYIQES QALAKRSCGL FQKLGEYYLQ NAFLVAYTKK
161 APQLTSSELM AITRKMAATA ATCCQLSEDK LLACGEGAAD
201 IIIIHLICIRH EMTPVNPVGQ QCCTSSYANR RPCFSSLVVD
241 ETYVPPAFSD DKFIFHKDLC QAQGVALQTM KQEFLLNLVK
281 QKPOITEEQE EAVIADFSGL LEKCCQGQEQ EVCFAEEGQK
321 LISKTRAAALG V

FIGURE 3

 α 4 integrin amino acid sequence (SEQ ID NO: 11)

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1 MAWEARREPG PRRAAVRETV MLLLCLGVPT GRPYNVDTES
41 ALLYQGPHT LFGYSVVLHS HGANRWLLVG APTANWLANA
81 SVINPGAIYR CRIGKNPGQT CEQLQLGSPN GEPCGKTCLE
121 ERDNQWLGVV LSRQPGENG IVTCGHRWKN IFYIKNENKL
161 PTGGCYGVPP DLRTLSKRI APCYQDYVKK FGENFASCQA
201 GISSFYTKDL IVMGAPGSSY WTGSLFVYNI TTNKYKAFLD
241 KQNQVKFGSY LGYSVGAGHF RSQHTTEVVG GAPQHEQIGK
281 AYIFSIDEKE LNILHEMKGK KLSYFGASV CAVDLNADGF
321 SDLLVGAPMQ STIREEGRVF VYINSGSGAV MNAMETNLVG
361 SDKYAARFGE SIVNLGDIDN DGFEDVAIGA PQEDDLQGAI
401 YIYNGRADGI SSTFSQRIEG LQISKLSMF GQSIGQIDA
441 DNNGYVDVAV GAFRSDSAVL LRTRPVVIVD ASLSHPESVN
481 RTKFDCVENG WPSVCIDLTL CFSYKGKEVP GYIVLFYNMS
521 LDVNRKAESP PRFYFSSNGT SDVITGSIQV SSREANCRTH
561 QAFMRKDVRD ILTPIQIEAA YHLGPHVISK RSTEEFPPLQ
601 PILQQKKEKD IMKKTINFAR FCAHENC SAD LQVSAKIGFL
641 KPHENKTYLA VGSMKTLMLN VSLFNAGDDA YETTLHVKLP
681 VGLYFIKILE LEEKQINCEV TDNSGVVQLD CSIGYIYVDH
721 LSRIDISFLL DVSSLSRAEE DLSITVHATC ENEEEMDNLK
761 HSRVTVAIPL KYEVKLTVHG FVNPTS FVYG SNDENEPETC
801 MVEKMNLTFH VINTGNSMAP NVSVEIMVPN SFSPQTDKLF
841 NILDVQTTTG ECHFENYQRV CALEQQKSAM QTLKGIVRFL
881 SKTDKRLLYC IKADPHCLNF LCNFGKMESG KEASVHIQLE
921 GRPSILEMDE TSALKFEIRA TGFPEPNPRV IELNKDENVA
961 HVLLEGLHHQ RPKRYFTIVI ISSSLLLGLI VLLLISYVMW
1001 KAGFFKRQYK SILQEENRRD SWSYINSKSN DD

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 α 4 integrin amino acid sequence (SEQ ID NO: 34)

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1 mfptesawlg krganpgpea avretvml11 clgvptgrpy
41 nvdtesally qgphntlfgy svvlhshgan rwillvgapta
81 nwlanasvin pgaiyrcrig knpgqtceql qlgspngepc
121 gktcleerdn qwlgvtlsrq pgengsivtc ghrwknifyi
161 knenklptgg cygvppdlrt elskriapcy qdyvkkfgen
201 fascqagiss fytkdlivmg apgssywtgs lfvynittnk
241 ykaflkqng vkfgsylvys vgaghfrsqh ttevvvggapq
281 heqigkayif sidekelnil hemkgkklgs yfgasvcavd
321 lnadgfsdll vgapmqstir eegrvfvyin sgsgavmnam
361 etnlvgdky aarfgesivn lgdidndgfe dvaigapped
401 dlqgaiyiyn gradgisstf sqrieglqis kslsmfgqsi
441 sgqidadnng yvdvavgafr sdsavllrtr pvvividasl
481 hpesvnrtkf dcvengwpsv cidltlcfsv kgkevpgyiv
521 lfynmsldvn rkaespprfy fssngtsdvi tgsiqvssre
561 ancrthqafm rkdvrtiltp iqieaayhlg phviskrste
601 efpplqpilq qkkekdimmk tinfarfcah encsadlqvs

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641 akigflkphe nktylavgsm ktlmlnvsif nagddayett
 681 lhvklpvgly fikileleek qincevtdns gvvqldcsig
 721 yiyvdhlsri disflldvss lsraeedlsi tvhatcenee
 761 emdnlkhsrv tvaiplkyev kltvhgfvnp tsfvygsnde
 801 nepetcmvek mnltfhvint gnsmapnsvv eimvpnsfsp
 841 qtdklfnild vqtttgechf enyqrvcale qqksamqtlk
 881 givrflsktd krllycikad phclnflcnf gkmesgkeas
 921 vhiqlegprs ilemdetsal kfeiratgfp epnprvieln
 961 kdenvahvll eglhhqrprkr yftiviiss lllglivlll
 1001 isyvmwkagf fkrqyksilq eenrrdswsy insksnnd

 α 4 integrin mRNA nucleic acid sequence (SEQ ID NO: 12)

1 ataacgtctt tgtcactaaa atgttcccca ggggccttcg
 41 gcgagtcctt ttgtttgggt ttttgttttt aatctgtggc
 81 tcttgataat ttatctagtg gttgcctaca cctgaaaaac
 121 aagacacagt gtttaactat caacgaaaga actggacggc
 161 tccccgccgc agtcccactc cccgagtttg tggctggcat
 201 ttggggccacg ccgggctggg cggtcacagc gaggggcgcg
 241 cagtttgggg tcacacagct ccgcttctag gcccacaacca
 281 ccgttaaaag gggaagcccg tgcccatca ggtccgctct
 321 tgctgagccc agagccatcc cgcgctctgc gggctgggag
 361 gcccgggcca ggacgcgagt cctgcgcagc cgaggttccc
 401 cagcgccccc tgcagccgcg cgtaggcaga gacggagccc
 441 ggccctgcgc ctccgcacca cgcccgggac cccaccagc
 481 ggcccgctacc cggagaagca gcgcgagcac ccgaagctcc
 521 cggctggcgg cagaaaccgg gaggggggcc gggcgagtgc
 561 gcggcatccc aggccggccc gaacgctccg cccgcggtgg
 601 gccgacttcc cctcctcttc cctctctcct tcctttagcc
 641 cgctggcgcc ggacacgctg cgcctcatct cttggggcgt
 681 tcttccccgt tggccaaccg tcgcatcccg tgcaactttg
 721 gggtagtggc cgtttagtgt tgaatgttcc ccaccgagag
 761 cgcattggctt gggaagcgag gcgcgaacc ggcccccgaa
 801 gggccgcgct ccgggagacg gtgatgctgt tgctgtgctt
 841 ggggttcccg accggccgcc cctacaacgt ggacactgag
 881 agcgcgctgc tttaccaggg cccccacaac acgctgttctg
 921 gctactcggg cgtgctgcac agccacgggg cgaaccgatg
 961 gctcctagtg ggtgcgccc ctgccaactg gctcgcacaac
 1001 gcttcagtga tcaatcccgg ggcgatttac agatgcagga
 1041 tcggaagaa tcccggccag acgtgcgaac agctccagct
 1081 gggtagccct aatggagaac cttgtggaaa gacttgtttg
 1121 gaagagagag acaatcagtg gttgggggtc aactttcca
 1161 gacagccag agaaaatgga tccatcgtga cttgtgggca
 1201 tagatggaaa aatatatttt acataaagaa tgaaaataag
 1241 ctcccactg gtggttgcta tggagtgcc cctgatttac
 1281 gaacagaact gagtaaaaga atagctccgt gttatcaaga
 1321 ttatgtgaaa aaatttggag aaaattttgc atcatgtcaa
 1361 gctggaatat ccagttttta cacaaaggat ttaattgtga

CONTINUED

1401 tgggggcccc aggatcatct tactggactg gctctctttt
1441 tgtctacaat ataactacaa ataaatacaa ggctttttta
1481 gacaaacaaa atcaagtaaa atttggaggt tatttaggat
1521 attcagtcgg agctgggcat ttctggagcc agcatactac
1561 cgaagtagtc ggaggagctc ctcaacatga gcagattggg
1601 aaggcatata tattcagcat tgatgaaaaa gaactaaata
1641 tcttacatga aatgaaaggt aaaaagcttg gatcgtactt
1681 tggagcttct gtctgtgctg tggacctcaa tgcagatggc
1721 ttctcagatc tgctcgtggg agcacccatg cagagcacca
1761 tcagagagga aggaagagtg tttgtgtaca tcaactctgg
1801 ctctgggagca gtaatgaatg caatggaaac aaacctcgtt
1841 ggaagtgaca aatatgctgc aagatttggg gaatctatag
1881 ttaatcttgg cgacattgac aatgatggct ttgaagatgt
1921 tgctatcggg gctccacaag aagatgactt gcaaggtgct
1961 atttatattt acaatggccg tgcagatggg atctcgtcaa
2001 ccttctcaca gagaattgaa ggacttcaga tcagcaaact
2041 gttaagtatg tttggacagt ctatatcagg acaaattgat
2081 gcagataata atggctatgt agatgtagca gttgggtgctt
2121 ttcgggtctga ttctgctgtc ttgctaagga caagacctgt
2161 agtaattggt gacgcttctt taagccacc tggatcagta
2201 aatagaacga aatttgactg tgttgaaaat ggatggcctt
2241 ctgtgtgcat agatctaaca ctttgtttct catataaggg
2281 caaggaagtt ccaggttaca ttgttttgtt ttataacatg
2321 agtttggatg tgaacagaaa ggacagagtct ccaccaagat
2361 tctatttctc ttctaattgga acttctgacg tgattacagg
2401 aagcatacag gtgtccagca gagaagctaa ctgtagaaca
2441 catcaagcat ttatgcgga aagatgtgagg gacatcctca
2481 ccccaattca gattgaagct gcttaccacc ttggctctca
2521 tgtcatcagt aaacgaagta cagaggaatt cccaccactt
2561 cagccaattc ttcagcagaa gaaagaaaaa gacataatga
2601 aaaaaacaat aaactttgca aggttttgtg cccatgaaaa
2641 ttgttctgct gatttacagg tttctgcaa gattgggttt
2681 ttgaagcccc atgaaaataa aacatatctt gctgttggga
2721 gtatgaagac attgatggtg aatgtgtcct tgtttaatgc
2761 tggagatgat gcatatgaaa cgactctaca tgtcaaacta
2801 cccgtgggctc tttatttcat taagatttta gagctggaag
2841 agaagcaaat aaactgtgaa gtcacagata actctggcgt
2881 ggtacaactt gactgcagta ttggctatat atatgtagat
2921 catctctcaa ggatagatat tagctttctc ctggatgtga
2961 gctcactcag cagagcggaa gaggacctca gtatcacagt
3001 gcatgctacc tgtgaaaatg aagaggaat ggacaatcta
3041 aagcacagca gagtgactgt agcaatacct ttaaaatag
3081 aggttaagct gactgttcat gggtttgtaa acccaacttc
3121 atttgtgtat ggatcaaatg atgaaaatga gcctgaaacg
3161 tgcattggtg agaaaatgaa cttactttc catgttatca
3201 aactggcaa tagtatggct cccaatgtta gtgtggaat
3241 aatggtacca aattctttta gccccaaac tgataagctg
3281 ttcaacattt tggatgtcca gactactact ggagaatgac

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3321 actttgaaaa ttatcaaaga gtgtgtgcat tagagcagca
 3361 aaagagtgca atgcagacct tgaaaggcat agtccggttc
 3401 ttgtccaaga ctgataagag gctattgtac tgcataaaag
 3441 ctgatccaca ttgtttaaata ttcttgtgta attttgggaa
 3481 aatggaaagt ggaaaagaag ccagtgttca tatccaactg
 3521 gaaggccggc catccatttt agaaatggat gagacttcag
 3561 cactcaagtt tgaaataaga gcaacagggt ttccagagcc
 3601 aaatccaaga gtaattgaac taaacaagga tgagaatggt
 3641 ggcgatgttc tactggaagg actacatcat caaagaccca
 3681 aacgttattt caccatagtg attatttcaa gtagcttgct
 3721 acttggactt attgtacttc tgttgatctc atatgttatg
 3761 tgggaaggctg gcttctttaa aagacaatac aaatctatcc
 3801 tacaagaaga aaacagaaga gacagttgga gttatatcaa
 3841 cagtaaaagc aatgatgatt aaggacttct ttcaaattga
 3881 gagaatggaa aacagactca ggttgtagta aagaaattta
 3921 aaagacactg tttacaagaa aaaatgaatt ttgtttggac
 3961 ttcttttact catgatcttg tgacatatta tgtcttcag
 4001 caaggggaaa atctcagcaa tgattactct ttgagataga
 4041 agaactgcaa aggtaataat acagccaaag ataatctctc
 4081 agctttttaa tgggtagaga aacactaaag cattcaattt
 4121 attcaagaaa agtaagccct tgaagatatac ttgaaatgaa
 4161 agtataactg agttaaatta tactggagaa gtcttagact
 4201 tgaataacta cttaccatat gtgcttgctc cagtaaaatg
 4241 aaccccactg ggtgggcaga ggttcatttc aaatacatct
 4281 ttgatacttg ttcaaaatat gttctttaa aatataattt
 4321 tttagagagc tgttcccaa ttttctaacg agtggacat
 4361 taccacttta aagcccttta tttataatac atttcttacg
 4401 ggctgtgttc caacaacat tttttttcag cagactatga
 4441 atattatagt attataggcc aaactggcaa acttcagact
 4481 gaacatgtac actggtttga gcttagtgaa attacttctg
 4521 gataattatt tttttataat tatggatttc accatctttc
 4561 tttctgtata tatacatgtg tttttatgta ggtatatatt
 4601 taccattctt cctatctatt ctctctataa cacaccttta
 4641 tcaagcatac ccaggagtaa tcttcaaate ttttgttata
 4681 ttctgaaaca aaagattgtg agtggtgcac tttacctgat
 4721 acacgctgat ttagaaaata cagaaacat acctcactaa
 4761 taactttaa atcaaagctg tgcaaagact agggggccta
 4801 tacttcatat gtattatgta ctatgtaaaa tattgactat
 4841 cacacaacta tttccttggg tgtaattctt tgttaccctt
 4881 tacaagtata agtgttacct tacatggaaa cgaagaaca
 4921 aaattcataa atttaaattc ataaatttag ctgaaagata
 4961 ctgattcaat ttgtatacag tgaatataaa tgagacgaca
 5001 gcaaaatttt catgaaatgt aaaatatttt tatagtttgt
 5041 tcatactata tgaggttcta ttttaaata ctttctggat
 5081 tttaaaaaat ttctttaaata acaatcattt ttgtaattt
 5121 tatttttatgc ttatgatcta gataattgca gaatatcatt
 5161 ttatctgact ctgccttcat aagagagctg tggccgaatt
 5201 ttgaacatct gttataggga gtgatcaaat tagaaggcaa
 5241 tgtggaaaa caattctggg aaagatttct ttatatgaag

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5281 tccctgccac tagccagcca tcctaattga tgaaagttat
 5321 ctgttcacag gcctgcagtg atggtgagga atgttctgag
 5361 atttgcgaag gcatttgagt agtgaaatgt aagcacaana
 5401 cctcctgaac ccagagtgtg tatacacagg aataaacttt
 5441 atgacattta tgtatTTTTa aaaaactttg tatcgttata
 5481 aaaaggctag tcattctttc aggagaacat ctaggatcat
 5521 agatgaaaaa tcaagccccg atttagaact gtcttctcca
 5561 ggatggcttc taaggaaatt tacatttggg tctttctac
 5601 tcagaactac tcagaaacaa ctatatattt caggttatct
 5641 gagcacagtg aaagcagagt actatgggtg tccaacacag
 5681 gcctctcaga tacaagggga acacaattac atattgggct
 5721 agatTTTgcc cagttcaaaa tagtatttgt tatcaactta
 5761 ctttgttact tgtatcatga attttaaAAC cctaccactt
 5801 taagaagaca gggatgggtt attctTTTTt ggcaggtagg
 5841 ctatataact atgtgatttt gaaatttaac tgctctggat
 5881 tagggagcag tgaatcaagg cagacttatg aaatctgtat
 5621 tatatttGta acagaatata ggaaatttaa cataattgat
 5661 gagctcaaat cctgaaaaat gaaagaatcc aaattatttc
 6001 agaattatct aggttaaata ttgatgtatt atgatgggtg
 6041 caaagTTTTt ttgtgtgtcc aataaacaca ttgtaaaaaa
 6081 aa

 α 4 integrin mRNA nucleic acid sequence (SEQ ID NO: 35)

1 cgccatcccc cgctctgcgg actgggaggc ccgggccagg
 41 acgcgagtct ggcagccga ggttccccag cgccccctgc
 81 agccgcgcgt aggcagagac ggagccccgc cctgcgcctc
 121 cgcaccacgc ccgggacccc acccagcggc ccgtaccggy
 161 agaagcagcg cgagcaccg aagctcccgg ctccggcgca
 201 gaaaccggga gtggggccgg gcgagtgcgc ggcattcccag
 241 gccggcccga acgtccgccc gcggtgggcc gacttcccct
 261 cctcttccct ctctccttc ttagccccgc tggcgccgga
 301 cacgtcgcgc ctcatctctt ggggcgttct tccccgttgg
 361 ccaaccgtcg catcccgtgc aactttgggg tagtggccgc
 401 ttagtggtga atgttcccc cagagagcgc atggcttggg
 441 aagcagggcg cgaaccggg cccgaagcc gccgtccggg
 481 agacggtgat gctgttgctg tgccctggggg tcccgaccgg
 521 ccgccccctac aacgtggaca ctgagagcgc gctgctttac
 561 cagggccccc acaacacgct gtteggctac tcggctcgtc
 601 tgcacagcca cggggcgaac cgatggctcc tagtgggtgc
 641 gccactgcc aactggctcg ccaacgcttc agtgatcaat
 681 cccggggcga tttacagatg caggatcgga aagaatcccg
 721 gccagacgtg cgaacagctc cagctgggta gccctaattg
 761 agaacctgt ggaaagactt gtttggaga gagagacaat
 801 cagtggttgg gggtcacact ttccagacag ccaggagaaa
 841 atggatccat cgtgacttgt gggcatagat ggaaaaatat
 881 attttacata aagaatgaaa ataagctccc cactgggtgg
 921 tgctatggag tgccccctga tttacgaaca gaactgagta
 961 aaagaatagc tccgtgttat caagattatg tgaaaaaatt

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1001 tggagaaaat tttgcatcat gtcaagctgg aatatccagt
 1041 ttttacacaa aggatttaat tgtgatgggg gccccaggat
 1081 catcttactg gactggctct ctttttgtct acaatataac
 1121 tacaataaaa tacaaggctt ttttagacaa acaaaatcaa
 1161 gtaaaatttg gaagttattht aggatattca gtcggagctg
 1201 gtcatttttcg gagccagcat actaccgaag tagtcggagg
 1241 agctcctcaa catgagcaga ttggtaaggc atatatattc
 1281 agcattgatg aaaaagaact aaatatctta catgaaatga
 1321 aaggtaaaaa gcttggatcg tactttggag cttctgtctg
 1361 tgctgtggac ctcaatgcag atggcttctc agatctgctc
 1401 gtgggagcac ccatgcagag caccatcaga gaggaaggaa
 1441 gagtgthttgt gtacatcaac tctggctcgg gagcagtaat
 1481 gaatgcaatg gaaacaaacc tcgthtgaag tgacaaatat
 1521 gctgcaagat ttggggaatc tatagthtaat cttggcgaca
 1561 ttgacaatga tggctthtga gatgthtgcta tcggagctcc
 1601 acaagaagat gacttgcaag gtgctattta tatttacaat
 1641 ggccgtgcag atgggatctc gtcaaccttc tcacagagaa
 1681 ttgaaggact tcagatcagc aaatcgthta gtatgthtgg
 1721 acagthctata tcaggacaaa ttgatgcaga taataatggc
 1761 tatgtagatg tagcagthtg tgctthtctg tctgattctg
 1801 ctgthcttgct aaggacaaga cctgtagthaa ttgthtgacgc
 1841 thctthtaagc caccctgagth cagthaaatag aacgaaattht
 1881 gactgthgtht gaaatggatg gcctthctgtht tgcatagatc
 1921 taacacttht gthctcatat aaggthcaag aagthtccagg
 1961 thacattgtht thgththtata acatgagtht ggatgthgaa
 2001 agaaaggcag agthctccacc aagatthctat thctctthcta
 2041 atggaacttc tgacgthgatt acaggaagca tacaggtgthc
 2081 cagcagagaa gctaaactgth gaacacatca agcattthtatg
 2121 cggaaagatg tgccgggacat cctcacccca atthcagatthg
 2161 aagthgctth ccaactthgth cctcatgthca thcagthaaacg
 2201 aagthacagag gaatthccac cactthcagcc aatthctthcag
 2241 cagaagaaag aaaaagacat aatgaaaaaa acaataaact
 2281 thgcaaggtht thgtgccccat gaaaatthgth ctgctgatttht
 2321 acaggtthct gcaaagattht ggthththtga gccccatgaa
 2361 aataaaacat atctthgctgth tgggagthatg aagacattgaa
 2401 thgtgaaatgth gthcctthgtht aatgctggag atgathgcata
 2441 thgaaacgact ctacatgthca aactaccctgth gggthctthtat
 2481 thcattaaaga ththtagagct ggaagagaa gcaataaact
 2521 thgaaagthcac agataactct ggcgthgthtac aactthgactg
 2561 cagthattggc thataatatht tagathcatct ctcaaggata
 2601 gatathtagct thctctgthga thgtgagctca ctcagcagag
 2641 cggaaagagga cctcagthatc acagthgcatg ctacctgthga
 2681 aatgaaagag gaaatggaca atctaaagca cagcagagthg
 2721 actgthagcaa thacctthtaa atathgagtht aagctgactg
 2761 thcatgggtht thgthaaaccca actthcatttht thgtatggatc
 2801 aatgathgaa aatgagcctg aaacgthgcat gthgagagaaa
 2841 atgaaactthaa cththccatgth ththcaacact ggcaatagth
 2881 thgctccccaa thgttagthgth gaaataatgth thaccaatthc
 2921 ththtagcccc caaactgata agctgththca cattthtggat

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2961 gtccagacta ctactggaga atgccacttt gaaaattatc
3001 aaagagtgtg tgcattagag cagcaaaaga gtgcaatgca
3041 gaccttgaaa ggcatagtcc agttcttgtc caagactgat
3081 aagaggctat tgtactgcat aaaagctgat ccacattggt
3121 taaatctctt gtgtaatctt gggaaaatgg aaagtggaaa
3161 agaagccagt gttcatatcc aactggaagg cggccatcc
3201 attttagaaa tggatgagac ttcagcactc aagtttgaaa
3241 taagagcaac aggttttcca gagccaaatc caagagtaat
3281 tgaactaac aaggatgaga atggtgcgca tgttctactg
3321 gaaggactac atcatcaaag acccaaactg tattcacca
3361 tagtgattat ttcaagtagc ttgctacttg gacttattgt
3401 acttctggtg atctcatatg ttatgtggaa ggctggcttc
3441 tttaaagac aatacaaatc taccctaaa gaagaaaaca
3481 gaagagacag ttggagttat atcaacagta aaagcaatga
3521 tgattaagga cttctttcaa attgagagaa tggaaaacag
3561 cccgccc

FIGURE 4

CD80 protein sequence (SEQ ID NO: 13)

```

1  MGHTRRQGTS  PSKCPYLNFF  QLLVLAGLSH  FCSGVIHVTK
41  EVKEVATLSC  GHNVSVEELA  QTRIIYWQKEK  KMVLTMMSGD
81  MNIWPEYKNR  TIFDITNNLS  IVILALRPSD  EGTYESVVLK
121  YEKDAFKREH  LAEVTLSVKA  DFPTPSISDF  EIPTSNIIRRI
161  ICSTSGGFPE  PHLSWLENGE  ELNAINTTVS  QDPETELYAV
201  SSKLDFNMTT  NHSFMCLIKY  GHLRVNQTFN  WNTTKQEHFP
241  DNLLPSWAIT  LISVNGIFVI  CCLTYCFAPR  CRERRRNERL
281  RRESVRPV

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CD80 mRNA nucleic acid sequence (SEQ ID NO: 14)

```

1  gacaagtact  gagtgaactc  aaaccctctg  taaagtaaca
41  gaagttagaa  ggggaaatgt  cgcctctctg  aagattacc
81  aaagaaaaag  tgatttgta  ttgctttata  gactgtaaga
121  agagaacatc  tcagaagtgg  agtcttacc  tgaaatcaaa
161  ggatttaaag  aaaaagtgga  atttttcttc  agcaagctgt
201  gaaactaaat  ccacaacctt  tggagacca  ggaacacct
241  ccaatctctg  tgtgtttgt  aaacatcact  ggagggctt
281  ctacgtgagc  aattggattg  tcatcagccc  tgctgtttt
321  gcacctggga  agtgccttg  tcttacttgg  gtccaaattg
361  ttggctttca  cttttgacce  taagcatctg  aagccatggg
401  ccacacacgg  aggcagggaa  catcaccatc  caagtgtcca
441  tacctcaatt  tctttcagct  cttggtgctg  gctggctctt
481  ctcacttctg  ttcaggtgtt  atccacgtga  ccaaggaagt
521  gaaagaagtg  gcaacgctgt  cctgtggtca  caatgtttct
561  gttgaagagc  tggcacaac  tcgcatctac  tggcaaaagg
601  agaagaaaat  ggtgctgact  atgatgtctg  gggacatgaa
641  tatatggccc  gagtacaaga  accggaccat  ctttgataatc
681  actaataacc  tctccattgt  gatcctggct  ctgcgcccat
721  ctgacgaggg  cacatacgag  tgtgttggtc  tgaagtatga
761  aaaagacgct  ttcaagcggg  aacacctggc  tgaagtgacg
801  ttatcagtca  aagctgactt  ccctacacct  agtatatctg
841  actttgaaat  tccaacttct  aatattagaa  ggataatttg
881  ctcaacctct  ggaggttttc  cagagcctca  cctctcctgg
921  ttggaaaatg  gagaagaatt  aatgccatc  aacacaacag
961  tttcccaaga  tcttgaact  gagctctatg  ctgttagcag
1001  caaactggat  ttcaatatga  caaccaacca  cagcttcatg
1041  tgtctcatca  agtatggaca  ttaagagtg  aatcagacct
1081  tcaactggaa  tacaaccaag  caagagcatt  ttctgataa
1121  cctgctccca  tcttgggcca  ttaccttaat  ctcagtaaat
1161  ggaatttttg  tgatatgctg  cctgacctac  tgctttgccc
1201  caagatgcag  agagagaagg  aggaatgaga  gattgagaag
1241  ggaaagtgta  cgccctgtat  aacagtgctc  gcagaagcaa
1281  ggggctgaaa  agatctgaag  gtcccacctc  catttgcaat
1321  tgacctcttc  tgggaacttc  ctcagatgga  caagattacc

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1361 ccaccttgcc ctttacgtat ctgctcttag gtgcttcttc
1401 acttcagttg ctttgcagga agtgtctaga ggaatatggg
1441 gggcacagaa gtagctctgg tgaccttgat caaggtgttt
1481 tgaaatgcag aattcttgag ttctggaagg gacttttagag
1521 aataccagtg ttattaatga caaaggcact gaggcccagg
1561 gaggtgaccc gaattataaa ggccagcgcc agaaccacaga
1601 tttcctaact ctggtgctct tccctttat cagtttgact
1641 gtggcctggt aactggtata tacatatata tgtcaggcaa
1681 agtgctgctg gaagtagaat ttgtccaata acaggtcaac
1721 ttcagagact atctgatttc ctaatgtcag agtagaagat
1761 tttatgctgc tgtttacaaa agcccaatgt aatgcatagg
1801 aagtatggca tgaacatctt taggagacta atggaaatat
1841 tattggtggt taccagtat tccatttttt tcattgtggt
1881 ctctattgct gctctctcac tccccatga ggtacagcag
1921 aaaggagaac tatccaaaac taatttcctc tgacatgtaa
1961 gacgaatgat ttaggtacgt caaagcagta gtcaaggagg
2001 aaagggatag tccaaagact taactggttc atattggact
2041 gataatctct ttaaattggct ttatgctagt ttgacctcat
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2121 tcgttgttta cagtgtatgt actaagcagt aagctatctt
2161 caaatgtcta aggtagtaac tttccatagg gcctccttag
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2241 ttctgacatc agcagagAAC tggaaagaca tagccaactg
2281 ctgttcatgt tactcatgac tcctttctct aaaactgcct
2321 tccacaattc actagaccag aagtggacgc aacttaagct
2361 gggataatca cattatcctc tgaaaatctg gagttgaaca
2401 gcaaaagaag acaacatttc tcaaatgcac atctcatggc
2441 agctaagcca catggctggg atttaaagcc tttagagcca
2481 gcccatggct ttagctacct cactatgctg cttcacaac
2521 cttgctcctg tgtaaaacta tattctcagt gtagggcaga
2561 gaggtctaac accaacataa ggtactagca gtgtttcccg
2601 tattgacagg aatacttaac tcaataattc ttttcttttc
2641 catttagtaa cagtttgat gactatgttt ctattctaag
2681 taattcctgt attctacagc agatactttg tcagcaatac
2721 taaggaaga aacaaagttg aaccgtttct ttaataa

FIGURE 5

P-selectin amino acid sequence (SEQ ID NO: 15)

```

1  mancqiaily  qrfqrvvfgi  sqllcfsali  seltnqkeva
41  awtyhystka  yswnisrkyc  qnrytdlvai  qnkneidyln
81  kvlpyyssyy  wigirknkt  wtwvgtkkal  tneaenwadn
121 epnnkrned  cveiyiksp  apgkwndehc  lkkkhalcyt
161 ascqdmcsk  qgecletign  ytcscypgfy  gpeceyvrec
201 gelelpqhvl  mncshplgnf  sfnsqcsfhc  tdgyqvngps
241 kleclasgiw  tnkppqclaa  qcpplkiper  gnmiclhsak
281 afqhqsccsf  sceegfalvg  pevvtctasg  vwtapapvck
321 avqcqhleap  segtmdcvhp  ltafaygssc  kfecqpgyrv
361 rgldmlrcid  sghwsaplpt  ceaisceple  spvhgsmdcs
401 pslrafqydt  ncsfrcaegf  mlrgadivrc  dnlggwtapa
441 pvcqalqcqd  lpvpnearvn  cshpfgafry  qsvcsftcne
481 glllvgasvl  qclatgnwns  vppecqaipc  tp11spqngt
521 mtcvqplgss  sykstcqfic  degyslsge  rldctrsgw
561 tdsppmceai  kcpelfapeq  gslcdsdtrg  efnvgstchf
601 scnngfkleg  pnnvecttsg  rwsatpptck  giaslptpgl
641 qcpalttpgq  gtmycrhhpg  tfgfnttcyf  gcnagftlig
681 dstlscrpsg  qwtavtpacr  avkcselhvn  kpiamncsnl
721 wgnfsygsic  sfhclegqll  ngsaqtacqe  nghwsttvtpt
761 cqagpltiqe  altyfggava  stiglimgt  llallrkrfr
801 qkddgkcpln  phshlgtygv  ftnaafdpsp

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P-selectin mRNA nucleic acid sequence (SEQ ID NO: 16)

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1  gtttttctaa  acagcctgac  actgagggga  ggcagtgaga
41  ctgtaagcag  tctgggttgg  gcagaaggca  gaaaaccagc
81  agagtcacag  aggagatggc  caactgccaa  atagccatct
121 tgtaccagag  attccagaga  gtggtctttg  gaatttcca
161 actcctttgc  ttcagtgcc  tgatctctga  actaacaac
201 cagaaagaag  tggcagcatg  gacttatcat  tacagcacia
241 aagcatactc  atggaatatt  tcccgtaaat  actgccagaa
281 tcgctacaca  gacttagtgg  ccatccagaa  taaaaatgaa
321 attgattacc  tcaataaggt  cctaccctac  tacagctcct
361 actactggat  tgggatccga  aagaacaata  agacatggac
401 atgggtggga  accaaaaagg  ctctaccaa  cgaggctgag
441 aactgggctg  ataatgaacc  taacaacaaa  aggaacaacg
481 aggactgcgt  ggagatatac  atcaagagtc  cgtcagcccc
521 tggcaagtgg  aatgatgagc  actgcttgaa  gaaaaagcac
561 gcattgtgtt  acacagcctc  ctgccaggac  atgtcctgca
601 gcaaacaagg  agagtgcctc  gagaccatcg  ggaactacac
641 ctgctcctgt  taccctggat  tctatgggcc  agaatgtgaa
681 tacgtgagag  agtgtggaga  acttgagctc  cctcaacacg
721 tgctcatgaa  ctgcagccac  cctctgggaa  acttctcttt
761 taactcgag  tgcagcttcc  actgcactga  cgggtaccaa
801 gtaaattggc  ccagcaagct  ggaatgcttg  gcttctggaa

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CONTINUED

841 tctggacaaa taagcctcca cagtgtttag ctgcccagtg
 881 cccaccctg aagattcctg aacgaggaaa catgatctgc
 921 cttcattctg caaaagcatt ccagcatcag tctagctgca
 961 gcttcagttg tgaagaggga tttgcattag ttggaccgga
 1001 agtggtgcaa tgcacagcct cgggggtatg gacagcccca
 1041 gccccagtg gtaaagctgt gcagtgtcag cacctggaag
 1081 cccccagtga aggaacctg gactgtgttc atccgctcac
 1121 tgcttttgcc tatggctcca gctgcaaatt tgagtgccag
 1161 cccggctaca gagtgagggg cttggacatg ctccgctgca
 1201 ttgactctgg aactggctc gcacccttgc caacctgtga
 1241 ggctatttcg tgtgagccgc tggagagtcc tgtccacgga
 1281 agcatggatt gctctccatc cttgagagcg tttcagtatg
 1321 acaccaactg tagcttccgc tgtgctgaag gtttcatgct
 1361 gagaggagcc gatatagttc ggtgtgataa cttgggacag
 1401 tggacagcac cagccccagt ctgtcaagct ttgcagtgcc
 1441 aggatctccc agttccaaat gagggccggg tgaactgctc
 1481 ccacccttc ggtgccttta ggtaccagtc agtctgcagc
 1521 ttcacctgca atgaaggctt gctcctggtg ggagcaagtg
 1561 tgctacagtg cttggctact ggaaactgga attctgttcc
 1601 tccagaatgc caagccattc cctgcacacc tttgctaagc
 1641 cctcagaatg gaacaatgac ctgtgttcaa cctcttgga
 1681 gttccagtta taaatccaca tgtcaattca tctgtgacga
 1721 gggatattct ttgtctggac cagaaagatt ggattgtact
 1761 cgatcgggac gctggacaga ctccccacca atgtgtgaag
 1801 ccatcaagtg cccagaactc tttgccccag agcagggcag
 1841 cctggattgt tctgacactc gtggagaatt caatgttggc
 1881 tccacctgtc atttctcttg taacaatggc tttaaagtgg
 1921 aggggcccaa taatgtggaa tgcacaactt ctggaagatg
 1961 gtcagctact ccaccaacct gcaaaggcat agcatcactt
 2001 cctactccag ggttgcaatg tccagccctc accactcctg
 2041 ggcagggaac catgtactgt aggcattcatc cgggaacctt
 2081 tggttttaat accacttgtt actttggctg caacgctgga
 2121 ttcacactca taggagacag cactctcagc tgcagacctt
 2161 caggacaatg gacagcagta actccagcat gcagagctgt
 2201 gaaatgctca gaactacatg ttaataagcc aatagcgatg
 2241 aactgctcca acctctgggg aaacttcagt tatggatcaa
 2281 tctgctcttt ccattgtcta gagggccagt tacttaatgg
 2321 ctctgcacaa acagcatgcc aagagaatgg ccactggtca
 2361 actaccgtgc caacctgcca agcaggacca ttgactatcc
 2401 aggaagccct gacttacttt ggtggagcgg tggcttctac
 2441 aataggtctg ataatgggtg ggacgctcct ggctttgcta
 2481 agaaagcgtt tcagacaaaa agatgatggg aatgccctt
 2521 tgaatcctca cagccaccta ggaacatatg gagtttttac
 2561 aaacgctgca tttgaccgga gtccttaagg tttccataaa
 2601 cacccatgaa tcaaagacat ggaattacct tagattagct
 2641 ctggaccagc ctggtggacc cgctctggac caacctggtt
 2681 tcctgagttt gggattgtgg tacaatctca aattctcaac
 2721 ctaccacccc ttctgtccc acctcttctc ttctgtaac
 2761 acaagccaca gaagccagga gcaaatgttt ctgcagtagt

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2801 ctctgtgctt tgactcacct gttacttgaa ataccagtga
2841 accaaagaga ctggagcatc tgactcacia gaagaccaga
2881 ctgtggagaa ataaaaatac ctctttattt tttgattgaa
2921 ggaaggtttt ctccactttg ttggaaagca ggtggcatct
2961 ctaattggaa gaaattcctg tagcatcttc tggagtctec
3001 agtggttgct gttgatgagg cctcttggac ctctgctctg
3041 aggcttcag agagtcctct ggatggcacc agaggctgca
3081 gaaggccaag aatcaagcta gaaggccaca tgtcaccgtg
3121 gaccttcctg ccaccagtca ctgtccctca aatgacccaa
3161 agaccaatat tcaaatgcgt aattaaaga attttccc

FIGURE 6

Sphingosine-1-phosphate-receptor 1 amino acid sequence (SEQ ID NO: 17)

```

1  mgptsvglvk  ahrssvsdyv  nydiivrhyn  ytgklnisad
41 kensikltsv  vfiliccfii  lenifvllti  wktkkfhrpm
81  yyfignlals  dllagvayta  nlllsgatty  kltpaqwflr
121 egsmfvalsa  svfsl্লাiai  eryitmlkkm  lhngsnnfrl
161 fllisacwvi  slilgglpim  gwncisalss  cstvlplyhk
201 hyilfcttvf  tllllsivil  ycriyslvrt  rsrrltfrkn
241 iskasrssen  vallktviiv  lsvfiacwap  lfilllldvg
281 ckvktcdilf  raeyflvlav  lnsqtnpiiy  tltknemrra
321 firimsckkc  psgdsagkfk  rpiiagmefs  rsksdnsshp
361 qkdegdnpet  imssgnvnss  s

```

Sphingosine-1-phosphate-receptor 1 mRNA nucleic acid sequence (SEQ ID NO: 19)

```

1  ggggagtcgg  gggcagcagc  aagatgcgaa  gcgagccgta  cagatcccgg  gctctccgaa
61  cgcaacttcg  ccctgcttga  gcgaggctgc  ggtttccgag  gccctctcca  gccaaggaaa
121 agctacacaa  aaagcctgga  tcaactcatc  aaccaccctc  gaagccagtg  aaggctctct
181 cgctcgcgcc  tctagcgttc  gtctggagta  gcgccacccc  ggcttccttg  ggacacaggt
241 ttggcaccat  ggggccacc  agcgtcccgc  tggccaaggc  ccaccgcagc  tcggtctctg
301 actacgtcaa  ctatgatata  atcgtccggc  attacaacta  cacgggaaaag  ctgaatatca
361 gcgcggacaa  ggagaacagc  attaaactga  cctcgggtgg  gttcattctc  atctgctgct
421 ttatcatcct  ggagaacatc  tttgtcttgc  tgaccatttg  gaaaaccaag  aaattccacc
481 gacccatgta  ctattttatt  ggcaatctgg  ccctctcaga  cctggtggca  ggagtagcct
541 acacagctaa  cctgctcttg  tctggggcca  ccacctaaa  gctcactccc  gccagtggtg
601 ttctgcggga  agggagtatg  tttgtggccc  tgtcagcctc  cgtgttcagt  ctctcgcaca
661 tcgccattga  gcgctataat  acaatgctga  aaatgaaact  ccacaacggg  agcaataact
721 tccgcctctt  cctgctaata  agcgcctgct  gggtcattct  cctcatcctg  ggtggcctgc
781 ctatcatggg  ctggaactgc  atcagtgcgc  tgtccagctg  ctccaccgtg  ctgcccctct
841 accacaagca  ctatatactc  ttctgcacca  cggctctcac  tctgcttctg  ctctccatcg
901 tcattctgta  ctgcagaata  tactccttgg  tcaggactcg  gagccgcccg  ctgacgttcc
961 gcaagaacat  ttccaaggcc  agccgcagct  ctgagaagtc  gctggcgctg  ctcaagaccg
1021 taattatcgt  cctgagcgtc  ttcatacgcct  gctgggcacc  gctcttcata  ctgctcctgc
1081 tggatgtggg  ctgcaagggt  aagacctgtg  acatcctctt  cagagcggag  tacttctctg
1141 tggtagctgt  gctcaactcc  ggcaccaacc  ccatacttta  cactctgacc  aacaaggaga
1201 tgcgtcgggc  cttcatccgg  atcatgtcct  gctgcaagtg  cccgagcggg  gactctgctg
1261 gcaaatcaa  gcgaccatc  atcgcgggca  tggaaattcag  ccgcagcaaa  tcggacaatt
1321 cctcccacc  ccagaaagac  gaaggggaca  acccagagac  cattatgtct  tctggaaacg
1381 tcaactcttc  ttcctagaac  tggaaagctg  ccaccaccg  gaagcgtctc  ttacttggtc
1441 gctggccacc  ccagtgtttg  gaaaaaaatc  tctgggcttc  gactgctgcc  agggaggagc
1501 tgctgcaagc  cagagggagg  aagggggaga  atacgaacag  cctgggtggtg  tggggtgttg
1561 gtggtagag  ttagttcctg  tgaacaatgc  actgggaagg  gtggagatca  ggtcccggcc
1621 tggaatatat  tttctacccc  cctggagcct  tgattttgca  ctgagccaaa  ggtctagcat
1681 tgcgaagctc  ctaaagggtt  catttggccc  ctctcaaag  actaatgtcc  ccagtgtgaa
1741 gcgtctcttt  gtctggagct  ttgaggagat  gttttccttc  actttagttt  caaaccaag
1801 tgagtgtgtg  cacttctgct  tctttaggga  tgccctgtac  atcccacacc  ccaccctccc
1861 ttccctcat  acccctcctc  aacgttcttt  tactttatac  ttaactacc  tgagagttat
1921 cagagctggg  gttgtggaat  gatcgcacat  ctatagcaaa  taggctatgt  tgagtacgta
1981 ggctgtggga  agatgaagat  ggtttggagg  tgtaaaacaa  tgcctctcgc  tgaggccaaa
2041 gtttccatgt  aagcgggatc  cgttttttgg  aatttggttg  aagtcacttt  gatttcttta
2101 aaaaacatct  tttcaatgaa  atgtgttacc  atttcatatc  cattgaagcc  gaaatctgca
2161 taaggaagcc  cactttatct  aaatgatatt  agccaggatc  cttgggtgct  taggagaac
2221 agacaagcaa  aacaaagtga  aaaccgaatg  gattaacttt  tgcaaaccaa  gggagatttc
2281 tttagcaaatg  agtctaacaa  atatgacatc  tgtctttggc  acttttgttg  atgtttat

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CONTINUED

2341 cagaatggtg tgtgattcat ttcaagcaac aacatgggtg tattttggtg tgttaaaagt
2401 acttttcttg atttttgaat gtatttggtt cagcagaagt cattttattg gatttttcta
2461 acccgtggtt acaccattga atgtgtattt ctttaagaaa taccaccctc ttgtgcctt
2521 aaaagcatta ctttaactgg tagggaacgc cagaaacttt tcagtccagc tattcattag
2581 atagtaattg aagatatgta taaatattac aaagaataaa aatatattac tgtctcttta
2641 gtatggtttt cagtgcaatt aaaccgagag atgtcttggt tttttaaaaa gaatagtatt
2701 taatagggtt ctgacttttg tggatcattt tgcacatagc tttatcaact tttaaacatt
2761 aataaactga tttttttaag gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a

FIGURE 7

Hyaluronate receptor amino acid sequence (SEQ ID NO: 19)

```

1 mdkfwwhaaw glclvplsla qidlnticrf agvfhvekng rysisrtea dlckafnstl
61 ptmagmekal sigfetcryg fieghvvi pr ihpnsicaan ntgvvilt sn tsgydytcf n
121 asappedct svtdlpnaf d gpititivnr dgtryvqkge yrtnpediyp snptdddvss
181 gssersssts ggyifytfst vhpipedesp wtdstdrip attlmsts atetatk rge
241 twdwfswfl pseknhlht ttqmagtssn tisagwepne enederdrhl sfgsgidd
301 edfisstist tprafdhtkq nqdw tqwnps hsnpevllqt ttrmtdvdrn gttayegnwn
361 peahpplih ehheeeetph ststiqatps stteetatqk eqwfgnrwhe gyrqtpred s
421 hsttgtaaas ahtshpmqgr ttpspedssw tdfnpi shp mgrghqagr mdmdsshst t
481 lqptanptg lvedldrtgp lsmttqqsns qsfstshegl eedkdhptts tltssnrndv
541 tggrrdpnhs egsttlleg y tshyphkes rtfipvt sak tgsfgvtavt vgdnsnsvnr
601 slsgdqdfh psggshthg sesdghshgs qegganttsg pirtpqipew liilasllal
661 alilavciav nsrrrcgqkk klvinsnga vedrkpsgl n geasksgemv hlvnkesset
721 pdqfmtadet rnlqnvdmki gv

```

Hyaluronate receptor mRNA nucleic acid sequence (SEQ ID NO: 20)

```

1 gggagacca agcttctaga gatccctcga cctcgagatc cattgtgctc taagagcgg
61 acccagcct ctgccaggtt cggctcgcga tctcgtccc gtcctccgcc ggcccctgcc
121 ccgcgccag ggatcctcca gctccttcg cccgcgccct ccgttcgctc cggacaccat
181 ggacaagttt tgggtggcac ggcctgggg actctgcctc gtgccgctga gcttggcga
241 gatcgattg aatataacct gccgctttgc aggtgtattc cacgtggaga aaaatggctg
301 ctacagcatc tctcggacgg aggcgctga cctctgcaag gctttcaata gcacctgcc
361 cacaatggc cagatggaga aagctctgag catcggattt gagacctgca ggtatgggtt
421 catagaagg catgtggtga ttccccgat ccacccaac tccatctgtg cagcaaaaa
481 cacaggggtg tacatcctca catacaaac ctcccagtat gacacatatt gcttcaatgc
541 ttcagctcca cctgaagaag attgtacatc agtcacagac ctgccaatg cctttgatgg
601 accaattacc ataactattg ttaaccgtga tggcaccgc tatgtccaga aaggagaata
661 cagaacgaat cctgaagaca tctaccccag caaccctact gatgatgacg tagcagcgg
721 ctctccagt gaaaggagca gcacttcagg aggttacatc ttttacacct tttctactgt
781 acacccatc ccagacgaag acagtcctg gatcaccgac agcacagaca gaatccctgc
841 taccactttg atgagacta gtgctacagc aactgagaca gcaaccaaga ggcaagaagc
901 ctgggattgg ttttcatggt tgtttctacc atcagagtca aagaatcatc ttcacacaac
961 aacacaaatg gctggtacgt cttcaaatac catctcagca ggctgggagc caaatgaaga
1021 aatgaagat gaaagagaca gacacctcag ttttctgga tcaggcattg atgatgatga
1081 agattttatc tccagcacca tttcaaccac accacgggcc tttgaccaca caaacagaa
1141 ccaggactgg acccagtgga acccaagcca tccaatccg gaagtgtac ttcagacaac
1201 cacaagatg actgatgtag acagaaatgg caccactgct tatgaaggaa actggaacc
1261 agaagcacac cctcccctca ttcaccatga gcatcatgag gaagaagaga cccacattc
1321 tacaagcaca atccaggcaa ctctagtag tacaacggaa gaaacagcta cccagaagga
1381 acagtggttt ggcaacagat ggcatgagg atatcgccaa acaccagag aagactccca
1441 ttcgacaaca gggacagctg cagcctcagc tcataccagc catccaatgc aaggaaggac
1501 aacaccaagc ccagaggaca gttcctggac tgatttctc aaccaatct cacacccat
1561 gggacgaggt catcaagcag gaagaaggat ggatattggac tccagtcata gtacaacgct
1621 tcagcctact gcaaatccaa acacaggttt ggtggaaaat ttggacagga caggacctct
1681 tcaatgaca acgcagcaga gtaattctca gagcttctct acatcacatg aaggcttgg
1741 agaagataaa gaccatccaa caacttctac tctgacatca agcaatagga atgatgtcac
1801 aggtggaaga agagacccaa atcattctga aggtcaact actttactgg aaggttatac
1861 ctctcattac ccacacacga aggaaagcag gaccttcac cagtgacct cagctaagac
1921 tgggtccttt ggagttactg cagttactgt tggagattcc aactcta atg tcaatcgttc
1981 cttatcagga gaccaagaca cattccacc cagtgggggg tcccatacca ctcatggatc
2041 tgaatcagat ggacactcac atgggagtca agaagggtg gcaaacacaa cctctgggtc
2101 tataaggaca ccccaaattc cagaatggct gatcatcttg gcatccctct tggccttggc
2161 tttgattctt gcagtttgca ttgcagtcaa cagtcgaaga aggtgtgggc agaagaaaa
2221 gctagtgatc aacagtggca atggagctgt ggaggacaga aagccaagt gactcaacgg
2281 agaggccagc aagtctcagg aaatgggtgca tttgggtgaac aaggagtcgt cagaaactcc

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CONTINUED

2341 agaccagttt atgacagctg atgagacaag gaacctgcag aatgtggaca tgaagattgg
2401 ggtgtaaac ctacaccatt atcttgaaa gaaacaaccg ttggaaacat aaccattaca
2461 gggagctggg acacttaaca gatgcaatgt gctactgatt gtttcattgc gaatctttt
2521 tagcataaaa ttttctactc tttttgtttt ttgtgttttg ttctttaaag tcaggtccaa
2581 tttgtaaaaa cagcattgct ttgtaaatta gggcccaatt aataatcagc aagaatttga
2641 tcgttcagtt ccacttgag gccttcatcc tcgggtgtgc tatggatggc ttctaacaaa
2701 aactacacat atgtattcct gatcgccaac ctttcccca ccagctaagg acatttcca
2761 gggttaatag ggcctggtcc ctgggaggaa atttgaatgg gtccattttg ccctccata
2821 gcctaattcc tgggcattgc tttccactga ggttgggtg tactagttac acatcttcaa
2881 cagaccctct ctagaaattt ttcagatgct tctgggagac accaaagggt gaagctattt
2941 atctgtagta aactatttat ctgtgtttt gaaatattaa accctggatc agtccttga
3001 tcagtataat tttttaagt tactttgtca gaggcacaaa agggtttaa ctgattcata
3061 ataaatatct gtacttcttc gatcttcaa a

FIGURE 8

LFA-1 α subunit amino acid sequence (SEQ ID NO: 21)

```

1  mkdscitvma mallsgffff apassynldv rgarsfsppr agrhfgyrvl qvngnvivga
61  pgegnstgsl yqcqsgtgshc lpvtlrgsny tskylgmtla tdptdgsila cdpglrsrcd
121 qntylsglcy lfrqnlqgpm lqgrpgfqec ikgnvdlvfl fdgsmqlqpd efqkildfmk
181 dvmkklnts yqfaavqfst syktefdfsd yvkrkdpdal lkhvkhmlll tntfgainyv
241 atevfreelg arpdatkvli iitdgeatds gnidaakdii ryiigigkhf qtkesqetlh
301 kfaskpasef vkildtfekl kdlftelqkk iyviegtskq dltsfnmels ssgisadlsr
361 ghavvgavga kdwaggfldl kadlqddtqi gnepltpivr agylgyvtw lpsrqktsll
421 asgapryqhm grvllfqepq gggghwsqvqt ihgtqigsyf ggelcgvdvd qdgetelli
481 gaplfygeqr ggrvfiyqrr qlgfeevsel qgdpgyplgr fgeaitald ingdglvdva
541 vgapleeqga vyifngrhgg lspqpsqrie gtqvlsgiqw fgrsihgvd legdgladva
601 vgaesqmilv ssrpvdmvt lmsfspaeip vhevecsyst snkmkegvni ticfqiiksli
661 pqfqqrlvan ltytlqldgh rtrrrglfpg grhelrrnia vttsmsctdf sfhfpvcvqd
721 lispinvsln fslweeegtp rdqraqgkdi ppilrpslhs etweipfkn cgedkkcean
781 lrsvsfpars ralrltafas lsvelslsln eedaywvqld lhfpplgsfr kvemlkphsq
841 ipvsceelpe esrllsrals cnvsspifka ghsvalqmmf ntlvnsswgd svelhanvte
901 nnedsdllled nsattiipil ypiniliqdq edstlyvsft pkgpkihqvk hmyqvriqps
961 ihdhniptle avvgvpqpps egpithqsv qmpeppvchy edlerlpdaa epclpgalfr
1021 cpvvrqeil vqvigtelvl geieassmfs lcsslsisfn sskhfhylys naslaqvvmk
1081 vdvyekqml ylyvlsiggg llllllifiv lykvgffkrn lkekmeagrv vpngipaeds
1141 eqlasgqeaq dpgclklphe kdsesgggkd

```

LFA-1 α subunit mRNA nucleic acid sequence (SEQ ID NO: 23)

```

1  cctctttcac cctgtctagg ttgccagcaa atccccacggg cctcctgacg ctgccctggg
61  ggccacaggt ccctcgagtg ctggaaggat gaaggattcc tgcatactg tgatggccat
121  ggcgctgctg tctgggttct ttttcttcgc gccggcctcg agctacaacc tggacgtgcg
181  gggcgcgcgg agcttctccc caccgcgcgc cgggaggcac tttggatacc gcgtcctgca
241  ggtcggaaac ggggtcatcg tgggagctcc aggggagggg aacagcacag gaagcctcta
301  tcagtgccag tcgggcacag gacactgcct gccagtcacc ctgagaggtt ccaactatac
361  ctccaagtac ttgggaatga ccttggcaac agaccccaca gatggaagca ttttggcctg
421  tgaccctggg ctgtctcgaa cgtgtgacca gaacacctat ctgagtggcc tgtgttacct
481  cttccgccag aatctgcagg gtcccatgct gcaggggcgc cctggttttc agaatgtat
541  caagggcaac gtagacctgg tatttctggt tgatggttcg atgagcttgc agccagatga
601  atttcagaaa attctggact tcatgaagga tgtgatgaag aaactcagca acacttcgta
661  ccagtttgct gctgttcagt tttccacaag ctacaaaaca gaatttgatt tctcagatta
721  tgtaaataag aaggaccctg atgctctgct gaagcatgta aagcacatgt tgctgtgac
781  caatacctt ggtgccatca attatgtcgc gacagagggt tccgggagg agctgggggc
841  ccggccagat gccaccaaag tgcttatcat catcacggat ggggaggcca ctgacagtgg
901  caacatcgat gcggccaaag acatcatccg ctacatcatc gggattggaa agcattttca
961  gaccaaggag agtcaggaga ccctccacaa atttgcatca aaaccgcgca gcgagtttgt
1021 gaaaattctg gacacatttg agaagctgaa agatctattc actgagctgc agaagaagat
1081 ctatgtcatt gagggcacia gcaaacagga cctgacttcc ttcaacatgg agctgtcctc
1141 cagcggcatc agtgcagacc tcagcagggg ccatgcagtc gtgggggcag taggagccaa
1201 ggactgggct gggggctttc ttgacctgaa ggcagacctg caggatgaca ctttattgg
1261 gaatgaacca ttgacaccag aagtgagagc aggctatttg ggttacaccg tgacctggct
1321 gccctccgg caaaagactt cgttgtctgg ctccgggagcc cctcgatacc agcacatggg
1381 ccgagtgtct ctgttccaag agccacaggg cggaggacac tggagccagg tccagacaat
1441 ccatgggacc cagattggct cttatttctg tggggagctg tgtggcgtcg acgtggacca
1501 agatggggag acagagctgc tgctgattgg tgccccactg ttctatgggg agcagagagg
1561 agcccggtg tttatctacc agagaagaca gttgggggtt gaagaagtct cagagctgca
1621 gggggacccc ggctaccac tcgggcgggt tggagaagcc atcactgctc tgacagacat
1681 caacggcgat gggctggtag acgtggctgt gggggcccct ctggaggagc agggggctgt
1741 gtacatcttc aatgggaggc acggggggct tagtccccag ccaagtccgc ggateagaag
1801 gaccaagtg ctctcaggaa ttcagtggtt tggacgctcc atccatgggg tgaaggacct

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CONTINUED

1861 tgaaggggat ggcttggcag atgtggctgt gggggctgag agccagatga tcgtgctgag
 1921 ctcccggccc gtggtggata tggtcaccct gatgtccttc tctccagctg agatcccagt
 1981 gcatgaagtg gagtgtcctt attcaaccag taacaagatg aaagaaggag ttaatatcac
 2041 aatctgtttc cagatcaagt ctctctaccc ccagttccaa ggccgcctgg ttgccaatct
 2101 cacttacact ctgcagctgg atggccaccg gaccagaaga cgggggttgt tcccaggagg
 2161 gagacatgaa ctcagaagga atatagctgt caccaccagc atgtcatgca ctgacttctc
 2221 atttcatttc ccggtatgtg ttcaagacct catctcccc atcaatgttt ccctgaattt
 2281 ctctctttgg gaggaggaag ggacaccgag ggaccaaagg gcgcagggca aggacatacc
 2341 gccatcctg agaccctccc tgcactcgga aacctgggag atcccttttg agaagaactg
 2401 tggggaggac aagaagtgtg aggcaaactt gagagtgtcc ttctctcctg caagatccag
 2461 agccctgctg ctaactgctt ttgccagcct ctctgtggag ctgagcctga gtaacttggg
 2521 agaagatgct tactgggtcc agctggacct gcaactcccc ccgggactct ccttccgcaa
 2581 ggtggagatg ctgaagcccc atagccagat acctgtgagc tgcgaggagc ttctgaaga
 2641 gtccaggctt ctgtccaggg cattatcttg caatgtgagc tctcccctct tcaaagcagg
 2701 ccaactcgggt gctctgcaga tgatgtttaa tacactggta aacagctcct ggggggactc
 2761 ggttgaattg cacgccaatg tgacctgtaa caatgaggac tcagacctcc tggaggacaa
 2821 ctcagccact accatcctcc ccatcctgta ccccatcaac atcctcctcc aggaccaaga
 2881 agactccaca ctctatgtca gtttcacccc caaaggcccc aagatccacc aagtcaagca
 2941 catgtaccag gtgaggatcc agccttccat ccacgaccac aacataccca ccctggaggc
 3001 tgtggttggg gtgccacagc ctcccagcga ggggcccac acacaccagt ggagcgtgca
 3061 gatggagcct cccgtgcctt gccactatga ggatctggag aggctcccgg atgcagctga
 3121 gccttgtctc cccggagccc tgttccgctg ccctgttgtc ttcaggcagg agatcctcgt
 3181 ccaagtgatc gggactctgg agctgggtgg agagatcgag gcctcttcca tgttcagcct
 3241 ctgcagctcc ctctccatct ccttcaacag cagcaagcat ttccacctct atggcagcaa
 3301 cgctcctctg gcccagggtg tcatgaaggt tgacgtgggt tatgagaagc agatgctcta
 3361 cctctacgtg ctgagcggca tcggggggct gctgctgctg ctgctcattt tcatagtgtc
 3421 gtacaagggt ggtttcttca aacggaacct gaaggagaag atggaggctg gcagagggtg
 3481 cccgaatgga atccctgcag aagactctga gcagctggca tctgggcaag aggctgggga
 3541 tcccggctgc ctgaagcccc tccatgagaa ggactctgag agtgggtggt gcaaggactg
 3601 agtccaggcc tgtgagggtc agagtgccca gaactggact caggatgccc agggccactc
 3661 tgctctgccc tgcattctgc cgtgtgccct cgggcgagtc actgcctctc cctggccctc
 3721 agtttcccta tctcgaacat ggaactcatt cctgaatgtc tcctttgcag gctcataggg
 3781 aagacctgct gagggaccag ccaagagggc tgcaaaagtg agggcttgtc attaccagac
 3841 ggttcaccag cctctcttgg ttcttctctt ggaagagaat gtctgatcta aatgtggaga
 3901 aactgtagtc tcaggacctc gggatgttct ggccctcacc ctgcccctgg gatgtccaca
 3961 gatgcctcca cccccagaa cctgtccttg cacactcccc tgcactggag tccagtctct
 4021 tctgctggca gaaagcaaat gtgacctgtg tcaactacgtg actgtggcac acgccttgtt
 4081 cttggccaaa gaccaaatc cttggcatgc cttccagcac cctgcaaaat gagaccctcg
 4141 tggccttccc cagcctcttc tagagccgtg atgcctccct gttgaagctc tgggtgacacc
 4201 agcctttctc ccaggccagg ctcttctctg tcttctgca ttcaccaga cagctcctc
 4261 tgctgaacc ttccatctcg cccaccctc cttccttgac cagcagatcc cagctcacgt
 4321 cacacacttg gttgggtcct cacatcttcc acacttccac caccctgcac tactcctca
 4381 aagcacacgt catgtttctt catccggcag cctggatgtt ttttccctgt ttaatgattg
 4441 acgtacttag cagctatctc tcagtgaact gtgagggtaa aggtatact tgtcttgttc
 4501 accttgggat gacgccgat gatatgtcag ggcgtgggac atctagtagg tgcttgacat
 4561 aatttactg aattaatgac agagccagtg ggaagataca gaaaaagagg gccggggctg
 4621 ggcgcggtgg ttcacgcctg taatcccagc actttgggag gccaaaggag gtggatcacc
 4681 tgaggtcagg agtttagagg cagcctggcg aaaccccatc tctactaaaa atacaaaatc
 4741 caggcgtggt ggcacacacc tgtagtccca gctactcagg aggttgaggt aggagaattg
 4801 ctgaaacctg ggaggtggag gttgcagtga gccaaagatt cgccattgca ctccagcctg
 4861 ggcaacacag cgagactccg tctcaaggaa aaaataaaaa taaaaagcgg gcacgggccc
 4921 ggacatcccc acccttggag gctgtcttct caggctctgc cctgccttag ctccacccc
 4981 tctcccagga cccatcacgc ctgtgcagtg gccccacag aaagactgag ctcaaggtgg
 5041 gaaccacgtc tgctaacttg gagccccagt gccaaagcaca gtgcctgcat gtatttatcc
 5101 aataaatgtg aaattctgtc caaaaaaaaa aaa

CONTINUED

LFA-1 β subunit amino acid sequence (SEQ ID NO: 22)

```

1  mlglrpplla  lvgl1slgcv  lsqectkfkv  sscreciesg  pgctwcqkln  ftgpgdpdsi
61  rcdtrpqlm  rgcaaddimd  ptslaetqed  hngggkqlsp  qkvtlylrpg  qaaafnvtfr
121 rakgypidly  ylm1dlsysml  ddlrnvkk1g  gdllralnei  tesgrigfgs  fvdktvlpfv
181 nthpdklrnp  cpnkekecqp  pfafrhvlkl  tnnsnqfqte  vgkqlisgnl  dapeggldam
241 mgvaacpeei  gwrnvtrllv  fatddgfhfa  gdgklgailt  pndgrchled  nlykrsnefd
301 ypsvgqlahk  laenniqipif  avtsrmvktv  eklteiipks  avgelsedss  nvvqliknay
361 nklssrvfld  hnalpdtlkv  tydsfcsngv  thrnqprgdc  dgvinvpit  fqvkvatec
421 iqeqsfvira  lgftdivtvq  vlpqcecrv  dqsdrslch  gkgflegcic  rcdtgyigkn
481 cecqtggrss  qelegscrkd  nnsiicsglg  dcvcgqclch  tsdvpgkliy  gqycecdtin
541 ceryngqvcg  gpgrglcfcg  kcrchpgfeg  sacqcerte  gclnprvec  sgrgrcrnv
601 cechsgyqlp  lcqecpgcps  pegkyisca  clkfekgpgf  kncsaacpgl  qlsnnpvkgr
661 tkerdsegc  wvaytleqqd  gmdryliyvd  esrecvagn  iaavvggtva  givligilll
721 viwkalihls  dlreyrrfek  eklksqwnnd  nplfksatt  vmnpkfaes
    
```

LFA-1 β subunit mRNA nucleic acid sequence (SEQ ID NO: 24)

```

1  ctgcacctgg  tggggctgct  ctccctcggg  tgcgtcctct  ctccaggagt  cacgaagtcc
61  aaggtcagca  gctgcccggg  atgcatcgag  tcggggcccg  gctgcacctg  gtgccagaag
121 ctgaacttca  cagggccggg  ggatcctgac  tccattcgct  gcgacaccgc  gccacagctg
181 ctcatgaggg  gctgtgcggc  tgacgacatc  atggacccca  caagcctcgc  tgaaacccag
241 gaagaccaca  atgggggcca  gaagcagctg  tccccacaaa  aagtgacgct  ttacctcgga
301 ccaggccagg  cagcagcgtt  caacgtgacc  ttccggcggg  ccaagggcta  ccccatcgac
361 ctgtactatc  tgatggacct  ctccactacc  atgcttgatg  acctcaggaa  tgtcaagaag
421 ctagggtggc  acctgctccg  ggccctcaac  gagatcaccg  agtccggccg  cattggcttc
481 gggtcctteg  tggacaagac  cgtgctgccc  ttcgtgaaca  cgcaccctga  taagctgcca
541 aacctatgcc  ccaacaagga  gaaagagtgc  ccgccccgt  ttgccttcag  gcacgtgctg
601 aagctgacca  acaactccaa  ccagtttcag  accgaggtcg  ggaagcagct  gatttccgga
661 aacctggatg  caccgagggg  tgggctggac  gccatgatgc  aggtcggcgc  ctgcccggag
721 gaaatcggct  ggcgcaacgt  cacgcggctg  ctgggtgttg  cactgatga  cggcttccat
781 ttcgcccggc  acggaaagct  gggcgccatc  ctgaccccc  acgacggccg  ctgtcacctg
841 gaggacaact  tgtacaagag  gagcaacgaa  ttcgactacc  catcgggtgg  ccagctggcg
901 cacaagctgg  ctgaaaacaa  catccagccc  atcttcgccc  tgaccagtag  gatggtgaag
961 acctacgaga  aactcaccga  gatcatcccc  aagtcagccc  tgggggagct  gtctgaggac
1021 tccagcaatg  tgggtccatc  cattaagaat  gttacaata  aactctctc  cagggctctc
1081 ctggatcaca  acgcccctcc  cgacaccctg  aaagtcacct  acgactcctt  ctgcagcaat
1141 ggagtgacgc  acaggaacca  gccagaggt  gactgtgatg  gctgacagat  caatgtcccg
1201 atcaccttcc  aggtgaaggt  cacggccaca  gactgcatcc  aggagcagtc  gtttgtcatc
1261 cgggcgctgg  gcttcacgga  catagtgacc  gtgcaggtcc  ttcccagtg  tgagtgcggc
1321 tgcccggacc  agagcagaga  ccgacgcctc  tgccatggca  agggcttctt  ggagtgcggc
1381 atctgcaggt  gtgacactgg  ctacattggg  aaaaactgtg  agtgccagac  acagggccgg
1441 agcagccagg  agctggaagg  aagctgcccg  aaggacaaca  actccatcat  ctgctcaggg
1501 ctgggggact  gtgtctgccc  gcagtgcctg  tgccacacca  gcgacgtccc  cggcaagctg
1561 atatacgggc  agtactgcca  gtgtgacacc  atcaactgtg  agcgtacaaa  cggccaggtc
1621 tgcggcggcc  cggggagggg  gctctgcttc  tgcgggaagt  gccgctgcca  cccgggcttt
1681 gagggctcag  cgtgccagtg  cgagaggacc  actgagggct  gcctgaacc  cggcgctgtt
1741 gagtgtagt  gtcgtggccc  gtgcccgtgc  aacgtatgcg  agtgccattc  aggctaccag
1801 ctgcctctgt  gccaggagt  ccccggctgc  cctcaccct  gtggcaagta  catctcctgc
1861 gccgagtgcc  tgaagtccga  aaagggcccc  tttgggaaga  actgcagcgc  ggcgtgtccc
1921 ggctgacgac  tgcgcaacaa  ccccgtaag  ggcaggacct  gcaaggagag  ggactcagag
1981 ggctgctggg  tggcctacac  gctggagcag  caggacggga  tggaccgcta  cctcatctat
2041 gtggatgaga  gccgagagt  tgtggcaggc  cccaacatcg  ccgcatcgt  cgggggacc
2101 gtggcaggca  tcgtgctgat  cggcattctc  ctgctggtca  tctggaaggc  tctgatccac
2161 ctgagcgacc  tccgggagta  caggcgcttt  gagaaggaga  agctcaagtc  ccagtggaac
2221 aatgataatc  cccttttcaa  gagcgccacc  acgacgttca  tgaaccccaa  gtttgcctgag
2281 agttaggagc  a
    
```

FIGURE 9

CD11a amino acid sequence (SEQ ID NO: 25)

```

1 mkdscitvma mallsgffff apassynldv rgarsfsppr agrhfgyrvl qvngnvivga
61 pgegenstgsl yqcqsgtghc lpvtlrgsny tskylgmtla tdptdgsila cdpglrctcd
121 qntylsglcy lfrqnlqgpm lqgrpgfqc ikgnvdlvfl fdgmsmlqpd efqkildfmk
181 dvmkklnts yqfaavqfst syktefdfsd yvkrkdpdal lkhvkhmlll tntfgainyv
241 atevfreelg arpdatkvli iitdgeatds gnidaakdii ryiigigkhf qtkesqetlh
301 kfaskpasef vkildtfekl kdlftelqkk iyviegtstkq dltsfnmels ssgisadlsr
361 ghavvgavga kdwaggfldl kadlqddtffi gnepltpivr agylgyvtvw lpsrqktsll
421 asgapryqhm grvllfqepq gggghwsqvqt ihgtqigsyf ggelcgvdvd qdgetelli
481 gaplfygeqr ggrvfiyqrr qlgfeevsel qgdpgyplgr fgeaitaltd ingdglvda
541 vgapleeqga vyifngrhgg lspqpsqrie gtqvlsgiqw fgrsihgvkd legdgladva
601 vgaesqmivl sspvvdmtv lmsfspaeip vhevecsyst snkmkegvni ticfqiksli
661 pqfqqrlvan ltytlqldgh rtrrrglfpg grhelrrnia vttsmsctdf sfhfpvcvqd
721 lispinvsln fslweeegtp rdqraqgkdi ppilrpslhs etweipfekon cgedkkcean
781 lrsvsfpars ralrltafas lsvslslsln eedaywvqld lhfpqglfkr kvemlkphsq
841 ipvsceelpe esrllsrals cnvsspifka ghsvallqmmf ntlvnsswgd svelhanvte
901 nnedsdllled nsattiipil ypiniliqdq edstlyvsft pkgpkihgvk hmyqvriqps
961 ihdhniptle avvgvpqpps egpithqsvv qmepvpchy edlerlpdaa epclpgalfr
1021 cpvvrqeil vqvigtelvl geieassmfs lcsslsisfn sskhfhlygs naslaqvvmk
1081 vdvyekqml ylyvlsiggg llllllifiv lykvqffkrn lkekmeagrg vpngipaeds
1141 eqlasgqeag dpgclklphe kdsesgggkd

```

CD11b amino acid sequence (SEQ ID NO: 26)

```

1 malrvlllta ltlchgnld tenamtqen argfgqsvvq lqgsrvvva ppeivaanqr
61 gslyqcdyst gscepirqlv pveavnmslg lsllaattsp qllacgptvh qtcsestyvk
121 glcflfgsnl rqqpqkfpea lrgcpqedsd iaflidgsgs iiphdfrrmk efvstvmekl
181 kkskltflsm qyseefrihf tfkefqnnpn prslvkpitq llgrthtatg irkvvrelfn
241 itngarknaf kilvvitdgc kfgdplgyed vipeadregv iryvigvga frseksrqel
301 ntiaskpprd hvfqvnnfea lktiqlre kifaiegtqt gssssfehem sqegfsaait
361 sngpllsvg sydwaggvfl ytskekstfi nmtrvdsdmn daylgyaaa ilrnrqslv
421 lgapryqhg lvamfrqntg mwesnanvkg tqigayfgas lcsvdvdsng stdlvligap
481 hyeqtrggq vsvcplprgr arwqcdavly geqqgpwgrf gaaltvlgdv ngdkltdvai
541 gapgeednrg avylfhgtsq sgispshsqr iagsklsprl qyfgqslsgg qdltmdglvd
601 ltvgaqghvl llrsqpvlrv kaimefnpre varnvfecnd qvvkgkeage vrvclhvqks
661 trdrlegqi qsvtydlal dsgrphsra vnetknstrr qtqvlglqt cetlklqlpn
721 ciedpvspiv lrlnflsvgt plsafgnlrp vlaedaqlf talpfeqnc gndnicqddl
781 sitfsfmsld clvvggpref nvtvtrndg edsyrtqvtf ffpldlsyrk vstlqnqrsq
841 rswrlacesa sstevsgalk stscsinhpi fpensevtn itfdvdskas lgnklkkan
901 vtsennmprt nktefqlp vkyavymvvt shgvstkyln ftasentsrv mqhqvqvsnl
961 gqrsllpislv flvpvrlngt viwdrpqvtf senlsstcht kerlpshsdf laelrkpvv
1021 ncsiavcqli qcdipffgiq eefnatlkgn lsfdwyikts hnhllivsta eilfndsvft
1081 llpgqgafvr sqtetkvepf evpnplpliv gssvqgllll alitaalykl gffkrqykdm
1141 msegppgae pq

```

CONTINUED

CD11c amino acid sequence (SEQ ID NO: 27)

```

1 mtrtraalll ftalatslgf nldteeltaf rvdsagfgds vvqyanswvv vgapqkitaa
61 nqtggglyqcg ystgacepig lqvpeavnm slglslastt spsqllacgp tvhhecgrnm
121 yltglcfllg ptqltqrlpv srqecprqeq divflidgsg sissrnfatm mnfvravisq
181 fqrpstqfsl mqfsnkfqth ftfeefrfts nplsllasvh qlqgftytat aiqnvvhrlf
241 hasygarrda tkilivitdg kkegdsldyk dvipmadaag iiryaigvgl afqnrnswe
301 lndiaskpsq ehifkvedfd alkdignqlk ekifaiegte ttssssfele magegfsavf
361 tpdgppvlgav gsftwsggaf lyppnmsptf inmsqenvdm rdsylgyste lalwkgvqsl
421 vlgapryqht gkaviftqvs rqrwmkaevt gtqigsyfga slcsvdvdtg gstdlvliga
481 phyyeqtrgg qsvvcplprg wrrowcdavl ygeqghpwgr fgaaltvlgd vngdkltdvv
541 igapgeeenr gavylfhgvl gpsispshsq riagsqlssr lqyfgqalsg gqdltdqglv
601 dlavgargqv lllrtrpvlw vgvsmqfipa eiprsafecr eqvvseqltv qsniclyidk
661 rsknllgsrd lqssvtldla ldpgrlspra tfqetknrsl srvrvlglka hcenfnlllp
721 scvedsvtpi tlrlnftlvg kpllafrnlr pmlaadaqry ftaslpfekn cgadhicqdn
781 lgisfsfpgl ksllvgsnle lnaevmvwnd gedsygttit fshpaglsyr yvaegqkqgg
841 lrslhltcds apvsgqgts tscrinhlif rggaqitfla tfdvspkavl gdrllltanv
901 ssenntprts kttfqlelpv kyavytvvss heqftkylnf seseekeshv amhryqvnnl
961 gqrdlpvsin fwvpvelnqe avwmdvevsh pqnpslrcss ekiappasdf lahiqknpvl
1021 dcsiagclrf rcdvpsfsvq eeldftlkgn lsfgwvrqil qkkvsvsva eitfdtsvys
1081 qlpgqeafmr aqtttvleky kvhnptpliv gssiggl111 alitavlykv gffkrqykem
1141 meeangqiap engtqtpssp sek

```

CD18 amino acid sequence (SEQ ID NO: 28)

```

1 mlglrpplla lvgllslgcv lsqectkfkv sscreciesg pgctwcqkln ftgpgdpdsi
61 rcdtrpqlm rgcaaddimd ptslaetqed hnggqkqlsp qkvtylrlpg qaaafnvtfr
121 rakgypidly ylmdlsysml ddlnrvkklg gdllralnei tesgrigfgs fvdktvlpfv
181 nthpdklrnp cpnkekecqp pfafrhvlkl tnnsnqfqt vqkqlisgnl dapegldam
241 mqvaacpeei gwrnvtrllv fatddgfhfa gdgklgail pndgrchled nlykrsnefd
301 ypsvgqlahk laenniqipf avtsrmvkt yeklteiipks avgelsedss nvvqliknay
361 nklssrvfld hnalpdtlkv tydsfcsngv thrnqprgdc dgvginvtat fqvkvatec
421 iqeqsfvira lgftdivtvq vlpqcecr crdqsrdslch gkgflecgc rcdtygikn
481 cecqtqgrss qelegscrkd nnsiicsglg dcvcgqclch tsdvpqkliy gqycecdtin
541 ceryngqvcg gpgrglcfcg kcrchpgfeg sacqcerte gclnprvec sgrgrcrnv
601 cechsgyqlp lcqecpgcps pcgkyisca clkfekgpgf kncsaacpgl qlsnpvkgr
661 tckerdsegc wwaytleqgd gmdryliyvd esrecvagnp iaavvggtva givligilll
721 viwkalihls dlreyrrfek eklksqwnnd nplfksatt vmnpkfaes

```

CD11a mRNA nucleic acid sequence (SEQ ID NO: 29)

```

1 cctctttcac cctgtctagg ttgccagcaa atcccacggg cctcctgacg ctgcccctgg
61 ggccacaggt ccctcgagt ctggaaggat gaaggattcc tgcactactg tgatggccat
121 ggcgctgctg tctgggttct ttttcttcgc gccggcctcg agctacaacc tggacgtgcg
181 gggcgcgcg agcttctccc caccgcgcgc cgggaggcac tttggatacc gcgtcctgca
241 ggtcggaaac ggggtcatcg tgggagctcc aggggagggg aacagcacag gaagcctcta
301 tcagtgccag tcgggcacag gacactgcct gccagtcacc ctgagaggtt ccaactatac
361 ctccaagtac ttgggaatga ccttggcaac agaccccaca gatggaagca ttttggcctg
421 tgaccctggg ctgtctcgaa cgtgtgacca gaacacctat ctgagtggcc tgtgtacct
481 ctaccgcccag aatctgcagg gtcccactgt gcaggggcgc cctggttttc aggaatgtat
541 caatggcaac gtagacctgg tatttctggt tgatgggttc atgagcttgc agccagatga
601 atttcagaaa attctggact tcatgaagga tgtgatgaag aaactcagca aacttcgta
661 ccagtttgct gctgttcagt tttccacaag ctacaaaaca gaatttgatt tctcagatta
721 tgttaaattg aaggaccctg atgctctgct gaagcatgta aagcacatgt tgctgttgac
781 caataccttt ggtgccatca attatgtcgc gacagaggtg ttccgggagg agctgggggc
841 ccggccagat gccaccaaag tgcttatcat catcacggat ggggaggcca ctgacagtgg

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CONTINUED

901 caacatcgat gcggccaaag acatcatccg ctacatcatc gggattggaa agcattttca
 961 gaccaaggag agtcaggaga ccctccacaa atttgcatac aaacccgcga gcgagtttgt
 1021 gaaaattctg gacacatttg agaagctgaa agatctattc actgagctgc agaagaagat
 1081 ctatgtcatt gagggcacia gcaaacagga cctgacttcc ttcaacatgg agctgtcctc
 1141 cagcggcatc agtgctgacc tcagcagggg ccatgcagtc gtgggggag taggagccaa
 1201 ggactgggct gggggctttc ttgacctgaa ggcagacctg caggatgaca catttattgg
 1261 gaatgaacca ttgacaccag aagtgagagc aggctatttg ggttacaccg tgacctggct
 1321 gccctcccgg caaaagactt cgttgctggc ctccgggagcc cctcgatacc agcacatggg
 1381 ccgagtgcct ctgttccaag agccacaggg cggaggacac tggagccagg tccagacaat
 1441 ccatgggacc cagattggct cttatttcgg tggggagctg tgtggcgtcg acgtggacca
 1501 agatggggag acagagctgc tgctgattgg tgccccactg ttctatgggg agcagagagg
 1561 aggccgggtg tttatctacc agagaagaca gttggggttt gaagaagtct cagagctgca
 1621 gggggacccc ggctaccacac tcgggcggtt tggagaagcc atcactgctc tgacagacat
 1681 caacggcgat gggctggtag acgtggctgt gggggcccct ctggaggagc agggggctgt
 1741 gtacatcttc aatgggaggg acggggggct tagtccccag ccaagtgcgc ggaatagaag
 1801 gaccaagtgc ctctcaggaa ttcagtgggt tggagcctcc atccatgggg tgaaggacct
 1861 tgaaggggat ggcttggcag atgtggctgt gggggctgag agccagatga tctgtctgag
 1921 ctcccggccc gtggtggata tggtcaccct gatgtccttc tctccagctg agatcccagt
 1981 gcatgaagtg gagtgtcctc attcaaccag taacaagatg aaagaaggag ttaatatcac
 2041 aatctgtttc cagatcaagt ctctctaccc ccagttccaa ggccgcctgg ttgccaatct
 2101 cacttacact ctgcagctgg atggccaccg gaccagaaga cgggggttgt tcccaggagg
 2161 gagacatgaa ctcagaagga atatagctgt caccaccagc atgtcatgca ctgacttctc
 2221 atttcatttc ccggtatgtg ttcaagacct catctcccc atcaatgttt ccctgaattt
 2281 ctctctttgg gaggaggaag ggacaccgag ggaccaaagg gcgcagggca aggacatacc
 2341 gccatcctg agaccctccc tgcactcggg aacctgggag atcccttttg agaagaactg
 2401 tggggaggac aagaagtgtg aggcaaactt gagagtgtcc ttctctcctg caagatccag
 2461 agccctgcgt ctaactgctt ttgccagcct ctctgtggag ctgagcctga gtaacttggg
 2521 agaagatgct tactgggtcc agctggacct gcacttcccc ccgggactct ccttccgcaa
 2581 ggtggagatg ctgaagcccc atagccagat acctgtgagc tgcgaggagc ttctgaaga
 2641 gtccaggctt ctgtccaggg cattatcttg caatgtgagc tctcccatct tcaaagcagg
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 4801 cttgaacctg ggaggtggag gttgcagtga gccaaagattg cgccattgca ctccagcctg
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 4921 ggacatcccc acccttggag gctgtcttct caggctctgc cctgccctag ctccacaccc
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CD11b mRNA nucleic acid sequence (SEQ ID NO: 30)

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 121 taacagcctt gaccttatgt catgggttca acttggacac tgaaaacgca atgaccttcc
 181 aagagaacgc aaggggcttc gggcagagcg tgggccagct tcagggatcc aggggtgggtg
 241 ttggagcccc ccaggagata gtggctgcca accaaagggg cagcctctac cagtgcgact
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CD11c mRNA nucleic acid sequence (SEQ ID NO: 31)

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CD18 mRNA nucleic acid sequence (SEQ ID NO: 32)

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1521 gcagtgcctg tgccacacca gcgacgtccc cggcaagctg
1561 atatacgggc agtactgcca gtgtgacacc atcaactgtg
1601 agcgtacaaa cggccaggtc tgcggcggcc cggggagggg
1641 gctctgcttc tgcgggaagt gccgctgcca cccgggcttt
1681 gagggctcag cgtgccagtg cgagaggacc actgagggct
1721 gcctgaacct gcggcgtgtt gactgtagtg gtcgtggccc
1761 gtgccgctgc aacgtatgca agtgccattc aggctaccag
1801 ctgcctctgt gccaggagtg ccccggtgca cctcaccct

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1841 gtggcaagta catctcctgc gccgagtgcc tgaagttcga
1881 aaagggccc ttgggaaga actgcagcgc ggcgtgtccg
1921 ggcctgcagc tgtcgaacaa ccccgtaag ggcaggacct
1961 gcaaggagag ggactcagag ggctgctggg tggcctacac
2001 gctggagcag caggacggga tggaccgcta cctcatctat
2041 gtggatgaga gccgagagtg tgtggcaggc cccaacatcg
2081 ccgccatcgt cgggggcacc gtggcaggca tcgtgctgat
2121 cggcattctc ctgctggtea tctggaaggc tctgatccac
2161 ctgagcgacc tccgggagta caggcgcttt gagaaggaga
2201 agctcaagtc ccagtggaac aatgataatc cccttttcaa
2241 gagcgccacc acgacggtea tgaaccccaa gtttgctgag
2281 agttaggagc a