CD86 ANTAGONIST MULTI-TARGET BINDING PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application Nos. 61/102,288 filed October 2, 2008; 61/102,297 filed October 2, 2008; 61/102,307 filed October 2, 2008; 61/102,315 filed October 2, 2008; 61/102,319 filed October 2, 2008; 61/102,327 filed October 2, 2008; 61/102,331 filed October 2, 2008; 61/102,334 filed October 2, 2008; and 61/102,336 filed October 2, 2008, where these *(nine)* provisional applications are incorporated herein by reference in their entireties.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 910180_421PC_SEQUENCE_LISTING.txt. The text file is 705 KB, was created on October 2, 2009, and is being submitted electronically via EFS-Web, concurrent with the filing of the specification.

BACKGROUND

Technical Field

This disclosure relates generally to the field of multi-specific binding molecules and therapeutic applications thereof and more specifically to a fusion protein composed of a CD86 antagonist binding domain, and another binding domain that is specific for a heterologous target, such as an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist, as well as compositions and therapeutic uses thereof.

Description of the Related Art

The human immune system generally protects the body from damage by foreign substances and pathogens. One way in which the immune system protects the body is by producing specialized cells, referred to as T lymphocytes or T-cells. Intercellular interactions between T-cells and antigen-presenting cells (APCs) generate T-cell costimulatory signals that in turn lead to

T-cell responses to antigens. Full T cell activation requires both binding of the T-cell receptor (TCR) to antigen-MHC complex present on antigen-presenting cells and binding of the receptor CD28 on the surface of the T-cell to the CD86 and/or CD80 ligands present on antigen-presenting cells, particularly dendritic cells.

CD80 (also known as B7-1) was originally described as a human B-cell associated activation antigen and was subsequently found to be a receptor for the related T-cell molecules CD28 and cytotoxic T lymphocyte-associated antigen-4 (CTLA4). In later studies, another counterreceptor for CTLA4 known as CD86 (also known as B7-0 or B7-2) was identified. CD86 shares about 25% sequence identity with CD80 in its extracellular region. While CD80 and CD86 are generally believed to be functionally equivalent in their ability to initiate and maintain proliferation of CD4(+) T cells (Vasilevko et al. (2002) DNA Cell Biol. 21:137-49), and clinical data with a soluble CTLA4 Ig fusion protein that blocks this activity for both molecules has shown clinical benefit (Genovese et al. (2005) NEJM 353:114-1123), there is some evidence that specific inhibition of CD86 might be of benefit. For example, engagement of CD86 or CD80 has different effects on B cells. Specifically, CD80 has been shown to provide a negative signal for the proliferation and IgG secretion of both normal B cells and B cell lymphomas, while CD86 enhances the activity of B cells (Suvas et al. (2002) J. Biol. Chem. 277:7766-7775). There is also some evidence that engagement of CD80 on T cells is immunosuppressive (Lang et al. (2002) J. Immunol. 168:3786-3792; Taylor et al. (2004) J. Immunol. 172:34-39; Paust et al. (2004) PNAS 101:10398-10403) and that it may mediate further immunosuppression through PD-L1 (CD274) signaling on activated APCs or T cells (Butte et al. (2007) Immunity 27:111-122; Keir (2008) Ann. Rev. Immunol. 26:677-704). Accordingly, inhibition of CD86 in the absence of CD80 inhibition may be beneficial in the treatment of autoimmune and inflammatory disease as well as B cell lymphomas.

CTLA4 is a type 1 transmembrane glycoprotein of the immunoglobulin superfamily that is mainly expressed in activated T-cells, with some expression also being found in the CD4+CD25+ regulatory T-cell (Treg) subset. CD86 and CD80 are believed to be the only endogenous ligands for CTLA4. CTLA4 has been shown to bind CD86 and CD80 with greater affinity and avidity compared with CD28 (Linsley *et al.* (1991) J. Exp. Med. 174:561-69; Linsley *et al.* (1994) Immunity 1:793-801), and plays a key role as a negative

regulator of T-cell activation. Specifically, binding of CTLA4 to CD80/CD86 leads to downregulation of T-cell responses and to the preservation of T-cell homeostasis and peripheral tolerance. This is believed to be due to both antagonism of CD28-dependent costimulation and directive negative signaling through the CTLA4 cytoplasmic tail. For a review of CTLA4 structure and function, *see* Teft et al. (2006) Annu. Rev. Immunol. 24:65-97.

As mentioned above, a productive immune response requires both engagement of TCR and binding of CD28 to CD80 and/or CD86. TCR binding in the absence of CD28 binding leads to T cells either undergoing apoptosis or becoming anergic. In addition, CD28 signaling has been shown to increase cytokine production by T cells. Specifically, CD28 stimulation has been shown to increase production of IL-2, TNFα, lymphotoxin, IFNγ and GM-CSF 5- to 50-fold in activated T cells. Furthermore, induction of lymphokine and/or cytokine gene expression by CD28 has been shown to occur even in the presence of the immunosuppressant cyclosporine (Thompson et al. (1989) Proc. Natl. Acad. Sci. USA 86:1333-1337). CD28 has also been shown to promote T cell survival by inducing upregulation of the anti-apoptotic BCL-XL (Alegre et al. (2001) Nature Rev. Immunol. 1:220-228).

Soluble forms of CTLA4 have been constructed by fusing the variable-like extracellular domain of CTLA4 to immunoglobulin constant domains to provide CTLA4-Ig fusion proteins. Soluble CTLA-4-Ig has been shown to prevent CD28-dependent costimulation by binding to both CD86 and CD80 (Linsley et al. (1991) J. Exp. Med., 174:561-69), and to inhibit costimulation of T cells and have beneficial immunosuppression effects in humans (Bruce & Boyce (2007) Ann. Pharmacother. 41:1153-1162). The CTLA4-Ig fusion protein abatacept is currently employed for the treatment of rheumatoid arthritis in cases of inadequate response to anti-TNFα therapy. However, not all patients respond to CTLA4-Ig and continued response requires frequent drug administration, perhaps in part because blockage of interaction of CD28 with CD86/CD80 is a weak inducer of Tregs and insufficient for blocking activated effector T cell responses in a disease milieu.

SUMMARY

In one aspect, there is provided a multi-specific fusion protein, comprising a CD86 binding domain linked to a heterologous binding domain by an intervening domain, wherein the heterologous binding domain is an IL-10 agonist, and wherein the IL-10 agonist binding domain comprises an IL-10 or a functional region thereof; or a multi-specific fusion protein, comprising a CD86 binding domain linked to a heterologous binding domain by an intervening domain, wherein the heterologous binding domain comprises an IL-10 agonist, and wherein the IL-10 agonist is an IL-10 or a functional region thereof.

In another aspect, there is provided a composition comprising one or more multi-specific fusion proteins as defined above and a pharmaceutically acceptable carrier, diluent, or excipient.

In yet another aspect, there is provided a polynucleotide encoding the multi-specific fusion protein as defined above.

In yet another aspect, there is provided an expression vector comprising the polynucleotide as defined above operably linked to an expression control sequence.

In yet another aspect, there is provided a host cell comprising the expression vector as defined above.

In yet another aspect, there is provided the use of the fusion protein as defined above or the composition as defined above in the manufacture of the medicament for treating a subject with a disorder associated with CD86, IL-10, or a combination thereof.

In yet another aspect, there is provided the use of the fusion protein as defined above or the composition as defined above in the manufacture of the medicament for treating a subject with an autoimmune disease selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, asthma, systemic lupus erythematosus (SLE), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), graft versus host disease, psoriasis, multiple sclerosis, dermatomyositis, polymyositis, pernicious anaemia, primary biliary cirrhosis, acute disseminated encephalomyelitis (ADEM), Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS) autoimmune hepatitis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, lupus erythematosus, pemphigus vulgaris, Sjögren's syndrome, temporal arthritis (also known as "giant cell arthritis"), autoimmune hemolytic anemia, bullous pemphigoid, vasculitis, celiac disease, endometriosis, hidradenitis suppurativa, interstitial cystitis, morphea, scleroderma, narcolepsy, neuromyotonia, vitiligo and autoimmune inner ear disease or for suppressing a detrimental alloresponse to an organ transplant.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure1 shows binding to CD80 by various proteins, including abatacept, a CTLA4-Ig(N2) (SEQ ID NO:11), and a multi-specific xceptor fusion protein containing a CTLA4 ectodomain fused to an IL10 (SEQ ID NO:9).

Figure 2 shows that CTLA4-Ig(N2) (SEQ ID NO:11) and a multi-specific xceptor fusion protein containing a CTLA4 ectodomain fused to an IL10 (SEQ ID NO:9) can bind to soluble IL10Ra (sIL10Ra).

Figs. 3 and 4 show that a multi-specific xceptor fusion protein containing a CTLA4 ectodomain fused to an IL10 (SEQ ID NO:9) can induce STAT3 phosphorylation in PBMC.

Figure 5 shows that xceptors containing anti-CD86 binding domains from 3D1 and humanized FUN1 monoclonal antibodies bind to CD86 on WIL2-S cells.

Figure 6 shows that an xceptor containing a CD86 binding domain and IL10 can simultaneously bind cell surface CD86 and and sIL10Ra.

Figure 7 shows that various different versions of humanized anti-CD86 FUN1 SMIPs can bind CD86.

Figure 8 shows that CTLA4::IL10 xceptor molecules having various linkers joining IL10 to the carboxy-terminus (BD2) of the xceptor can bind IL10R1-Ig. Δ-SEQ ID NO:9 ; ◊-SEQ ID NO: 171 ; •-SEQ ID NO:302 ; ▲-SEQ ID NO:173.

Figure 9 shows that CTLA4::IL10 xceptor molecules having shorter linkers joining IL10 to the carboxy-terminus (BD2) of the xceptor can bind IL10R1-Ig. Δ-SEQ ID NO:171; ◊-SEQ ID NO:175 ; •-SEQ ID NO:177 ; ▲-SEQ ID NO:179.

Figure 10 shows that several xceptor proteins bind to CD80.

Figure 11 shows that several xceptor proteins bind to CD86.

Figure 12 shows that several xceptor proteins bind to sIL10Ra.

Figure 13 shows that several xceptor proteins can simultaneously bind to CD80 and sIL10Ra.

Figure 14 shows that several xceptor proteins are crossreactive with mouse CD80.

Figure 15 shows that several xceptor proteins are crossreactive with mouse CD86.

Figures 16 and 17 show that several xceptor proteins block a human T cell response in an MLR assay.

Figures 18 to 20 show that several xceptor proteins block a mouse T cell response in an MLR assay.

Figures 21 and 22 show that several xceptor proteins containing a variant IL10 (either IL10 with an I87 mutation or monoIL10) or a variant CTLA4 block a human T cell response in an MLR assay.

Figure 23 shows that several xceptor proteins containing a variant IL10 (either IL10 with an I87 mutation or monoIL10) are less immunostimulatory than mouse IL10 in an MC/9 cell proliferation assay.

Figure 24 shows that several xceptor proteins containing a variant IL10 (either IL10 with an I87 mutation or monoIL10) are less immunostimulatory than human IL10 in an MC/9 cell proliferation assay.

DETAILED DESCRIPTION

The present disclosure makes possible the targeting of antigen presenting cells (APCs) to alter activity. For example, T-cell activity can be modulated by providing multi-specific xceptor fusion proteins that comprise a first binding domain that preferentially binds a CD86, and a second binding domain (a heterologous binding domain). In certain embodiments, a multi-specific xceptor fusion protein comprises a first and second binding domain, a first and second linker, and an intervening domain, wherein one end of the intervening domain is fused via a linker to the first binding domain that is a CD86 binding domain and the other end is fused via a linker to the second binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist.

In certain embodiments, the CD86 binding domain is a CTLA4 ectodomain, a CD28 ectodomain, or an immunoglobulin variable region binding domain (such as a scFv) specific for CD86 (*e.g.*, from monoclonal antibodies 3D1 or FUN1). In some embodiments, less than an entire ectodomain is used. For example, domains within the CTLA4 ectodomain that bind CD86 and prevent binding of CD86 to CD28 can be used. In further embodiments, the IL10 agonist is IL10 or a functional region thereof. In further embodiments, the HLA-G agonist is an HLA-G5, an HLA-G1, an HLA-G mutein, or a functional region thereof; an ectodomain of an HLA-G5, an HLA-G1 or an HLA-G mutein; or an immunoglobulin variable region binding domain (such as a scFv) specific for ILT2, ILT4 or KIR2DL4. In still further embodiments, the heterologous binding domain is an HGF agonist, such as an HGF or a sub-domain thereof. In another embodiment, the heterologous binding domain is an IL35 agonist,

such as an immunoglobulin variable region binding domain (such as a scFv) specific for IL35R or IL35, or a functional region thereof. In further embodiments, the LIGHT antagonist is an immunoglobulin variable region binding domain (such as a scFv) specific for LIGHT, or a HVEM ectodomain or a functional region thereof. In further embodiments, the PD-1 agonist is an immunoglobulin variable region binding domain (such as a scFv) specific for PD-1, or a PD-1 ligand (e.g. PD-L1 or PD-L2) or a functional region thereof. In further embodiments, the BTLA agonist is an immunoglobulin-like variable region binding domain (such as a scFv) specific for BTLA, or a HVEM ectodomain or a functional region thereof. In certain embodiments, the GITRL antagonist is an immunoglobulin-like variable region binding domain (such as a scFv) specific for GITRL, or a GITR ectodomain, soluble GITR, or a functional region thereof. In certain embodiments, the CD40 antagonist is an immunoglobulin-like variable region binding domain (such as a scFv) specific for CD40.

Exemplary structures of such multi-specific fusion proteins, referred to herein as Xceptor molecules, include N-BD-ID-ED-C, N-ED-ID-BD-C, N-BD1-ID-BD2-C, and N-ED-ID-ED-C, wherein N- and –C refer to the amino- and carboxy terminus, respectively; BD is an immunoglobulin-like or immunoglobulin variable region binding domain; ID is an intervening domain; and ED is an extracellular or ectodomain, such as a receptor ligand binding domain, ligand, C-type lectin domain, semaphorin or semaphorin-like domain, or the like. In some constructs, the ID can comprise an immunoglobulin constant region or sub-region disposed between the first and second binding domains. In still further constructs, the BD and ED are each linked to the ID via the same or different linker (*e.g.*, a linker comprising one to 50 amino acids), such as an immunoglobulin hinge region (made up of, for example, the upper and core regions) or functional variant thereof, or a lectin interdomain region or functional variant thereof, or a cluster of differentiation (CD) molecule stalk region or functional variant thereof.

Prior to setting forth this disclosure in more detail, it may be helpful to an understanding thereof to provide definitions of certain terms to be used herein. Additional definitions are set forth throughout this disclosure.

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof

(such as one tenth and one hundredth of an integer), unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. As used herein, "about" or "consisting essentially of" mean ± 20% of the indicated range, value, or structure, unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. The use of the alternative (e.g., "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously. In addition, it should be understood that the individual compounds, or groups of compounds, derived from the various combinations of the structures and substituents described herein, are disclosed by the present application to the same extent as if each compound or group of compounds was set forth individually. Thus, selection of particular structures or particular substituents is within the scope of the present disclosure.

A "binding domain" or "binding region" according to the present disclosure may be, for example, any protein, polypeptide, oligopeptide, or peptide that possesses the ability to specifically recognize and bind to a biological molecule (*e.g.*, CD86) or a complex of more than one of the same or different molecule or assembly or aggregate, whether stable or transient (*e.g.* CD86/CD28 complex). Such biological molecules include proteins, polypeptides, oligopeptides, peptides, amino acids, or derivatives thereof, lipids, fatty acids, or derivatives thereof; carbohydrates, saccharides, or derivatives thereof; nucleotides, nucleosides, peptide nucleic acids, nucleic acid molecules, or derivatives thereof; glycoproteins, glycopeptides, glycolipids, lipoproteins, proteolipids, or derivatives thereof; other biological molecules that may be present in, for example, a biological sample; or any combination thereof. A binding region includes any naturally occurring, synthetic, semi-synthetic, or recombinantly produced binding partner for a biological molecule or other target of interest. A variety of assays are known for identifying binding domains of the present disclosure that specifically bind with a particular target, including FACS, Western blot, ELISA, or Biacore analysis.

Binding domains and fusion proteins thereof of this disclosure can be capable of binding to a desired degree, including "specifically or selectively binding" a target while not significantly binding other components present in a

test sample, if they bind a target molecule with an affinity or K_a (*i.e.*, an equilibrium association constant of a particular binding interaction with units of 1/M) of, for example, greater than or equal to about 10^5 M^{-1}, 10^6 M^{-1}, 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1}, 10^{12} M^{-1}, or 10^{13} M^{-1}. "High affinity" binding domains refers to those binding domains with a K_a of at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 10^9 M^{-1}, at least 10^{10} M^{-1}, at least 10^{11} M^{-1}, at least 10^{12} M^{-1}, at least 10^{13} M^{-1}, or greater. Alternatively, affinity may be defined as an equilibrium dissociation constant (K_d) of a particular binding interaction with units of M (*e.g.*, 10^{-5} M to 10^{-13} M). Affinities of binding domain polypeptides and fusion proteins according to the present disclosure can be readily determined using conventional techniques (*see, e.g.*, Scatchard *et al.* (1949) Ann. N.Y. Acad. Sci. 51:660; and U.S. Patent Nos. 5,283,173; 5,468,614, or the equivalent).

Binding domains of this disclosure can be generated as described herein or by a variety of methods known in the art (*see, e.g.*, US Patent Nos. 6,291,161; 6,291,158). Sources include antibody gene sequences from various species (which can be formatted as antibodies, sFvs, scFvs or Fabs, such as in a phage library), including human, camelid (from camels, dromedaries, or llamas; Hamers-Casterman *et al.* (1993) Nature, 363:446 and Nguyen *et al.* (1998) J. Mol. Biol., 275:413), shark (Roux *et al.* (1998) Proc. Nat'l. Acad. Sci. (USA) 95:11804), fish (Nguyen *et al.* (2002) Immunogenetics, 54:39), rodent, avian, ovine, sequences that encode random peptide libraries or sequences that encode an engineered diversity of amino acids in loop regions of alternative non-antibody scaffolds, such as fibrinogen domains (*see, e.g.*, Weisel *et al.* (1985) Science 230:1388), Kunitz domains (*see, e.g.*, US Patent No. 6,423,498), lipocalin domains (*see, e.g.*, WO 2006/095164), V-like domains (*see, e.g.*, US Patent Application Publication No. 2007/0065431), C-type lectin domains (Zelensky and Gready (2005) FEBS J. 272:6179), mAb^2 or Fcab™ (*see, e.g.*, PCT Patent Application Publication Nos. WO 2007/098934; WO 2006/072620), or the like. Additionally, traditional strategies for hybridoma development using, for example, a synthetic single chain CD86 as an immunogen in convenient systems (*e.g.*, mice, HuMAb mouse®, TC mouse™, KM-mouse®, llamas, chicken, rats, hamsters, rabbits, *etc.*) can be used to develop binding domains of this disclosure.

Terms understood by those in the art as referring to antibody technology are each given the meaning acquired in the art, unless expressly

defined herein. For example, the terms "V_L" and "V_H" refer to the variable binding region derived from an antibody light and heavy chain, respectively. The variable binding regions are made up of discrete, well-defined sub-regions known as "complementarity determining regions" (CDRs) and "framework regions" (FRs). The terms "C_L" and "C_H" refer to an "immunoglobulin constant region," *i.e.*, a constant region derived from an antibody light or heavy chain, respectively, with the latter region understood to be further divisible into C_{H1}, C_{H2}, C_{H3} and C_{H4} constant region domains, depending on the antibody isotype (IgA, IgD, IgE, IgG, IgM) from which the region was derived. A portion of the constant region domains makes up the Fc region (the "fragment crystallizable" region), which contains domains responsible for the effector functions of an immunoglobulin, such as ADCC (antibody-dependent cell-mediated cytotoxicity), CDC (complement-dependent cytotoxicity) and complement fixation, binding to Fc receptors, greater half-life *in vivo* relative to a polypeptide lacking an Fc region, protein A binding, and perhaps even placental transfer (*see* Capon *et al.* (1989) Nature, 337:525). Further, a polypeptide containing an Fc region allows for dimerization or multimerization of the polypeptide. A "hinge region," also referred to herein as a "linker," is an amino acid sequence interposed between and connecting the variable binding and constant regions of a single chain of an antibody, which is known in the art as providing flexibility in the form of a hinge to antibodies or antibody-like molecules.

The domain structure of immunoglobulins is amenable to engineering, in that the antigen binding domains and the domains conferring effector functions may be exchanged between immunoglobulin classes and subclasses. Immunoglobulin structure and function are reviewed, for example, in Harlow *et al.*, Eds., *Antibodies: A Laboratory Manual*, Chapter 14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, 1988). An extensive introduction as well as detailed information about all aspects of recombinant antibody technology can be found in the textbook *Recombinant Antibodies* (John Wiley & Sons, NY, 1999). A comprehensive collection of detailed antibody engineering lab Protocols can be found in R. Kontermann and S. Dübel, Eds., *The Antibody Engineering Lab Manual* (Springer Verlag, Heidelberg/New York, 2000). Further related protocols are also available in *Current Protocols in Immunology (*August 2009*)* published by John Wiley & Sons, Inc., Boston, MA.

"Derivative" as used herein refers to a chemically or biologically modified version of a compound that is structurally similar to a parent compound and (actually or theoretically) derivable from that parent compound. Generally, a "derivative" differs from an "analogue" in that a parent compound may be the starting material to generate a "derivative," whereas the parent compound may not necessarily be used as the starting material to generate an "analogue." An analogue may have different chemical or physical properties of the parent compound. For example, a derivative may be more hydrophilic or it may have altered reactivity (*e.g.*, a CDR having an amino acid change that alters its affinity for a target) as compared to the parent compound.

The term "biological sample" includes a blood sample, biopsy specimen, tissue explant, organ culture, biological fluid (*e.g.*, serum, urine, CSF) or any other tissue or cell or other preparation from a subject or a biological source. A subject or biological source may, for example, be a human or non-human animal, a primary cell culture or culture adapted cell line including genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, somatic cell hybrid cell lines, immortalized or immortalizable cell lines, differentiated or differentiatable cell lines, transformed cell lines, or the like. In further embodiments of this disclosure, a subject or biological source may be suspected of having or being at risk for having a disease, disorder or condition, including a malignant disease, disorder or condition or a B cell disorder. In certain embodiments, a subject or biological source may be suspected of having or being at risk for having a hyperproliferative, inflammatory, or autoimmune disease, and in certain other embodiments of this disclosure the subject or biological source may be known to be free of a risk or presence of such disease, disorder, or condition.

CD86 Binding Domains

As set forth herein, CD86 comprises a type I membrane protein that is a member of the immunoglobulin superfamily. CD86 is expressed by antigen-presenting cells, and is the ligand for the two T-cell proteins CD28 and CTLA4. Binding of CD28 with CD28 is a costimulatory signal for activation of the T-cell, while binding of CD28 with CTLA4 downregulates T-cell activation and reduces the immune response. Alternative splicing results in two transcript

variants encoding different isoforms (Genbank Accessions NP_787058.3 and NP_008820.2).

A CD86 binding domain of this disclosure can block binding of CD86 to CD28 and thereby downregulate T-cell activation. CD86 binding domains contemplated include a CTLA4 extracellular domain, or sub-domain thereof, a CD28 extracellular domain or sub-domain, or a CD86-specific antibody-derived binding domain (such as derived from the FUN1 monoclonal antibody (see *e.g.*, J Pathol. 1993 Mar;169(3):309-15); or derived from the 3D1 anti-CD86 monoclonal antibody.

In some embodiments, a CD86 binding domain is an extracellular domain ("ectodomain") of a human CTLA4 (Genbank Accession NP_005205), such as the mature polypeptide sequence of SEQ ID NO: 1 (signal peptide: amino acids 1-37). The amino acid sequence of the CTLA4 ectodomain without the signal peptide is provided in SEQ ID NO: 410. Applicants note that certain studies have indicated that the mature polypeptide of the CTLA4 ectodomain begins at the methionine at position 38 of SEQ ID NO: 1, other studies have indicated that the mature polypeptide begins at the alanine at position 37. In further embodiments, a CD86 binding domain is an ectodomain of CTLA4 that has been mutated in order to have a higher avidity for CD86 than wildtype, or non-mutated, CTLA4 as disclosed, for example, in US Patent Publication No. US 2003/0035816. In certain embodiments, the mutated CTLA4 ectodomain comprises an alanine or tyrosine at amino acid position 29, and/or a glutamic acid, asparagine, aspartic acid, glutamine, isoleucine, leucine or threonine at position 104 of SEQ ID NO:410. The amino acid sequence for the A29Y L104E CTLA 4 ectodomain variant is provided in SEQ ID NO:411. In certain embodiments, a CD86 binding domain is a CTLA-4 variable-like domain, such as the sequence provided in SEQ ID NO:3, or a CDR of a CTLA-4 variable-like domain, such as SEQ ID NO: 4 (CDR1), SEQ ID NO:5, (CDR2) or SEQ ID NO:6 (CDR3). Such CDRs are described, for example, in US Patent 7,405,288. In alternative embodiments, a CD86 binding domain is an extracellular domain ("ectodomain") of a CD28 (Genbank Accession NP_006130.1), such as the sequence provided in SEQ ID NO:2. Amino acids 1-18 of SEQ ID NO:2 are the signal peptide. The amino acid sequence of the ectodomain of CD28 without the signal peptide is provided in SEQ ID NO:412.

In yet further embodiments, a CD86 binding domain comprises a single chain immunoglobulin-like domain, such as a scFv, that is specific for

CD86. In certain embodiments, the CD86 binding domain contains the light and heavy variable binding domains from monoclonal antibody FUN1 or 3D1. The sequences for the heavy chain, light chain, scFv linker, and CDRs from the FUN1 and 3D1 anti-CD86 monoclonal antibodies are set forth in SEQ NOS:305-313 and 318-326, respectively, which can be used in the xceptor molecules of the instant disclosure.

In one aspect, a CD86 binding domain or fusion protein thereof of this disclosure is specific for CD86 and has an affinity with a dissociation constant (K_d) of about 10^{-3} M to less than about 10^{-8} M. In certain preferred embodiments, the CD86 binding domain or fusion protein thereof binds CD86 with an affinity of about 0.3 μM.

In an illustrative example, CD86 binding domains of this disclosure can be identified using a Fab phage library of fragments (*see, e.g.*, Hoet *et al.* (2005) Nature Biotechnol. 23:344) by screening for binding to a synthetic or recombinant CD86 (using an amino acid sequence or fragment thereof as set forth in GenBank Accession No. NP_787058.3 or NP_008820.2). In certain embodiments, a CD86 molecule used to generate a CD86 binding domain can further comprise an intervening domain or a dimerization domain, as described herein, such as an immunoglobulin Fc domain or fragment thereof.

In some embodiments, CD86 binding domains of this disclosure comprise V_H and V_L domains as described herein (*e.g.*, FUN1, 3D1, or humanized derivatives thereof). Other exemplary V_H and V_L domains include those described in US Patent 6,827,934. In certain embodiments, the V_H and V_L domains are human. In further embodiments, there are provided CD86 binding domains of this disclosure that have a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 100% identical to the amino acid sequence of one or more light chain variable regions (V_L) or to one or more heavy chain variable regions (V_H), or both, of SEQ NOS:305 and 306, SEQ NOS:318 and 319, or those disclosed in US Patent 6,827,934 (incorporated herein by reference), wherein each CDR can have zero, one, two,or three amino acid changes (*i.e.*, most changes are in the framework region(s)).

The terms "identical" or "percent identity," in the context of two or more polypeptide or nucleic acid molecule sequences, means two or more

sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same over a specified region (*e.g.*, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identity), when compared and aligned for maximum correspondence over a comparison window, or designated region, as measured using methods known in the art, such as a sequence comparison algorithm, by manual alignment, or by visual inspection. For example, preferred algorithms suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) Nucleic Acids Res. 25:3389 and Altschul *et al.* (1990) J. Mol. Biol. 215:403, respectively.

In any of these or other embodiments described herein where V_L and V_H domains may be desired, the V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_H and V_L domains comprises an amino acid sequence as set forth in any one or more of SEQ ID NOS: 43-166, 244, 307, 320, 355-379 and 383-398, such as Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), Linker 131 (SEQ ID NO:164), Linker 115 (SEQ ID NO:148), or the linker provided in SEQ ID NO:244. Multi-specific binding domains will have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_H and V_L chains.

CDRs are defined in various ways in the art, including the Kabat, Chothia, AbM, and contact definitions. The Kabat definition is based on sequence variability and is the most commonly used definition to predict CDR regions (Johnson *et al.* (2000) Nucleic Acids Res. 28:214). The Chothia definition is based on the location of the structural loop regions (Chothia et al. (1986) J. Mol. Biol. 196:901; Chothia et al. (1989) Nature 342:877). The AbM definition, a compromise between the Kabat and Chothia definitions, is an integral suite of programs for antibody structure modeling produced by the Oxford Molecular Group (Martin *et al.* (1989) Proc. Nat'l. Acad. Sci. (USA) 86:9268; Rees *et al.*, ABMTM, a computer program for modeling variable regions of antibodies, Oxford, UK; Oxford Molecular, Ltd.). An additional

definition, known as the contact definition, has been recently introduced (*see* MacCallum *et al.* (1996) J. Mol. Biol. 5:732), which is based on analysis of available complex crystal structures.

By convention, the CDR domains in the heavy chain are referred to as H1, H2, and H3, which are numbered sequentially in order moving from the amino terminus to the carboxy terminus. The CDR-H1 is about ten to 12 residues in length and starts four residues after a Cys according to the Chothia and AbM definitions, or five residues later according to the Kabat definition. The H1 can be followed by a Trp, Trp-Val, Trp-Ile, or Trp-Ala. The length of H1 is approximately ten to 12 residues according to the AbM definition, while the Chothia definition excludes the last four residues. The CDR-H2 starts 15 residues after the end of H1 according to the Kabat and AbM definitions, which is generally preceded by sequence Leu-Glu-Trp-Ile-Gly (but a number of variations are known) and is generally followed by sequence Lys/Arg-Leu/Ile/Val/Phe/Thr/Ala-Thr/Ser/Ile/Ala. According to the Kabat definition, the length of H2 is about 16 to 19 residues, while the AbM definition predicts the length to be nine to 12 residues. The CDR-H3 usually starts 33 residues after the end of H2, is generally preceded by the amino acid sequence Cys-Ala-Arg and followed by the amino acid Gly, and has a length that ranges from three to about 25 residues.

By convention, CDR regions in the light chain are referred to as L1, L2, and L3, which are numbered sequentially in order moving from the amino terminus to the carboxy terminus. The CDR-L1 (approximately ten to 17 residues in length) generally starts at about residue 24 and generally follows a Cys. The residue after the CDR-L1 is always Trp, which begins one of the following sequences: Trp-Tyr-Gln, Trp-Leu-Gln, Trp-Phe-Gln, or Trp-Tyr-Leu. The CDR-L2 (about seven residues in length) starts about 16 residues after the end of L1 and will generally follow residues Ile-Tyr, Val-Tyr, Ile-Lys, or Ile-Phe. The CDR-L3 usually starts 33 residues after the end of L2 and generally follows a Cys, which is generally followed by the sequence Phe-Gly-XXX-Gly and has a length of about seven to 11 residues.

Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-CD86 antibody, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_H and V_L domains specific for a CD86 comprising framework regions and CDR1, CDR2 and CDR3 regions,

wherein (a) the V_H domain comprises an amino acid sequence of a heavy chain CDR3; or (b) the V_L domain comprises an amino acid sequence of a light chain CDR3; or (c) the binding domain comprises a V_H amino acid sequence of (a) and a V_L amino acid sequence of (b); or the binding domain comprises a V_H amino acid sequence of (a) and a V_L amino acid sequence of (b) and wherein the V_H and V_L are found in the same reference sequence. In further embodiments, binding domains of this disclosure comprise V_H and V_L domains specific for an CD86 comprising framework regions and CDR1, CDR2 and CDR3 regions, wherein (a) the V_H domain comprises an amino acid sequence of a heavy chain CDR1, CDR2, and CDR3; or (b) the V_L domain comprises an amino acid sequence of a light chain CDR1, CDR2, and CDR3; or (c) the binding domain comprises a V_H amino acid sequence of (a) and a V_L amino acid sequence of (b); or the binding domain comprises a V_H amino acid sequence of (a) and a V_L amino acid sequence of (b), wherein the V_H and V_L amino acid sequences are from the same reference sequence.

In any of the embodiments described herein comprising specific CDRs, a binding domain can comprise (i) a V_H domain having an amino acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence of a V_H domain; or (ii) a V_L domain having an amino acid sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the amino acid sequence of a V_L domain; or (iii) both a V_H domain of (i) and a V_L domain of (ii); or both a V_H domain of (i) and a V_L domain of (ii) wherein the V_H and V_L are from the same reference sequence, wherein each CDR has up to three amino acid changes (*i.e.*, many of the changes are in the framework region(s)).

A CD86 binding domain in xceptor fusion proteins of this disclosure may be an immunoglobulin-like domain, such as an immunoglobulin scaffold. Immunoglobulin scaffolds contemplated by this disclosure include a scFv, a domain antibody, or a heavy chain-only antibody. In a scFv, this disclosure contemplates the heavy and light chain variable regions are joined by any linker peptide described herein or known in the art to be compatible with joining domains or regions in a binding molecule. Exemplary linkers are linkers based on the Gly_4Ser linker motif, such as $(Gly_4Ser)_n$, where n=1-5. If a binding domain of a fusion protein of this disclosure is based on a non-human immunoglobulin or includes non-human CDRs, the binding domain may be "humanized" according to methods known in the art.

Alternatively, a CD86 binding domain of fusion proteins of this disclosure may be a scaffold other than an immunoglobulin scaffold. Other scaffolds contemplated by this disclosure present the CD86-specific CDR(s) in a functional conformation. Other scaffolds contemplated include, but are not limited an A domain molecule, a fibronectin III domain, an anticalin, an ankyrin-repeat engineered binding molecule, an adnectin, a Kunitz domain or a protein AZ domain affibody.

IL10

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is an IL10 agonist (*i.e.*, can increase IL10 signaling). In some embodiments, the IL10 agonist binding domain is an IL10 or a IL10Fc, or a functional sub-domain thereof. In other embodiments, the IL10 agonist binding domain is a single chain binding protein, such as an scFv, that specifically binds to IL10R1 or IL10R2. In some embodiments, the IL10 agonist binding domain is an IL10 containing a point mutation at position 87 of SEQ ID NO:7, such as from "I" to "A" or "S" (referred to herein as I87A or I87S, respectively). The I87 variant IL10 molecules are known to be less immuno-stimulatory compared to wildtype IL10 (Ding *et al.*, *J. Exp. Med. 191*:213, 2000). Additionally, IL10 normally forms a homodimer with the amino terminal domain of each monomer molecule binding to the carboxy terminal domain of the other monomer). In one embodiment, the IL10 agonist binding domain is an IL10 molecule having a short linker (gggsgg SEQ ID NO:379) that separates the two subdomains of the molecule (amino and carboxy end domains) so that these subdomains can form an intramolecular dimer was also examined. These are referred to herein as monoIL10 molecules.

IL10 (Genbank Accession no. NP_000563.1; SEQ ID NO:7) is a member of a cytokine superfamily that share an alpha-helical structure. Amino acids 1-18 of SEQ ID NO:7 are the signal peptide of the precursor IL10 protein. The amino acid sequence of the mature IL10 protein is provided in SEQ ID NO:418. Although no empirical evidence exists, it has been suggested that all the family members possess six alpha-helices (Fickenscher, H. *et al.*, (2002) Trends Immunol. 23: 89). IL10 has four cysteines, only one of which is conserved among family members. Since IL10 demonstrates a V-shaped fold that contributes to its dimerization, it appears that disulfide bonds are not critical

to this structure. Amino acid identity of family members to IL10 ranges from 20% (IL-19) to 28% (IL-20) (Dumouter *et al.*, (2002) Eur. Cytokine Netw. 13:5).

IL10 was first described as a Th2 cytokine in mice that inhibited IFN-α and GM-CSF cytokine production by Th1 cells (Moore *et al.*, 2001, Annu. Rev. Immunol. 19:683; Fiorentino et al., (1989) J. Exp. Med. 170: 2081). Human IL10 is 178 amino acids in length with an 18 amino acid signal sequence and a 160 amino acid mature segment. Its molecular weight is approximately 18 kDa (monomer). Human IL10 contains no potential N-linked glycosylation site and is not glycosylated (Dumouter *et al.*, (2002) Eur. Cytokine Netw. 13:5; Vieira et al., (1991) Proc. Natl. Acad. Sci. USA 88:1172). It contains four cysteine residues that form two intrachain disulfide bonds. Helices A --> D of one monomer noncovalently interact with helices E and F of a second monomer, forming a noncovalent V-shaped homodimer. Functional areas have been mapped on the IL10 molecule. In the N-terminus, pre-helix A residues #1-9 are involved in mast cell proliferation, while in the C-terminus, helix F residues #152-160 mediate leukocyte secretion and chemotaxis.

Cells known to express IL10 include CD8+ T cells, microglia, CD14+ (but not CD16+) monocytes, Th2 CD4+ cells (mice), keratinocytes, hepatic stellate cells, Th1 and Th2 CD4+ T cells (human), melanoma cells, activated macrophages, NK cells, dendritic cells, B cells (CD5+ and CD19+) and eosinophils. On T cells, the initial observation of IL10 inhibition of IFN-gamma production is now suggested to be an indirect effect mediated by accessory cells. Additional effects on T cells, however, include: IL10 induced CD8+ T cell chemotaxis, an inhibition of CD4+ T cell chemotaxis towards IL-8, suppression of IL-2 production following activation, an inhibition of T cell apoptosis via Bcl-2 up-regulation, and an interruption of T cell proliferation following low antigen exposure accompanied by CD28 costimulation (Akdis *et al.*, (2001) Immunology 103:131).

On B cells, IL10 has a number of related, yet distinct functions. In conjunction with TNF-β and CD40L, IL10 induces IgA production in naïve (IgD+) B cells. It is believed that TGF-β/CD40L promotes class switching while IL10 initiates differentiation and growth. When TGF-β is not present, IL10 cooperates with CD40L in inducing IgG1 and IgG3 (human), and thus may be a direct switch factor for IgG subtypes. Interestingly, IL10 has divergent effects on IL-4 induced IgE secretion. If IL10 is present at the time of IL-4 induced class switching, it reverses the effect; if it is present after IgE commitment, it

augments IgE secretion. Finally, CD27/CD70 interaction in the presence of IL10 promotes plasma cell formation from memory B cells (Agematsu et al., (1998) Blood 91: 173).

Mast cells and NK cells are also impacted by IL10. On mast cells, IL10 induces histamine release while blocking GM-CSF and TNF-α release. This effect may be autocrine as IL10 is known to be released by mast cells in rat. As evidence of its pleiotrophic nature, IL10 has the opposite effects on NK cells. Rather than blocking TNF-α and GM-CSF production, IL10 actually promotes this function on NK cells. In addition, it potentiates IL-2 induced NK cell proliferation and facilitates IFN-γ secretion in NK cells primed by IL-18. In concert with both IL-12 and/or IL-18, IL10 potentiates NK cell cytotoxicity (Cai et al., 1999, Eur. J. Immunol. 29: 2658).

IL10 has a pronounced anti-inflammatory impact on neutrophils. It inhibits the secretion of the chemokines MIP-1α, MIP-1β and IL-8, and blocks production of the proinflammatory mediators IL-1β and TNF-α. In addition, it decreases the ability of neutrophils to produce superoxide, and as a result interferes with PMN-mediated antibody-dependent cellular cytotoxicity. It also blocks IL-8 and fMLP-induced chemotaxis, possibly via CXCR1 (Vicioso *et al.*, (1998) Eur. Cytokine Netw. 9:247).

On dendritic cells (DCs), IL10 generally exhibits immunosuppressive effects. It would appear to promote CD14+ macrophage differentiation at the expense of DCs. IL10 seems to decrease the ability of DCs to stimulate T cells, particularly for Th1 type cells. Relative to MHC-II expression, it can be down-regulated, unchanged, or up-regulated (Sharma et al., (1999) J. Immunol. 163:5020). With respect to CD80 and CD86, IL10 will either up-regulate or down-regulate its expression. B7-2/CD86 plays a key role in T cell activation. For this molecule, IL10 is involved in both up-regulation and down-regulation. Perhaps the most significant modulation, however, occurs with CD40 (IL10 seems to reduce its expression). At the regional level, IL10 may block immunostimulation by inhibiting Langerhans cell migration in response to proinflammatory cytokines. Alternatively, IL10 blocks an inflammation-induced DC maturation step that normally involves CCR1, CCR2 and CCR5 down-regulation and CCR7 up-regulation. This blockage, with retention of CCR1, CCR2 and CCR5, results in a failure of DCs to migrate to regional nodes. The result is an immobile DC that will not stimulate T cells but

will bind (and clear) proinflammatory chemokines without responding to them (D-Amico et al., (2000) Nat. Immunol. 1:387).

On monocytes, IL10 has a number of documented effects. For example, IL10 seems to clearly reduce cell surface MHC-II expression. It also inhibits IL-12 production following stimulation. While it promotes a monocyte to macrophage transition in conjunction with M-CSF, the phenotype of the macrophage is not clear (i.e. CD16+/cytotoxic vs. CD16-). IL10 also reduces monocyte GM-CSF secretion and IL-8 production, while promoting IL-1ra release (Gesser et al., (1997) Proc. Natl. Acad. Sci. USA 94:14620). Hyaluronectin, a connective tissue component, is now known to be secreted by monocytes in response to IL10. This may have some importance in cell migration, particularly tumor cell metastases, where hyaluronectin is known to interrupt cell migration through extracellular space (Gesser et al., (1997) Proc. Natl. Acad. Sci. USA 94:14620).

Fusion proteins of IL10 with either murine or macaque Fc regions (referred to as IL10Fc) have been shown to inhibit macrophage function and prolong pancreatic islet xenograft survival (Feng et al. (1999) Transplantation 68:1775; Asiedu et al. (2007) Cytokine 40:183), as well as reduce septic shock in a murine model (Zheng et al. (1995) J. Immunol. 154:5590).

Human IL10R1 is a 90-110 kDa, single-pass type I transmembrane glycoprotein that is expressed on a limited number of cell types (Liu et al., 1994, J. Immunol. 152: 1821). Weak expression being seen in pancreas, skeletal muscle, brain, heart, and kidney. Placenta, lung, and liver showed intermediate levels. Monocytes, B-cells, large granular lymphocytes, and T-cells express high levels (Liu et al., 1994, J. Immunol. 152: 1821). The expressed protein is a 578 amino acid protein that contains a 21 amino acid signal peptide, a 215 amino acid extracellular region, a 25 amino acid transmembrane segment, and a 317 amino acid cytoplasmic domain. There are two FNIII motifs within the extracellular region and a STAT3 docking site plus a JAK1 association region within the cytoplasmic domain (Kotenko et al., 2000 Oncogene 19: 2557; Kotenko et al., 1997, EMBO J. 16: 5894). IL10R1 binds human IL10 with a Kd of 200 pM.

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for an IL10R1 or IL10R2 as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by

up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains. In further embodiments, binding domains specific for IL10R1 or IL10R2 of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-IL10R1 or IL10R2 scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti- IL10R1 or IL10R2, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for an IL10R1 or IL10R2 comprising framework regions and CDR1, CDR2 and CDR3 regions.

HLA-G

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is an HLA-G agonist (*i.e.*, can increase HLA-G signaling). In some embodiments, the HLA-G agonist binding domain is an HLA-G1 (SEQ ID NO: 14), an HLA-G5 (SEQ ID NO: 15) or an HLA-G mutein in which the cysteine at position of 147 of the mature protein has been mutated to an alternative amino acid, for example a serine. Amino acids 1-24 and 1-23 of HLA-G1 and HLA-G5, respectively, represent the signal peptides. In other embodiments, the HLA-G agonist domain is an ectodomain of HLA-G1 or HLA-G5, either with or without a β-2 microglobulin attached to the N-terminus by a flexible linker. Examples of such linkers include those provided in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398 and described below. The preparation of soluble HLA-G1 is described in US Patent Publication no. US 2004/0044182.

In yet other embodiments, the HLA-G agonist binding domain is an immunoglobulin variable binding domain, or a derivative thereof (*e.g.*, an antibody, Fab, scFv, or the like) that specifically binds to ILT2, ILT4 or KIR2DL4. Antibodies that are specific for ILT2, ILT4 or KIR2DL4 include, for example, those described in US Patent Publication no. US 2003/0232051.

Human leukocyte antigen G (HLA-G) is a nonclassical major histocompatability complex (MHC) class I molecule that is a heterodimer consisting of a heavy chain and a light chain (beta-2 microglobulin), with the heavy chain being anchored in the membrane. HLA-G functions as an immunomodulatory molecule that protects fetal tissues from the maternal immune system. While constitutive expression of HLA-G is limited to fetal tissues, adult thymic medulla, cornea, pancreatic islets and erythroid and endothelial cell precursors, its expression can be induced in cancers, transplantation, multiple sclerosis, inflammatory diseases and viral infections. The HLA-G primary transcript generates seven alternative mRNAs that encode the membrane-bound protein isoforms HLA-G1, -G2, -G3 and -G4, and the soluble protein isoforms HLA-G5, HLA-G6 and HLA-G7, with HLA-G5 being the soluble form of the cell surface-bound HLA-G1 protein.

While HLA-G does not seem to have significant immune stimulatory functions, it has been shown to bind to inhibitory receptors, namely ILT2, ILT4, KIR2DL4 and CD8, and thereby interact with B-cells, T-cells, NK cells and antigen-presenting cells. Dimeric forms of HLA-G have an affinity for ILT2 that is several orders of magnitude greater than the affinity for ILT4, KIR2DL4 or CD8. HLA-G1 has been shown to inhibit the cytolytic function of uterine and peripheral blood NK cells, the antigen-specific cytolytic function of cytotoxic T lymphocytes, the alloproliferative response of CD4+ T-cells, the proliferation of T-cells and peripheral blood NK cells, and the maturation and function of dendritic cells (see, for example, Wiendl et al. (2003) Blood, 126:176-185). It has been suggested that HLA-G may be useful in reducing inflammatory responses in the CNS associated with multiple sclerosis (Wiendl et al. (2005) Blood, 128:2689-2704), and as a therapeutic agent in promoting tolerance to grafts in transplantations (Carosella et al. (2008) Blood 111:4862-4870).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a ILT2, ILT4 or KIR2DL4 as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L

and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in any one or more of SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as Linker 115 (SEQ ID NO:148), the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for ILT2, ILT4 or KIR2DL4 of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti- ILT2, -ILT4 or -KIR2DL4 scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti- ILT2, -ILT4 or -KIR2DL4, or it can comprise multiple CDRs that can be the same or different.

HGF

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is an HGF agonist (*i.e.*, can increase HGF signaling). In some embodiments, the HGF agonist binding domain is an HGF or a functional sub-domain thereof.

Hepatocyte growth factor (HGF) regulates cell growth, cell motility, and morphogenesis by activating a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor. HGF influences a number of cell types and regulates various biological activities including cytokine production, cell migration, proliferation and survival. HGF is secreted as a single inactive polypeptide and is cleaved by serine proteases into a 69-kDa alpha-chain and 34-kDa beta-chain. A disulfide bond between the alpha and beta chains produces the active, heterodimeric molecule. Alternative splicing of the HGF gene gives rise to five different isoforms (isoforms 1-5; Genbank Accessions nos. NP_000592.3, NP_001010931.1, NP_001010932.1,

NP_001010933.1 and NP_001010934.1, respectively; SEQ ID NOs: 18-22; amino acids 1-31 of each of these sequences is the signal peptide).

HGF is believed to be a key factor in the prevention and attenuation of disease progression (Ito et al. (2008) Int. Arch. Allergy Immunol. 146 Suppl 1:82-87). For example, HGF has been shown to be effective in suppressing collagen-induced arthritis in mice (Okunishi et al. (2007) Jnl. Immunol. 179:5504-5513), and to play a protective role in a mouse model of allergic airway inflammation (Okunishi et al. (2005) Jnl. Immunol. 175:4745-4753; Ito et al. Am. J. Respir. Cell. Mol. Biol. (2005) 32:268-280).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for HGF as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in any one or more of SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains. In further embodiments, binding domains specific for HGF of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-HGF scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-HGF, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for an HGF comprising framework regions and CDR1, CDR2 and CDR3 regions.

IL35

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is an IL35 agonist (*i.e.*, can increase IL35 signaling). In some embodiments, the IL35 agonist binding domain is an IL35 (*e.g.* SEQ ID NO: 25 and 26) or a functional sub-domain thereof. In certain embodiments, the IL35 agonist binding domain is a single chain polypeptide comprising the sequences of SEQ ID NO: 25 and 26, or functional sub-domains thereof. Such single chain polypeptides may include one or more linkers, including linkers as described herein. In other embodiments, the IL35 agonist binding domain is a single chain immunoglobulin variable domain, such as a scFv, specific for IL35R that has IL35 agonist activity.

IL-35 is a newly described cytokine of the IL-12 cytokine subfamily. The heterodimeric molecule is comprised of the IL-12 p35 and the IL-27 Ebi3 subunits. It has recently been shown to be a potent inducer of Treg function and capable of altering a TH17 response in a mouse model of arthritis (Niedbala et al. (2007) Eur. J. Immunol. 37:3021; Collison et al. (2007) Nature 450:566). Therefore, combining IL-35 agonism with CD86 inhibition is predicted to increase the therapeutic benefit of CD28 inhibition alone.

Regulatory T-cells (TREGS) are a critical sub-population of CD4+ T cells that are important for maintaining self tolerance and preventing autoimmunity, for limiting chronic inflammatory diseases, such as asthma and inflammatory bowel disease, and for regulating homeostatic lymphocyte expansion. IL35 is an anti-inflammatory cytokine that has been shown to suppress immune responses by stimulating expansion of regulatory T cells and suppression of Th17 cell development (Collison et al. (2007) Nature 450:566-9). IL35 is a heterodimer formed from Epstein-Barr virus-induced gene 3 (EBI3; SEQ ID NO: 25; signal peptide: amino acids 1-20) and the p35subunit of IL12 (SEQ ID NO: 26; signal peptide: amino acids 1-56) (Devergne et al. (1997) Proc. Natl. Acad. Sci. USA 94:12041-12046; US Patent 5,830,451; US Patent Publication no. US 2007/0299026). It has been shown to have a therapeutic effect equivalent to that of Enbrel™ in a murine collagen-induced arthritis model (Niedbala et al. (2007) Eur. J. Immunol. 37:3021-3029), and has thus been proposed as a therapeutic agent against clinical rheumatoid arthritis.

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for an IL35R as described herein. In

certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in any one or more of SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains. In further embodiments, binding domains specific for IL35R of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-IL35R scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-IL35R, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for an IL-35R comprising framework regions and CDR1, CDR2 and CDR3 regions.

LIGHT

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is a LIGHT antagonist (*i.e.*, can inhibit LIGHT signaling). In some embodiments, the LIGHT antagonist binding domain is an HVEM ectodomain (also referred to as sHVEM; SEQ ID NO: 29; signal peptide: amino acids 1-38) or a functional sub-domain thereof. In other embodiments, the LIGHT antagonist binding domain is a single chain immunoglobulin-like variable domain, such as a scFv, specific for LIGHT. In certain embodiments, the LIGHT antagonist domain is a single chain immunoglobulin-like variable domain comprising V_H and V_L domains as described in PCT Patent Publication no. WO 08/027338.

LIGHT is a member of the TNF superfamily that is expressed on activated T lymphocytes, monocytes, granulocytes and immature dendritic

cells. Two distinct isoforms of LIGHT have been reported (Genbank Accession nos. NP_003798.2 and NP_742011.1). LIGHT has been shown to regulate T cell immune responses by signaling through the herpes virus entry mediator (HVEM) and the lymphotoxin beta receptor (LTβR). Both HVEM and LTβR bind LIGHT with high affinity, with expression of HVEM being detected in T cells, B cells, natural killer cells and endothelial cells, and LTβR being expressed in monocytes and stromal cells but not T cells and B cells. LIGHT has been shown to be a co-stimulatory molecule for CD28-independent T cell activation and to preferentially induce IFN-γ and GM-CSF production. Blockade of LIGHT by *in vivo* administration of LTβR-Ig fusion protein or anti-LIGHT antibodies results in decreased T cell-mediated immune responses and ameliorates graft-versus-host disease in a murine model (Tamada et al. (2000) Nat. Med. 6:283-9). Constitutive expression of LIGHT leads to tissue destruction and autoimmune-like disease syndromes (Granger & Rickert (2003) Cytokine Growth Factor Rev. 14:289-96).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for LIGHT as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in any one or more of SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for LIGHT of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-LIGHT scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable

region of an anti-LIGHT, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a LIGHT comprising framework regions and CDR1, CDR2 and CDR3 regions.

PD-1

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is a PD-1 agonist (*i.e.*, can increase PD-1 signaling). In some embodiments, the PD-1 agonist binding domain is a PD1-L1 (*e.g.* SEQ ID NO: 32; signal peptide: amino acids 1-18), a PD1-L2 (*e.g.* SEQ ID NO: 33; signal peptide: amino acids 1-19), or a functional sub-domain thereof. In other embodiments, the PD-1 agonist binding domain is a single chain immunoglobulin-like variable domain, such as a scFv, specific for PD-1. Antibodies specific for PD-1 include, for example, those described in US Patent Publication No. US 2006/0210567.

PD-1 (Genbank Accession NP_005009.1) is a member of the CD28/CTLA4 family that is expressed on activated T cells, B cells and myeloid cells. PD-1 contains an immunoreceptor tyrosine-based inhibitory motif. PD-1 functions by binding to programmed death-1 ligand 1 (PD1-L1; also known as CD274) and programmed death-1 ligand 2 (PD1-L2). Human PD-L1 and PD-L2 are expressed on both immature and mature dendritic cells, IFNγ-treated monocytes and follicular dendritic cells. Mice deficient in PD-1 show a variety of autoimmune pathologies, demonstrating that PD-1 is a negative regulator of the immune response (Nishimura & Honjo (2001) Trends Immunol. 2:265; Nishimura et al. (1999) Immunity 11:141). Binding of PD-1 to PD1-L1 and PD1-L2 has been shown to result in down-regulation of T cell activation (Freeman et al. (2000) J. Exp. Med. 192:1027; Latchman et al. (2001) Nat. Immunol. 2:261; Carter et al. (2002) Eur. J. Immunol. 32:634).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a PD-1 as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in SEQ ID NOs:43-

166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for PD-1 of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-PD-1 scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-PD-1, or it can comprise multiple CDRs that can be the same or different.

BTLA

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is a BTLA agonist (*i.e.*, can increase BTLA signaling). In some embodiments, the BTLA agonist binding domain is a HVEM ectodomain (also referred to as sHVEM; SEQ ID NO: 29; signal peptide: amino acids 1-38) or a functional sub-domain thereof (*e.g.* amino acids 54-78 of SEQ ID NO: 29). In other embodiments, the BTLA agonist binding domain is a single chain immunoglobulin-like variable domain, such as a scFv, specific for BTLA. Agonist antibodies specific for BTLA are described, for example, in Krieg et al. (2005) J. Immunol. 175:6420-6472.

BTLA (Genbank Accession nos. NP_001078826.1 and NP_861445.3; isoforms 2 and 1, respectively) is a cell surface protein that is a member of the immunoglobulin family and is expressed on B-cells, T-cells and antigen presenting cells. The ligand for BTLA is herpes virus entry mediator (HVEM), which is a member of the tumor-necrosis factor receptor family and also acts as a ligand for LIGHT (Sedy et al. (2005) Nat. Immunol. 6:90-98). A binding site for BTLA has been identified in CRD1 of HVEM (amino acids 54-78 of SEQ ID NO: 29; PCT Patent Publication no. WO 2006/063067). This site is distinct from that occupied by LIGHT but overlaps the gD binding site of HVEM. While binding of HVEM to LIGHT induces a strong immune response, binding

of HVEM to BTLA results in negative regulation of T cell responses (Murphy et al. (2006) Nat. Rev. Immunol. 6:671-681). It has been indicated that binding of BTLA to HVEM activates tyrosine phosphorylation of BTLA thereby inducing association with the protein tyrosine phosphatases SHP-1 and SHP-2 (Gavrieli et al. (2003) Biochem. Biophys. Res. Commun. 312:1236), although some data question whether SHP recruitment is responsible for the negative regulatory activity of BTLA (Chemnitz et al. (2006) J. Immunol. 176:6603-6614).

Soluble HVEM has been shown to inhibit anti-CD3-induced proliferation of CD4+ T cells, with this effect being reversed by anti-BTLA antibodies (Gonzalez et al. (2005) Proc. Natl. Acad. Sci. USA 102:1116-1121). Similarly, an agonistic anti-BTLA monoclonal antibody was shown to inhibit anti-CD3-mediated CD4+ T-cell proliferation and cytokine production (Krieg et al. (2005) J. Immunol. 175:6420-6472). Mice lacking an intact BTLA gene show an increased sensitivity to experimental autoimmune encephalomyelitis, (Watanabe et al. (2003) Nat. Immunol. 4:670-679) and prolonged airway inflammation (Deppong et al. (2006) J. Immunol. 176:3909-3913).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a BTLA as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for BTLA of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-BTLA scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable

region of an anti-BTLA, or it can comprise multiple CDRs that can be the same or different.

GITRL

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is a GITRL antagonist (*i.e.*, can inhibit GITRL signaling). In some embodiments, the GITRL antagonist binding domain is a GITR ectodomain (also referred to as sGITR; SEQ ID NO: 39 and 40; signal peptides: amino acids 1-25 for each of these sequences) or a functional sub-domain thereof. In other embodiments, the GITRL antagonist binding domain is a single chain immunoglobulin-like variable domain, such as a scFv, specific for GITRL. Antagonistic antibodies against GITRL are described, for example, in US Patent Publication No. 2005/0014224.

Glucocorticoid-induced tumor necrosis factor receptor (GITR; also known as AITR), a type I transmembrane protein, is a member of the TNF receptor superfamily (Nocentini et al. (2007) Eur. J Immunol. 37:1165-69). GITR plays an important role in the regulation of T cell proliferation and TCR-mediated apoptosis. GITR expression is upregulated on T cells, with a high level of GITR being constitutive expressed on $CD4^+CD25^+$ regulatory T cells (Kwon et al. (2003) Exp. Mol. Med. 35:8-16), with expression also occurring on macrophages, B cells and NK cells (Liu et al. (2008) J. Biol. Chem. 283:8202-8210). GITR's cognate ligand, GITRL is constitutively expressed on antigen-presenting cells, such as dendritic cells and B cells. Binding of GITR to GITRL has been shown to render $CD4^+CD25^-$ effector T cells resistant to the inhibitory effects of $CD4^+CD25^+$ regulatory T cells. GITR activation by either GITRL or an agonistic antibody has been shown to increase TCR-induced T cell proliferation and cytokine production, and to rescue T cells from anti-CD3-induced apoptosis (Nocentini et al. (1997) Proc. Natl. Acad. Sci. USA 94:6216-6221). In addition, binding of GITR to GITRL can inhibit T regulatory cells and/or render effector T cells more resistant to T regulatory cell-mediated suppression (Kanamaru et al. (2004) J. Immunol. 172:7306-7314).

Studies have shown that administration of anti-GITR mAb during the induction phase of experimental autoimmune encephalomyelitis significantly enhances the severity of clinical disease as well as increasing CNS inflammation and autoreactive T cell responses (Kohm et al. (2004) J. Immunol. 172:4686-4690). In addition, activation of GITR signaling exacerbates both

murine asthma and collagen-induced arthritis (Patel et al. (2005) Eur. J., Immunol. 35:3581-90).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for GITRL as described herein. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for GITRL of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-GITRL scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-GITRL, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a GITRL comprising framework regions and CDR1, CDR2 and CDR3 regions.

CD40

As noted above, in certain embodiments the present disclosure provides polypeptides containing a binding region or domain that is a CD40 antagonist (*i.e.*, can inhibit CD40 signaling). In some embodiments, the CD40 antagonist binding domain is a single chain immunoglobulin-like variable domain, such as a scFv, specific for CD40. Antagonistic antibodies against CD40 are described, for example in US Patent Publication no. US 2008/0057070, and US Patents 5,874,082 and 6,838,261.

CD40 is a 55 kDa cell-surface antigen found on the surface of normal and neoplastic B cells, dendritic cells, antigen presenting cells, endothelial cells, monocytic cells and epithelial cells. CD40 expression on antigen presenting cells plays an important co-stimulatory role in the action of T-helper and cytotoxic T lymphocytes. Expression of the CD40 ligand (CD40L, also known as CD154) is upregulated on T cells during a normal immune response. Binding of T cell expressed CD40L to B cell expressed CD40 leads to B cell proliferation and differentiation, antibody production, isotope switching and B-cell memory generation. A human anti-CD40 antagonistic antibody has been shown to have antileukemia activity on human chronic lymphocytic leukemia cells (Luqman et al. (2008) Blood 112:711-720).

In some embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for CD40 as described, for example, in US Patent Publication no. US 2008/0057070. In certain embodiments, the V_L and V_H domains are human. The V_L and V_H domains may be arranged in either orientation and may be separated by up to about a 30 amino acid linker as disclosed herein or any other amino acid sequence capable of providing a spacer function compatible with interaction of the two sub-binding domains. In certain embodiments, a linker joining the V_L and V_H domains comprises an amino acid sequence as set forth in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398, such as the linker provided in SEQ ID NO:244, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). Multi-specific binding domains can have at least two specific sub-binding domains, by analogy to camelid antibody organization, or at least four specific sub-binding domains, by analogy to the more conventional mammalian antibody organization of paired V_L and V_H chains.

In further embodiments, binding domains specific for CD40 of this disclosure may comprise one or more complementarity determining region ("CDR"), or multiple copies of one or more such CDRs, which have been obtained, derived, or designed from variable regions of an anti-CD40 scFv or Fab fragment or from heavy or light chain variable regions thereof. Thus, a binding domain of this disclosure can comprise a single CDR from a variable region of an anti-CD40, or it can comprise multiple CDRs that can be the same or different. In certain embodiments, binding domains of this disclosure comprise V_L and V_H domains specific for a CD40 comprising framework regions

and CDR1, CDR2 and CDR3 regions as described, for example, in US Patent Publication no. US 2008/0057070.

Multi-Specific Fusion Proteins

The present disclosure provides multi-specific fusion proteins comprising a domain that binds to a CD86 ("CD86 binding domain") and a domain that binds a molecule other than a CD86 ("heterologous binding domain"). In certain embodiments, the heterologous binding domain is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist.

In certain embodiments, the heterologous binding domain is an IL10 agonist, such as IL10, IL10Fc or a single chain binding domain that specifically binds to IL10R1 or IL10R2. In certain embodiments, the heterologous binding domain is an HLA-G agonist, such as an HLA-G1, an HLA-G5, an HLA-G mutein, or a functional region thereof (such as an ectodomain), or a single chain binding domain that specifically binds to ILT2, ILT4 or KIR2DL4. In certain embodiments, the heterologous binding domain is an HGF agonist, such as an HGF or a sub-domain thereof. In certain embodiments, the heterologous binding domain is an IL35 agonist, such as an IL35 or a sub-domain thereof, a single chain IL35 or subdomain thereof, or a single chain immunoglobulin-like variable domain specific for IL35R and having IL35 agonist activity. In certain embodiments, the heterologous binding domain is a LIGHT antagonist, such as a HVEM ectodomain or a sub-domain thereof, or a single chain immunoglobulin-like variable domain specific for LIGHT. In certain embodiments, the heterologous binding domain is a PD-1 agonist, such as a PD1-L1, PD1-L2 or a sub-domain thereof, or a single chain immunoglobulin-like variable domain specific for PD-1. In certain embodiments, the heterologous binding domain is a BTLA agonist, such as a HVEM ectodomain or a sub-domain thereof, or a single chain immunoglobulin-like variable domain specific for BTLA. In certain embodiments, the heterologous binding domain is a GITRL antagonist, such as a GITR ectodomain or a sub-domain thereof, or a single chain immunoglobulin-like variable domain specific for GITRL. In certain embodiments, the heterologous binding domain is a CD40 antagonist, such as a single chain immunoglobulin-like variable domain specific for CD40.

Generally, the fusion proteins of the present invention make use of mature proteins that do not include the leader peptide (signal peptide). Accordingly, while certain sequences provided herein for binding domain proteins (such as for CTLA4, CD28, HLA-G1 and HLA-G5 and others described herein) include the leader peptide, the skilled person would readily understand how to determine the mature protein sequence from sequences including a signal peptide. In certain embodiments, it may be useful to include the leader sequence.

It is contemplated that a CD86 binding domain may be at the amino-terminus and the heterologous binding domain at the carboxy-terminus of a fusion protein. In certain embodiments, the xceptor molecule is as set forth in SEQ ID NO:9, 13, 17, 24, 28, 31, 35, 42, 171, 173, 175, 177, 179, 181, 187, 189, 191, 193, 219, 221, 223, 237, 262, 302, 330, 336, 338, 340, or 400. It is also contemplated that the heterologous binding domain may be at the amino-terminus and the CD86 binding domain may be at the carboxy-terminus. In certain embodiments, the xceptor molecule is as set forth in SEQ ID NO:183, 185, 199, 201, 203, 205, 207, 211, 213, 254, 258, 266, 276, 350, 352, or 354. As set forth herein, the binding domains of this disclosure may be fused to each end of an intervening domain (*e.g.*, an immunoglobulin constant region or sub-region thereof). Furthermore, the two or more binding domains may be each joined to an intervening domain via a linker, as described herein.

As used herein, an "intervening domain" refers to an amino acid sequence that simply functions as a scaffold for one or more binding domains so that the fusion protein will exist primarily (*e.g.*, 50% or more of a population of fusion proteins) or substantially (*e.g.*, 90% or more of a population of fusion proteins) as a single chain polypeptide in a composition. For example, certain intervening domains can have a structural function (*e.g.*, spacing, flexibility, rigidity) or biological function (*e.g.*, an increased half-life in plasma, such as in human blood). Exemplary intervening domains that can increase half-life of the fusion proteins of this disclosure in plasma include albumin, transferrin, a scaffold domain that binds a serum protein, or the like, or fragments thereof.

In certain embodiments, the intervening domain contained in a multi-specific fusion protein of this disclosure is a "dimerization domain," which refers to an amino acid sequence that is capable of promoting the association of at least two single chain polypeptides or proteins via non-covalent or covalent interactions, such as by hydrogen bonding, electrostatic interactions,

Van der Waal's forces, disulfide bonds, hydrophobic interactions, or the like, or any combination thereof. Exemplary dimerization domains include immunoglobulin heavy chain constant regions or sub-regions. It should be understood that a dimerization domain can promote the formation of dimers or higher order multimer complexes (such as trimers, tetramers, pentamers, hexamers, septamers, octamers, *etc.*).

A "constant sub-region" is a term defined herein to refer to a peptide, polypeptide, or protein sequence that corresponds to or is derived from part or all of one or more constant region domains, but not all constant region domains of a source antibody. In a preferred embodiment, the constant sub-region is an IgG CH2CH3, preferably an IgG1 CH2CH3. In some embodiments, the constant region domains of a fusion protein of this disclosure may lack or have minimal effector functions of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement activation and complement-dependent cytotoxicity (CDC), while retaining the ability to bind some F_C receptors (such as F_CRn binding) and retaining a relatively long half life *in vivo*. In certain embodiments, a binding domain of this disclosure is fused to a human IgG1 constant region or sub-region, wherein the IgG1 constant region or sub-region has one or more of the following amino acids mutated: leucine at position 234 (L234), leucine at position 235 (L235), glycine at position 237 (G237), glutamate at position 318 (E318), lysine at position 320 (K320), lysine at position 322 (K322), or any combination thereof (numbering according to Kabat). For example, any one or more of these amino acids can be changed to alanine. In a further embodiment, an IgG1 Fc domain has each of L234, L235, G237, E318, K320, and K322 (according to EU numbering) mutated to an alanine (*i.e.*, L234A, L235A, G237A, E318A, K320A, and K322A, respectively), and optionally an N297A mutation as well (*i.e.*, essentially eliminating glycosylation of the CH2 domain).

Methods are known in the art for making mutations inside or outside an Fc domain that can alter Fc interactions with Fc receptors (CD16, CD32, CD64, CD89, FcεR1, FcRn) or with the complement component C1q (*see, e.g.*, US Patent No. 5,624,821; Presta (2002) Curr. Pharma. Biotechnol. 3:237). Particular embodiments of this disclosure include compositions comprising immunoglobulin or fusion proteins that have a constant region or sub-region from human IgG wherein binding to FcRn and protein A are preserved and wherein the Fc domain no longer interacts or minimally interacts

with other Fc receptors or C1q. For example, a binding domain of this disclosure can be fused to a human IgG1 constant region or sub-region wherein the asparagine at position 297 (N297 under the Kabat numbering) has been mutated to another amino acid to reduce or eliminate glycosylation at this site and, therefore, abrogate efficient Fc binding to FcγR and C1q. Another exemplary mutation is a P331S, which diminishes C1q binding but does not affect Fc binding.

In further embodiments, an immunoglobulin Fc region may have an altered glycosylation pattern relative to an immunoglobulin reference sequence. For example, any of a variety of genetic techniques may be employed to alter one or more particular amino acid residues that form a glycosylation site (*see* Co *et al.* (1993) Mol. Immunol. 30:1361; Jacquemon *et al.* (2006) J. Thromb. Haemost. 4:1047; Schuster *et al.* (2005) Cancer Res. 65:7934; Warnock *et al.* (2005) Biotechnol. Bioeng. 92:831), such as N297 of the CH2 domain (EU numbering). Alternatively, the host cells producing fusion proteins of this disclosure may be engineered to produce an altered glycosylation pattern. One method known in the art, for example, provides altered glycosylation in the form of bisected, non-fucosylated variants that increase ADCC. The variants result from expression in a host cell containing an oligosaccharide-modifying enzyme. Alternatively, the Potelligent technology of BioWa/Kyowa Hakko is contemplated to reduce the fucose content of glycosylated molecules according to this disclosure. In one known method, a CHO host cell for recombinant immunoglobulin production is provided that modifies the glycosylation pattern of the immunoglobulin Fc region, through production of GDP-fucose.

Alternatively, chemical techniques are used to alter the glycosylation pattern of fusion proteins of this disclosure. For example, a variety of glycosidase and/or mannosidase inhibitors provide one or more of desired effects of increasing ADCC activity, increasing Fc receptor binding, and altering glycosylation pattern. In certain embodiments, cells expressing a multispecific fusion protein of the instant disclosure (containing a CD86 antagonist domain linked to an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist) are grown in a culture medium comprising a carbohydrate modifier at a concentration that increases the ADCC of immunoglycoprotein molecules produced by said host cell, wherein said

carbohydrate modifier is at a concentration of less than 800 μM. In a preferred embodiment, the cells expressing these multispecific fusion proteins are grown in a culture medium comprising castanospermine or kifunensine, more preferably castanospermine at a concentration of 100-800 μM, such as 100 μM, 200 μM, 300 μM, 400 μM, 500 μM, 600 μM, 700 μM, or 800 μM. Methods for altering glycosylation with a carbohydrate modifier such as castanospermine are provided in US Patent Application Publication No. 2009/0041756 or PCT Publication No. WO 2008/052030.

In another embodiment, the immunoglobulin Fc region may have amino acid modifications that affect binding to effector cell Fc receptors. These modifications can be made using any technique known in the art, such as the approach disclosed in Presta *et al.* (2001) *Biochem. Soc. Trans. 30*:487. In another approach, the Xencor XmAb™ technology is available to engineer constant sub-regions corresponding to Fc domains to enhance cell killing effector function (*see* Lazar *et al.* (2006) Proc. Nat'l. Acad. Sci. (USA) *103*:4005). Using this approach, for example, one can generate constant sub-regions with improved specificity and binding for FCγR, thereby enhancing cell killing effector function.

In still further embodiments, a constant region or sub-region can optionally increase plasma half-life or placental transfer in comparison to a corresponding fusion protein lacking such an intervening domain. In certain embodiments, the extended plasma half-life of a fusion protein of this disclosure is at least two, at least three, at least four, at least five, at least ten, at least 12, at least 18, at least 20, at least 24, at least 30, at least 36, at least 40, at least 48 hours, at least several days, at least a week, at least two weeks, at least several weeks, at least a month, at least two months, at least several months, or more in a human.

A constant sub-region may include part or all of any of the following domains: a C_{H2} domain, a C_{H3} domain (IgA, IgD, IgG, IgE, or IgM), and a C_{H4} domain (IgE or IgM). A constant sub-region as defined herein, therefore, can refer to a polypeptide that corresponds to a portion of an immunoglobulin constant region. The constant sub-region may comprise a C_{H2} domain and a C_{H3} domain derived from the same, or different, immunoglobulins, antibody isotypes, or allelic variants. In some embodiments, the C_{H3} domain is truncated and comprises a carboxy-terminal sequence listed in US Patent Application No. 12/041,590 (which is a CIP of

PCT/US2007/071052) as SEQ ID NOS:366-371. In certain embodiments, a constant sub-region of a polypeptide of this disclosure has a C_{H2} domain and C_{H3} domain, which may optionally have an amino-terminal linker, a carboxy-terminal linker, or a linker at both ends.

A "linker" is a peptide that joins or links other peptides or polypeptides, such as a linker of about 2 to about 150 amino acids. In fusion proteins of this disclosure, a linker can join an intervening domain (*e.g.*, an immunoglobulin-derived constant sub-region) to a binding domain or a linker can join two variable regions of a binding domain, or two regions within a single chain polypeptide formed from a heterodimeric molecule, such as EBI3 (SEQ ID NO: 25) and the p35subunit of IL12 (SEQ ID NO: 26) of IL35. For example, a linker can be an amino acid sequence obtained, derived, or designed from an antibody hinge region sequence, a sequence linking a binding domain to a receptor, or a sequence linking a binding domain to a cell surface transmembrane region or membrane anchor. In some embodiments, a linker can have at least one cysteine capable of participating in at least one disulfide bond under physiological conditions or other standard peptide conditions (*e.g.*, peptide purification conditions, conditions for peptide storage). In certain embodiments, a linker corresponding or similar to an immunoglobulin hinge peptide retains a cysteine that corresponds to the hinge cysteine disposed toward the amino-terminus of that hinge. In further embodiments, a linker is from an IgG1 or IgG2A hinge and has one cysteine or two cysteines corresponding to hinge cysteines. In certain embodiments, one or more disulfide bonds are formed as inter-chain disulfide bonds between intervening domains. In other embodiments, fusion proteins of this disclosure can have an intervening domain fused directly to a binding domain (*i.e.*, absent a linker or hinge). In some embodiments, the intervening domain is a dimerization domain, such as an IgG1 CH2CH3 Fc portion.

The intervening or dimerization domain of multi-specific fusion proteins of this disclosure may be connected to one or more terminal binding domains by a peptide linker. In addition to providing a spacing function, a linker can provide flexibility or rigidity suitable for properly orienting the one or more binding domains of a fusion protein, both within the fusion protein and between or among the fusion proteins and their target(s). Further, a linker can support expression of a full-length fusion protein and stability of the purified protein both in vitro and in vivo following administration to a subject in need thereof, such as

a human, and is preferably non-immunogenic or poorly immunogenic in those same subjects. In certain embodiments, a linker of an intervening or a dimerization domain of multi-specific fusion proteins of this disclosure may comprise part or all of a human immunoglobulin hinge.

Additionally, a binding domain may comprise a V_H and a V_L domain, and these variable region domains may be combined by a linker. Exemplary variable region binding domain linkers include those belonging to the (Gly_nSer) family, such as $(Gly_3Ser)_n(Gly_4Ser)_1$, $(Gly_3Ser)_1(Gly_4Ser)_n$, $(Gly_3Ser)_n(Gly_4Ser)_n$, or $(Gly_4Ser)_n$, wherein n is an integer of 1 to 5 (*see, e.g.*, Linkers 22, 29, 46, 89, 90, 116, 130, and 131 corresponding to SEQ ID NOS:64, 71, 88, 131, 132, 149, 163 and 164, respectively) . In preferred embodiments, these (Gly_4Ser)-based linkers are used to link variable domains and are not used to link a binding domain (*e.g.*, scFv) to an intervening domain (*e.g.*, an IgG CH2CH3).

Exemplary linkers that can be used to join an intervening domain (*e.g.*, an immunoglobulin-derived constant sub-region) to a binding domain or a linker that can join two variable regions of a binding domain are listed in SEQ ID NOS:43-166, 244, 307, 320, 355-379 and 383-398.

Linkers contemplated in this disclosure include, for example, peptides derived from any inter-domain region of an immunoglobulin superfamily member (*e.g.*, an antibody hinge region) or a stalk region of C-type lectins, a family of type II membrane proteins. These linkers range in length from about two to about 150 amino acids, or about two to about 40 amino acids, or about eight to about 20 amino acids, preferably about ten to about 60 amino acids, more preferably about 10 to about 30 amino acids, and most preferably about 15 to about 25 amino acids. For example, Linker 1 is two amino acids in length and Linker 116 is 36 amino acids in length (Linkers 1-133 are provided in SEQ ID NOS:43-166, respectively; additional exemplary linkers are provided in SEQ ID NOS:244, 307, 320, 355-379, and 383-398).

Beyond general length considerations, a linker suitable for use in the fusion proteins of this disclosure includes an antibody hinge region selected from an IgG hinge, IgA hinge, IgD hinge, IgE hinge, or variants thereof. In certain embodiments, a linker may be an antibody hinge region (upper and core region) selected from human IgG1, human IgG2, human IgG3, human IgG4, or fragments or variants thereof. As used herein, a linker that is an "immunoglobulin hinge region" refers to the amino acids found between the

carboxyl end of CH1 and the amino terminal end of CH2 (for IgG, IgA, and IgD) or the amino terminal end of CH3 (for IgE and IgM). A "wild type immunoglobulin hinge region," as used herein, refers to a naturally occurring amino acid sequence interposed between and connecting the CH1 and CH2 regions (for IgG, IgA, and IgD) or interposed between and connecting the CH2 and CH3 regions (for IgE and IgM) found in the heavy chain of an antibody. In preferred embodiments, the wild type immunoglobulin hinge region sequences are human.

According to crystallographic studies, an IgG hinge domain can be functionally and structurally subdivided into three regions: the upper hinge region, the core or middle hinge region, and the lower hinge region (Shin *et al.* (1992) *Immunological Reviews* 130:87). Exemplary upper hinge regions include EPKSCDKTHT (SEQ ID NO:383) as found in IgG1, ERKCCVE (SEQ ID NO:384) as found in IgG2, ELKTPLGDTTHT (SEQ ID NO:385) or EPKSCDTPPP (SEQ ID NO:386) as found in IgG3, and ESKYGPP (SEQ ID NO:387) as found in IgG4. Exemplary middle hinge regions include CPPCP (SEQ ID NO:398) as found in IgG1 and IgG2, CPRCP (SEQ ID NO:388) as found in IgG3, and CPSCP (SEQ ID NO:389) as found in IgG4. While IgG1, IgG2, and IgG4 antibodies each appear to have a single upper and middle hinge, IgG3 has four in tandem – one of ELKTPLGDTTHTCPRCP (SEQ ID NO:390) and three of EPKSCDTPPPCPRCP (SEQ ID NO:391).

IgA and IgD antibodies appear to lack an IgG-like core region, and IgD appears to have two upper hinge regions in tandem (*see* SEQ ID NOS:392 and 393). Exemplary wild type upper hinge regions found in IgA1 and IgA2 antibodies are set forth in SEQ ID NOS: 394 and 395, respectively.

IgE and IgM antibodies, in contrast, instead of a typical hinge region have a CH2 region with hinge-like properties. Exemplary wild-type CH2 upper hinge-like sequences of IgE and IgM are set forth in SEQ ID NO:396 (VCSRDFTPPT VKILQSSSDG GGHFPPTIQL LCLVSGYTPG TINITWLEDG QVMDVDLSTA STTQEGELAS TQSELTLSQK HWLSDRTYTC QVTYQGHTFE DSTKKCA) and SEQ ID NO:397 (VIAELPPKVS VFVPPRDGFF GNPRKSKLIC QATGFSPRQI QVSWLREGKQ VGSGVTTDQV QAEAKESGPT TYKVTSTLTI KESDWLGQSM FTCRVDHRGL TFQQNASSMC VP), respectively.

An "altered wild type immunoglobulin hinge region" or "altered immunoglobulin hinge region" refers to (a) a wild type immunoglobulin hinge region with up to 30% amino acid changes (*e.g.*, up to 25%, 20%, 15%, 10%, or

5% amino acid substitutions or deletions), (b) a portion of a wild type immunoglobulin hinge region that is at least 10 amino acids (*e.g.*, at least 12, 13, 14 or 15 amino acids) in length with up to 30% amino acid changes (*e.g.*, up to 25%, 20%, 15%, 10%, or 5% amino acid substitutions or deletions), or (c) a portion of a wild type immunoglobulin hinge region that comprises the core hinge region (which portion may be 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, or at least 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids in length). In certain embodiments, one or more cysteine residues in a wild type immunoglobulin hinge region may be substituted by one or more other amino acid residues (*e.g.*, one or more serine residues). An altered immunoglobulin hinge region may alternatively or additionally have a proline residue of a wild type immunoglobulin hinge region substituted by another amino acid residue (*e.g.*, a serine residue).

Alternative hinge and linker sequences that can be used as connecting regions may be crafted from portions of cell surface receptors that connect IgV-like or IgC-like domains. Regions between IgV-like domains where the cell surface receptor contains multiple IgV-like domains in tandem and between IgC-like domains where the cell surface receptor contains multiple tandem IgC-like regions could also be used as connecting regions or linker peptides. In certain embodiments, hinge and linker sequences are from five to 60 amino acids long, and may be primarily flexible, but may also provide more rigid characteristics, and may contain primarily an α-helical structure with minimal β-sheet structure. Preferably, sequences are stable in plasma and serum and are resistant to proteolytic cleavage. In some embodiments, sequences may contain a naturally occurring or added motif such as CPPC (SEQ ID NO:422) that confers the capacity to form a disulfide bond or multiple disulfide bonds to stabilize the C-terminus of the molecule. In other embodiments, sequences may contain one or more glycosylation sites. Examples of hinge and linker sequences include interdomain regions between the IgV-like and IgC-like or between the IgC-like or IgV-like domains of CD2, CD4, CD22, CD33, CD48, CD58, CD66, CD80, CD86, CD96, CD150, CD166, and CD244. Alternative hinges may also be crafted from disulfide-containing regions of Type II receptors from non-immunoglobulin superfamily members such as CD69, CD72, and CD161.

In certain embodiments, a linker of the present invention comprises a scorpion linker. Scorpion linkers include peptides derived from

interdomain regions of an immunoglobulin superfamily member, e.g., hinge-like peptides derived from immunoglobulin hinge regions, such as IgG1, IgG2, IgG3, IgG4, IgA, and IgE hinge regions. In certain embodiments, a hinge-like scorpion linker will retain at least one cysteine capable of forming an interchain disulfide bond under physiological conditions. Scorpion linkers derived from IgG1 may have 1 cysteine or two cysteines, and may retain the cysteine corresponding to an N-terminal hinge cysteine of wild-type IgG1. Non-hinge-like peptides are also contemplated as scorpion linkers, provided that such peptides provide sufficient spacing and flexibility to provide a single-chain protein capable of forming two binding domains, one located towards each protein terminus (N and C) relative to a more centrally located constant sub-region domain. Exemplary non-hinge-like scorpion linkers include peptides from the stalk region of C-type lectin stalk regions of Type II membrane proteins, such as the stalk regions of CD69, CD72, CD94, NKG2A and NKG2D. In some embodiments, the scorpion linker comprises a sequence selected from the group consisting of SEQ ID NOs:355-359 and 365.

In some embodiments, a linker has a single cysteine residue for formation of an interchain disulfide bond. In other embodiments, a linker has two cysteine residues for formation of interchain disulfide bonds. In further embodiments, a linker is derived from an immunoglobulin interdomain region (*e.g.*, an antibody hinge region) or a Type II C-type lectin stalk region (derived from a Type II membrane protein; *see, e.g.*, exemplary lectin stalk region sequences set forth in of PCT Application Publication No. WO 2007/146968, such as SEQ ID NOS:111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 287, 289, 297, 305, 307, 309-311, 313-331, 346, 373-377, 380, or 381 from that publication, which sequences are incorporated herein by reference).

In one aspect, exemplary multi-specific fusion proteins containing a CD86 binding domain as described herein will also contain at least one additional binding region or domain that is specific for a target other than a CD86 (a "heterologous binding domain"). For example, a multi-specific fusion protein of this disclosure has a CD86 binding domain linked by an intervening domain to a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist,

a GITRL antagonist or a CD40 antagonist. In certain embodiments, a multi-specific fusion protein comprises a first and second binding domain, a first and second linker, and an intervening domain, wherein one end of the intervening domain is fused via the first linker to a first binding domain that is a CD86 binding domain (*e.g.*, a CTLA4 ectodomain, a CD28 ectodomain, an anti-CD86) and at the other end is fused via the second linker to a different binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist.

In certain embodiments, the first linker and second linker of a multi-specific fusion protein of this disclosure are each independently selected from, for example, Linkers 1-133 as provided in SEQ ID NOS:43-166 and the linkers provided in SEQ ID NOS:244, 307, 320, 355-379 and 383-398. For example, the first or second linker can be any one of Linkers 47, 58, 126-131 (SEQ ID NOS:89, 100, and 159-164, respectively), or the linkers provided in SEQ ID NO:244 or 355-379, or any combination thereof. In further examples, one linker is Linker 47 (SEQ ID NO:89) or Linker 132 (SEQ ID NO:165) and the other linker is the linker provided in SEQ ID NO:355, or Linker 127 (SEQ ID NO:160) or one linker is Linker 58 (SEQ ID NO:100) or Linker 133 (SEQ ID NO:166) and the other linker is Linker 126 (SEQ ID NO:159), or one linker is Linker 58 (SEQ ID NO:100) or Linker 133 (SEQ ID NO:166) and the other linker is Linker 127 (SEQ ID NO:160), or one linker is Linker 58 (SEQ ID NO:100) or Linker 133 (SEQ ID NO:166) and the other linker is Linker 128 (SEQ ID NO:161), or one linker is Linker 58 (SEQ ID NO:100) or Linker 133 (SEQ ID NO:166) and the other linker is Linker 129 (SEQ ID NO:162). In further examples, binding domains of this disclosure that comprise V_H and V_L domains, such as those specific for CD86, can have a further (third) linker between the V_H and V_L domains, such as the linker provided in SEQ ID NO:244, SEQ ID NO:89, Linker 46 (SEQ ID NO:88), Linker 130 (SEQ ID NO:163), or Linker 131 (SEQ ID NO:164). In any of these embodiments, the linkers may be flanked by one to five additional amino acids internally (*e.g.*, Linker 131 has an alanine internal to the (G_4S) core sequence), on either end (*e.g.*, Linker 130 has a serine on the amino-end of the (G_4S) core sequence) or on both ends (*e.g.*, Linker 120 has two amino acids (asparagine-tyrosine) on one end and three amino acids (glycine-asparagine-serine) one the other end of the (G_4S) core sequence), which may simply be a result of creating such a recombinant

molecule (*e.g.*, use of a particular restriction enzyme site to join nucleic acid molecules may result in the insertion of one to several amino acids), and for purposes of this disclosure may be considered a part of any particular linker core sequence.

In further embodiments, the intervening domain of a multi-specific fusion protein of this disclosure is comprised of an immunoglobulin constant region or sub-region, wherein the intervening domain is disposed between a CD86 binding domain and a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist. In certain embodiments, the intervening domain of a multi-specific fusion protein of this disclosure has a CD86 binding domain at the amino-terminus and a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist at the carboxy-terminus. In other embodiments, the intervening domain of a multi-specific fusion protein of this disclosure has a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist at the amino-terminus and a CD86 binding domain at the carboxy-terminus.

In further embodiments, the immunoglobulin constant region sub-region includes CH2 and CH3 domains of immunoglobulin G1 (IgG1). In related embodiments, the IgG1 CH2 and CH3 domains have one or more of the following amino acids mutated (*i.e.*, have a different amino acid at that position): leucine at position 234 (L234), leucine at position 235 (L235), glycine at position 237 (G237), glutamate at position 318 (E318), lysine at position 320 (K320), lysine at position 322 (K322), or any combination thereof (numbering according to Kabat). For example, any one of these amino acids can be changed to alanine. In a further embodiment, according to Kabat numbering, the CH2 domain has each of L234, L235, and G237 mutated to an alanine (*i.e.*, L234A, L235A, and G237A, respectively), and the IgG1 CH3 domain has each of E318, K320, and K322 mutated to an alanine (*i.e.*, E318A, K320A, and K322A, respectively).

In certain embodiments, a multi-specific fusion protein of this disclosure may comprise a small modular immunopharmaceutical" (SMIP^{TM}). In this regard, the term SMIP^{TM} refers to a highly modular compound class having

enhanced drug properties over monoclonal and recombinant antibodies. SMIPs comprise a single polypeptide chain including a target-specific binding domain, based, for example, upon an antibody variable domain, in combination with a variable FC region that permits the specific recruitment of a desired class of effector cells (such as, *e.g.*, macrophages and natural killer (NK) cells) and/or recruitment of complement-mediated killing. Depending upon the choice of target and hinge regions, SMIPs can signal or block signaling via cell surface receptors. As used herein, engineered fusion proteins, termed "small modular immunopharmaceutical" or "SMIP™ products", are as described in US Patent Publication Nos. 2003/133939, 2003/0118592, and 2005/0136049, and International Patent Publications WO02/056910, WO2005/037989, and WO2005/017148.

In some embodiments, a multi-specific fusion protein may comprise a PIMS molecule such as those described in US Patent Publication No. 2009/0148447 and International Patent Publication WO2009/023386.

In certain embodiments, the muti-specific fusion proteins of the invention can be engineered with different front and back end affinities in order to target specific cell types. For example, use of an anti-CD86 binding domain (*e.g.*, 3D1, FUN1, or humanized variants thereof) that has a higher affinity for CD86 than an engineered IL10 agonist (*e.g.*, having an I87A or I87S mutation, or a monoIL10 structure) has for hulL10R1, and combining such molecules in an xceptor molecule of this disclcosure can be used to favor targeting to a specific cell type of interest, such as antigen-presenting cells (APCs). In this regard, fusion proteins can be made that have higher or lower affinity for CD86 or higher or lower affinity for any of the heterologous target proteins described herein, depending on the desired cell type to target. In preferred embodiments, the CD86 antagonist binding domain preferentially targets the multi-target specific xceptor molecule to APCs by having a greater affinity for CD86 than the heterologous binding domain has for its binding partner.

In some embodiments, a multi-specific fusion protein of this disclosure has a CD86 binding domain that comprises a CTLA4 extracellular domain or sub-domain, a CD28 extracellular domain or sub-domain, or a CD86-specific antibody-derived binding domain. In certain embodiments, a CD86-specific antibody-derived binding domain is derived from the FUN1 monoclonal antibody (see *e.g.*, J Pathol. 1993 Mar;169(3):309-15); or derived from the 3D1 anti-CD86 monoclonal antibody. In certain embodiments, a CD86

binding domain is a sCTLA4, such as the mature polypeptide sequence of SEQ ID NO:1. In certain embodiments, the CD86 binding domain is a sCTLA4, such as the sequence of SEQ ID NO:1 or a variable-like domain of CTLA4, such as SEQ ID NO:3, or a sub-domain thereof. In other embodiments, a CD86 binding domain is a sCD28, such as the mature polypeptide sequence of SEQ ID NO:2 (signal peptide: amino acids 1-18). In still further embodiments, the CD86 binding domain comprises light and heavy chain variable domains from FUN1 (*e.g.*, SEQ ID NOS:305 and 306) or 3D1 (*e.g.*, SEQ ID NOS:318 and 319), preferably in the form of an scFv.

In further embodiments, a multi-specific fusion protein of this disclosure has a CD86 binding domain and a heterologous binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist (see *e.g.*, the amino acid sequences of heterologous binding domains provided in SEQ ID NOS:7, 14, 15, 18-22, 25, 26, 29, 32, 33, 36, 39 and 40).

Exemplary structures of such multi-specific fusion proteins, referred to herein as Xceptor molecules, include N-BD1-ID-BD2-C, N-BD2-ID-BD1-C, wherein N and C represent the amino-terminus and carboxy-terminus, respectively; BD1 is a CD86 binding domain, such as an immunoglobulin-like or immunoglobulin variable region binding domain, or an ectodomain; X is an intervening domain, and BD2 is binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist. In some constructs, X can comprise an immunoglobulin constant region or sub-region disposed between the first and second binding domains. In some embodiments, a multi-specific fusion protein of this disclosure has an intervening domain (X) comprising, from amino-terminus to carboxy-terminus, a structure as follows: -L1-X-L2-, wherein L1 and L2 are each independently a linker comprising from two to about 150 amino acids; and X is an immunoglobulin constant region or sub-region. In further embodiments, the multi-specific fusion protein will have an intervening domain that is albumin, transferrin, or another serum protein binding protein, wherein the fusion protein remains primarily or substantially as a single chain polypeptide in a composition.

The amino acid sequences of exemplary Xceptor fusion proteins are provided in SEQ ID NOS:9, 13, 17, 24, 28, 31, 35, 38, 42, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 237, 239, 252, 254, 256, 258, 260, 262, 266, 276, 302, 330, 334, 336, 338, 340, 350, 352, and 354; encoded by the polynucleotide sequences provided in SEQ ID NOS:8, 12, 16, 23, 27, 30, 34, 37, 41, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 236, 238, 251, 253, 255, 257, 259, 261, 265, 275, 301, 329, 333, 335, 337, 339, 349, 351 and 353 respectively.

In still further embodiments, a multi-specific fusion protein of this disclosure has the following structure: N-BD1-X-L2-BD2-C, wherein BD1 is a CD86 binding domain, such a binding domain that is at least about 90% identical to a CTLA4 ectodomain; -X- is -L1-CH2CH3-, wherein L1 is a first IgG1 hinge, optionally mutated by substituting the first or second cysteine and wherein -CH2CH3- is the CH2CH3 region of an IgG1 Fc domain; L2 is a linker selected from SEQ ID NOS:43-166, 244, 307, 320, 355-379 and 383-398; and BD2 is a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist, as described herein.

In particular embodiments, a multi-specific Xceptor fusion protein has (a) a CD86 binding domain comprising an amino acid sequence at least 80%, 90%, 95%, 96%, 97%, 98%, 99% or at least 100% identical to a mature polypeptide sequence of SEQ ID NO:1 or SEQ ID NO: 2, and (b) a binding domain that is an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist, a GITRL antagonist or a CD40 antagonist comprising an amino acid sequence at least 80%, 90%, 95%, 96%, 97%, 98%, 99% or at least 100% identical to a corresponding mature polypeptide sequence of the aforementioned heterologous binding proteins as provided in SEQ ID NOS:7, 14, 15, 18-22, 25, 26, 29, 32, 33, 36, 39 and 40), wherein, from amino-terminus to carboxy-terminus or from carboxy-terminus to amino-terminus, (i) a CD86 binding domain of (a) or binding domain of (b) is fused to a first linker, (ii) the first linker is fused to an immunoglobulin heavy chain constant region of CH2 and CH3 as set forth in any one of SEQ ID NOS:409 and 415-417, (iii) the CH2CH3 constant region polypeptide is fused to a second linker, and (iv) the second

linker is fused to a CD86 binding domain of (a) or a binding domain of (b). In certain embodiments, the first linker is Linker 47 (SEQ ID NO:89), Linker 132 (SEQ ID NO:165) or Linker 133 (SEQ ID NO:166), the second linker is any one of Linkers 126-129 (SEQ ID NOS:159-162), and a further (third) linker between the CD86 binding domain V_H and V_L domains is Linker 130 (SEQ ID NO:163) or Linker 131 (SEQ ID NO:164).

The amino acid sequences of exemplary Xceptor fusion proteins are provided in SEQ ID NOS:9, 13, 17, 24, 28, 31, 35, 38, 42, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 237, 239, 252, 254, 256, 258, 260, 262, 266, 276, 302, 330, 334, 336, 338, 340, 350, 352, and 354; encoded by the polynucleotide sequences provided in SEQ ID Nos:8, 12, 16, 23, 27, 30, 34, 37, 41, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 236, 238, 251, 253, 255, 257, 259, 261, 265, 275, 301, 329, 333, 335, 337, 339, 349, 351 and 353 respectively.

Making Multi-Specific Fusion Proteins

To efficiently produce any of the binding domain polypeptides or fusion proteins described herein, a leader peptide is used to facilitate secretion of expressed polypeptides and fusion proteins. Using any of the conventional leader peptides (signal sequences) is expected to direct nascently expressed polypeptides or fusion proteins into a secretory pathway and to result in cleavage of the leader peptide from the mature polypeptide or fusion protein at or near the junction between the leader peptide and the polypeptide or fusion protein. A particular leader peptide will be chosen based on considerations known in the art, such as using sequences encoded by polynucleotides that allow the easy inclusion of restriction endonuclease cleavage sites at the beginning or end of the coding sequence for the leader peptide to facilitate molecular engineering, provided that such introduced sequences specify amino acids that either do not interfere unacceptably with any desired processing of the leader peptide from the nascently expressed protein or do not interfere unacceptably with any desired function of a polypeptide or fusion protein molecule if the leader peptide is not cleaved during maturation of the polypeptides or fusion proteins. Exemplary leader peptides of this disclosure include natural leader sequences (*i.e.*, those expressed with the native protein)

or use of heterologous leader sequences, such as H_3N-MDFQVQIFSFLLISASVIMSRG$(X)_n$-CO_2H, wherein X is any amino acid and n is zero to three (SEQ ID NOS:167, 419, 420, and 421) or H_3N-MEAPAQLLFLLLLWLPDTTG-CO_2H (SEQ ID NO:168).

As noted herein, variants and derivatives of binding domains, such as ectodomains, light and heavy variable regions, and CDRs described herein, are contemplated. In one example, insertion variants are provided wherein one or more amino acid residues supplement a specific binding agent amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the specific binding agent amino acid sequence. Variant products of this disclosure also include mature specific binding agent products, *i.e.*, specific binding agent products wherein a leader or signal sequence is removed, and the resulting protein having additional amino terminal residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived from a specific protein. Polypeptides with an additional methionine residue at position -1 are contemplated, as are polypeptides of this disclosure with additional methionine and lysine residues at positions -2 and -1. Variants having additional Met, Met-Lys, or Lys residues (or one or more basic residues in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

As used herein, "amino acids" refer to a natural (those occurring in nature) amino acid, a substituted natural amino acid, a non-natural amino acid, a substituted non-natural amino acid, or any combination thereof. The designations for natural amino acids are herein set forth as either the standard one- or three-letter code. Natural polar amino acids include asparagine (Asp or N) and glutamine (Gln or Q); as well as basic amino acids such as arginine (Arg or R), lysine (Lys or K), histidine (His or H), and derivatives thereof; and acidic amino acids such as aspartic acid (Asp or D) and glutamic acid (Glu or E), and derivatives thereof. Natural hydrophobic amino acids include tryptophan (Trp or W), phenylalanine (Phe or F), isoleucine (Ile or I), leucine (Leu or L), methionine (Met or M), valine (Val or V), and derivatives thereof; as well as other non-polar amino acids such as glycine (Gly or G), alanine (Ala or A), proline (Pro or P), and derivatives thereof. Natural amino acids of intermediate polarity include serine (Ser or S), threonine (Thr or T), tyrosine (Tyr or Y), cysteine (Cys or C),

and derivatives thereof. Unless specified otherwise, any amino acid described herein may be in either the D- or L-configuration.

Substitution variants include those fusion proteins wherein one or more amino acid residues in an amino acid sequence are removed and replaced with alternative residues. In some embodiments, the substitutions are conservative in nature; however, this disclosure embraces substitutions that are also non-conservative. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table 1 (*see* WO 97/09433, page 10, published March 13, 1997), immediately below.

Table 1. Conservative Substitutions I

Side Chain	Characteristic	Amino Acid
Aliphatic	Non-polar	G, A, P, I, L, V
	Polar – uncharged	S, T, M, N, Q
	Polar – charged	D, E, K, R
Aromatic		H, F, W, Y
Other		N, Q, D, E

Alternatively, conservative amino acids can be grouped as described in Lehninger (Biochemistry, Second Edition; Worth Publishers, Inc. NY:NY (1975), pp.71-77) as set out in Table 2, immediately below.

Table 2. Conservative Substitutions II

Side Chain	Characteristic	Amino Acid
Non-polar (hydrophobic)	Aliphatic:	A, L, I, V, P
	Aromatic	F, W
	Sulfur-containing	M
	Borderline	G
Uncharged-polar	Hydroxyl	S, T, Y
	Amides	N, Q
	Sulfhydryl	C
	Borderline	G
Positively Charged (Basic)		K, R, H
Negatively Charged (Acidic)		D, E

Variants or derivatives can also have additional amino acid residues which arise from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of a glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at position -1 after cleavage of the GST component from the desired polypeptide. Variants which result from expression in other vector systems are also contemplated, including those wherein histidine tags are incorporated into the amino acid sequence, generally at the carboxy and/or amino terminus of the sequence.

Deletion variants are also contemplated wherein one or more amino acid residues in a binding domain of this disclosure are removed. Deletions can be effected at one or both termini of the fusion protein, or from removal of one or more residues within the amino acid sequence.

In certain illustrative embodiments, fusion proteins of this disclosure are glycosylated, the pattern of glycosylation being dependent upon a variety of factors including the host cell in which the protein is expressed (if prepared in recombinant host cells) and the culture conditions.

This disclosure also provides derivatives of fusion proteins. Derivatives include specific binding domain polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. In certain embodiments, the modifications are covalent in nature, and include for

example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Derivatives of this disclosure may be prepared to increase circulating half-life of a specific binding domain polypeptide, or may be designed to improve targeting capacity for the polypeptide to desired cells, tissues, or organs.

This disclosure further embraces fusion proteins that are covalently modified or derivatized to include one or more water-soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol, as described U.S. Patent Nos: 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 and 4,179,337. Still other useful polymers known in the art include monomethoxy-polyethylene glycol, dextran, cellulose, and other carbohydrate-based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of these polymers. Particularly preferred are polyethylene glycol (PEG)–derivatized proteins. Water-soluble polymers may be bonded at specific positions, for example at the amino terminus of the proteins and polypeptides according to this disclosure, or randomly attached to one or more side chains of the polypeptide. The use of PEG for improving therapeutic capacities is described in US Patent No. 6,133,426.

A particular embodiment of this disclosure is an immunoglobulin or an Fc fusion protein. Such a fusion protein can have a long half-life, *e.g.*, several hours, a day or more, or even a week or more, especially if the Fc domain is capable of interacting with FcRn, the neonatal Fc receptor. The binding site for FcRn in an Fc domain is also the site at which the bacterial proteins A and G bind. The tight binding between these proteins can be used as a means to purify antibodies or fusion proteins of this disclosure by, for example, employing protein A or protein G affinity chromatography during protein purification.

Protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the polypeptide and non-polypeptide fractions. Further purification using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity) is frequently desired. Analytical methods particularly suited to the preparation of a pure fusion protein are ion-exchange chromatography; exclusion chromatography; polyacrylamide gel

electrophoresis; and isoelectric focusing. Particularly efficient methods of purifying peptides are fast protein liquid chromatography and HPLC.

Certain aspects of the present disclosure concern the purification, and in particular embodiments, the substantial purification, of a fusion protein. The term "purified fusion protein" as used herein, is intended to refer to a composition, isolatable from other components, wherein the fusion protein is purified to any degree relative to its naturally obtainable state. A purified fusion protein therefore also refers to a fusion protein, free from the environment in which it may naturally occur.

Generally, "purified" will refer to a fusion protein composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation refers to a fusion binding protein composition in which the fusion protein forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 99% or more of the protein, by weight, in the composition.

Various methods for quantifying the degree of purification are known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific binding activity of an active fraction, or assessing the amount of fusion protein in a fraction by SDS/PAGE analysis. A preferred method for assessing the purity of a protein fraction is to calculate the binding activity of the fraction, to compare it to the binding activity of the initial extract, and to thus calculate the degree of purification, herein assessed by a "-fold purification number." The actual units used to represent the amount of binding activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the expressed fusion protein exhibits a detectable binding activity.

Various techniques suitable for use in protein purification are well known to those of skill in the art. These include, for example, precipitation with ammonium sulfate, PEG, antibodies and the like, or by heat denaturation, followed by centrifugation; chromatography steps such as ion exchange, gel filtration, reverse phase, hydroxylapatite, and affinity chromatography; isoelectric focusing; gel electrophoresis; and combinations of these and other techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps

may be omitted, and still result in a suitable method for the preparation of a substantially purified protein.

There is no general requirement that the fusion protein always be provided in its most purified state. Indeed, it is contemplated that less substantially purified proteins will have utility in certain embodiments. Partial purification may be accomplished by using fewer purification steps in combination, or by utilizing different forms of the same general purification scheme. For example, it is appreciated that a cation-exchange column chromatography performed utilizing an HPLC apparatus will generally result in greater purification than the same technique utilizing a low pressure chromatography system. Methods exhibiting a lower degree of relative purification may have advantages in total recovery of protein product, or in maintaining binding activity of an expressed protein.

It is known that the migration of a polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE (Capaldi et al. (1977) Biochem. Biophys. Res. Comm. 76:425). It will therefore be appreciated that under differing electrophoresis conditions, the apparent molecular weights of purified or partially purified fusion protein expression products may vary.

Polynucleotides, Expression Vectors, and Host Cells

This disclosure provides polynucleotides (isolated or purified or pure polynucleotides) encoding the multi-specific fusion protein of this disclosure, vectors (including cloning vectors and expression vectors) comprising such polynucleotides, and cells (*e.g.*, host cells) transformed or transfected with a polynucleotide or vector according to this disclosure.

In certain embodiments, a polynucleotide (DNA or RNA) encoding a binding domain of this disclosure, or a multi-specific fusion protein containing one or more such binding domains is contemplated. Expression cassettes encoding multi-specific fusion protein constructs are provided in the examples appended hereto.

The present disclosure also relates to vectors that include a polynucleotide of this disclosure and, in particular, to recombinant expression constructs. In one embodiment, this disclosure contemplates a vector comprising a polynucleotide encoding a multi-specific fusion protein containing a CD86 binding domain and an IL-10 agonist, an HLA-G agonist, an HGF agonist, an IL-35 agonist, a PD-1 agonist, a BTLA agonist, a LIGHT antagonist,

a GITRL antagonist or a CD40 antagonist domain of this disclosure, along with other polynucleotide sequences that cause or facilitate transcription, translation, and processing of such multi-specific fusion protein-encoding sequences.

Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described, for example, in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, NY, (1989). Exemplary cloning/expression vectors include cloning vectors, shuttle vectors, and expression constructs, that may be based on plasmids, phagemids, phasmids, cosmids, viruses, artificial chromosomes, or any nucleic acid vehicle known in the art suitable for amplification, transfer, and/or expression of a polynucleotide contained therein

As used herein, "vector" means a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. Exemplary vectors include plasmids, yeast artificial chromosomes, and viral genomes. Certain vectors can autonomously replicate in a host cell, while other vectors can be integrated into the genome of a host cell and thereby are replicated with the host genome. In addition, certain vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"), which contain nucleic acid sequences that are operatively linked to an expression control sequence and, therefore, are capable of directing the expression of those sequences.

In certain embodiments, expression constructs are derived from plasmid vectors. Illustrative constructs include modified pNASS vector (Clontech, Palo Alto, CA), which has nucleic acid sequences encoding an ampicillin resistance gene, a polyadenylation signal and a T7 promoter site; pDEF38 and pNEF38 (CMC ICOS Biologics, Inc.), which have a CHEF1 promoter; and pD18 (Lonza), which has a CMV promoter. Other suitable mammalian expression vectors are well known (*see, e.g.*, Ausubel *et al.*, 1995; Sambrook *et al.*, supra; *see also, e.g.*, catalogs from Invitrogen, San Diego, CA; Novagen, Madison, WI; Pharmacia, Piscataway, NJ). Useful constructs may be prepared that include a dihydrofolate reductase (DHFR)-encoding sequence under suitable regulatory control, for promoting enhanced production levels of the fusion proteins, which levels result from gene amplification following application of an appropriate selection agent (*e.g.*, methotrexate).

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell,

and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence, as described above. A vector in operable linkage with a polynucleotide according to this disclosure yields a cloning or expression construct. Exemplary cloning/expression constructs contain at least one expression control element, *e.g.*, a promoter, operably linked to a polynucleotide of this disclosure. Additional expression control elements, such as enhancers, factor-specific binding sites, terminators, and ribosome binding sites are also contemplated in the vectors and cloning/expression constructs according to this disclosure. The heterologous structural sequence of the polynucleotide according to this disclosure is assembled in appropriate phase with translation initiation and termination sequences. Thus, for example, the fusion protein-encoding nucleic acids as provided herein may be included in any one of a variety of expression vector constructs as a recombinant expression construct for expressing such a protein in a host cell.

The appropriate DNA sequence(s) may be inserted into a vector, for example, by a variety of procedures. In general, a DNA sequence is inserted into an appropriate restriction endonuclease cleavage site(s) by procedures known in the art. Standard techniques for cloning, DNA isolation, amplification and purification, for enzymatic reactions involving DNA ligase, DNA polymerase, restriction endonucleases and the like, and various separation techniques are contemplated. A number of standard techniques are described, for example, in Ausubel *et al.* (*Current Protocols in Molecular Biology*, Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., Boston, MA, 1993); Sambrook *et al.* (*Molecular Cloning*, Second Ed., Cold Spring Harbor Laboratory, Plainview, NY, 1989); Maniatis *et al.* (*Molecular Cloning*, Cold Spring Harbor Laboratory, Plainview, NY, 1982); Glover (Ed.) (*DNA Cloning* Vol. I and II, IRL Press, Oxford, UK, 1985); Hames and Higgins (Eds.) (*Nucleic Acid Hybridization*, IRL Press, Oxford, UK, 1985); and elsewhere.

The DNA sequence in the expression vector is operatively linked to at least one appropriate expression control sequence (*e.g.*, a constitutive promoter or a regulated promoter) to direct mRNA synthesis. Representative examples of such expression control sequences include promoters of eukaryotic cells or their viruses, as described above. Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from

retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art, and preparation of certain particularly preferred recombinant expression constructs comprising at least one promoter or regulated promoter operably linked to a nucleic acid encoding a protein or polypeptide according to this disclosure is described herein.

Variants of the polynucleotides of this disclosure are also contemplated. Variant polynucleotides are at least 90%, and preferably 95%, 99%, or 99.9% identical to one of the polynucleotides of defined sequence as described herein, or that hybridizes to one of those polynucleotides of defined sequence under stringent hybridization conditions of 0.015M sodium chloride, 0.0015M sodium citrate at about 65-68°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 50% formamide at about 42°C. The polynucleotide variants retain the capacity to encode a binding domain or fusion protein thereof having the functionality described herein.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Hybridization stringency is principally determined by temperature, ionic strength, and the concentration of denaturing agents such as formamide. Examples of stringent conditions for hybridization and washing are 0.015M sodium chloride, 0.0015M sodium citrate at about 65-68°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 50% formamide at about 42°C (*see* Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989).

More stringent conditions (such as higher temperature, lower ionic strength, higher formamide, or other denaturing agent) may also be used; however, the rate of hybridization will be affected. In instances wherein hybridization of deoxyoligonucleotides is concerned, additional exemplary stringent hybridization conditions include washing in 6x SSC, 0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligonucleotides), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

A further aspect of this disclosure provides a host cell transformed or transfected with, or otherwise containing, any of the polynucleotides or vector/expression constructs of this disclosure. The polynucleotides or cloning/expression constructs of this disclosure are introduced into suitable

cells using any method known in the art, including transformation, transfection and transduction. Host cells include the cells of a subject undergoing *ex vivo* cell therapy including, for example, *ex vivo* gene therapy. Eukaryotic host cells contemplated as an aspect of this disclosure when harboring a polynucleotide, vector, or protein according to this disclosure include, in addition to a subject's own cells (*e.g.*, a human patient's own cells), VERO cells, HeLa cells, Chinese hamster ovary (CHO) cell lines (including modified CHO cells capable of modifying the glycosylation pattern of expressed multivalent binding molecules, *see* US Patent Application Publication No. 2003/0115614), COS cells (such as COS-7), W138, BHK, HepG2, 3T3, RIN, MDCK, A549, PC12, K562, HEK293 cells, HepG2 cells, N cells, 3T3 cells, *Spodoptera frugiperda* cells (*e.g.*, Sf9 cells), *Saccharomyces cerevisiae* cells, and any other eukaryotic cell known in the art to be useful in expressing, and optionally isolating, a protein or peptide according to this disclosure. Also contemplated are prokaryotic cells, including *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, a Streptomycete, or any prokaryotic cell known in the art to be suitable for expressing, and optionally isolating, a protein or peptide according to this disclosure. In isolating protein or peptide from prokaryotic cells, in particular, it is contemplated that techniques known in the art for extracting protein from inclusion bodies may be used. The selection of an appropriate host is within the scope of those skilled in the art from the teachings herein. Host cells that glycosylate the fusion proteins of this disclosure are contemplated.

The term "recombinant host cell" (or simply "host cell") refers to a cell containing a recombinant expression vector. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

Recombinant host cells can be cultured in a conventional nutrient medium modified as appropriate for activating promoters, selecting transformants, or amplifying particular genes. The culture conditions for particular host cells selected for expression, such as temperature, pH and the like, will be readily apparent to the ordinarily skilled artisan. Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines

of monkey kidney fibroblasts, described by Gluzman (1981) Cell 23:175, and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and, optionally, enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5'-flanking nontranscribed sequences, for example, as described herein regarding the preparation of multivalent binding protein expression constructs. DNA sequences derived from the SV40 splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Introduction of the construct into the host cell can be effected by a variety of methods with which those skilled in the art will be familiar, including calcium phosphate transfection, DEAE-Dextran-mediated transfection, or electroporation (Davis *et al.* (1986) Basic Methods in Molecular Biology).

In one embodiment, a host cell is transduced by a recombinant viral construct directing the expression of a protein or polypeptide according to this disclosure. The transduced host cell produces viral particles containing expressed protein or polypeptide derived from portions of a host cell membrane incorporated by the viral particles during viral budding.

Compositions and Methods of Use

To treat human or non-human mammals suffering a disease state associated with CD86, IL-10, HLA-G, IL-35, PD-1, BTLA, LIGHT, GITRL or CD40 dysregulation, a multi-specific fusion protein of this disclosure is administered to the subject in an amount that is effective to ameliorate symptoms of the disease state following a course of one or more administrations. Being polypeptides, the multi-specific fusion proteins of this disclosure can be suspended or dissolved in a pharmaceutically acceptable diluent, optionally including a stabilizer of other pharmaceutically acceptable excipients, which can be used for intravenous administration by injection or infusion, as more fully discussed below.

A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence of, or treat (alleviate a symptom to some extent, preferably all symptoms of) a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of subject being treated, the physical characteristics of

the specific subject under consideration for treatment, concurrent medication, and other factors that those skilled in the medical arts will recognize. For example, an amount between 0.1 mg/kg and 100 mg/kg body weight (which can be administered as a single dose, or in multiple doses given hourly, daily, weekly, monthly, or any combination thereof that is an appropriate interval) of active ingredient may be administered depending on the potency of a binding domain polypeptide or multi-specific protein fusion of this disclosure.

In certain aspects, compositions of fusion proteins are provided by this disclosure. Pharmaceutical compositions of this disclosure generally comprise one or more type of binding domain or fusion protein in combination with a pharmaceutically acceptable carrier, excipient, or diluent. Such carriers will be nontoxic to recipients at the dosages and concentrations employed. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro (Ed.) 1985). For example, sterile saline and phosphate buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and the like may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid, or esters of *p*-hydroxybenzoic acid may be added as preservatives. *Id.* at 1449. In addition, antioxidants and suspending agents may be used. *Id.* The compounds of the present invention may be used in either the free base or salt forms, with both forms being considered as being within the scope of the present invention.

Pharmaceutical compositions may also contain diluents such as buffers; antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates (*e.g.*, glucose, sucrose, or dextrins), chelating agents (*e.g.*, EDTA), glutathione or other stabilizers or excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions as diluents.

Compositions of this disclosure can be used to treat disease states in human and non-human mammals that are a result of or associated with CD86, IL-10, HLA-G, IL-35, PD-1, BTLA, LIGHT, GITRL or CD40 dysregulation. As discussed above, blocking of binding of CD86 to CD28, for example by administration of CTLA4Ig, has been shown to be effective in

treating autoimmune disorders, such as rheumatoid arthritis. IL10 is known to have immunosuppressive properties (Commins *et al.* (2008) J. Allergy Clin. Immunol. 121:1108-11; Ming *et al.*, (2008) Immunity 28:468-476), and beneficial responses have been seen following administration of IL10 to patients with psoriasis (Asadullah *et al.* (1999) Arch. Dermatol. 135:187-92) and inflammatory bowel disease (Schreiber *et al.* (2000) Gastroenterology 119:1461-72). As noted above, it has been suggested that HLA-G may be useful in reducing inflammatory responses in the CNS associated with multiple sclerosis (Wiendl et al. (2005) Blood, 128:2689-2704), and as a therapeutic agent in promoting tolerance to grafts in transplantations (Carosella et al. (2008) Blood 111:4862-4870). HGF has been shown to be effective in reducing disease both in a mouse model of arthritis and in a mouse model of asthma. IL35 has been shown to be effective in reducing disease in a mouse model of arthritis and to suppress T-cell proliferation. As discussed above, LIGHT antagonists have been shown to be effective in reducing graft vs. host disease and to suppress T-cell proliferation. In addition, LIGHT is believed to play a role in inflammatory bowel disease and Crohn's disease. PD1-L1 or PD1-L2 to PD-1 has been shown to be effective in reducing T-cell activation and cytokine production. BTLA has been shown to be effective in reducing T-cell activation and cytokine production. Binding of GITRL to GITR has been shown to increase disease severity in animal models of asthma and arthritis, and is known to increase T cell inflammatory and immune responses. As discussed above, CD40 signaling is involved in diseases such as autoimmune diseases, cancers, and organ and tissue graft rejections.

Thus, multi-specific fusion proteins of this disclosure are useful in treating various autoimmune and/or inflammatory disorders, such as rheumatoid arthritis, juvenile rheumatoid arthritis, asthma, systemic lupus erythematosus (SLE), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), graft versus host disease, psoriasis, multiple sclerosis, dermatomyositis, polymyositis, pernicious anaemia, primary biliary cirrhosis, acute disseminated encephalomyelitis (ADEM), Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS) autoimmune hepatitis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, lupus erythematosus, pemphigus vulgaris, Sjögren's syndrome, temporal arteritis (also known as "giant cell arteritis"), autoimmune hemolytic

anemia, bullous pemphigoid, vasculitis, coeliac disease, endometriosis, hidradenitis suppurativa, interstitial cystitis, morphea, scleroderma, narcolepsy, neuromyotonia, vitiligo and autoimmune inner ear disease. In addition, multi-specific fusion proteins of this disclosure are useful in suppressing detrimental immune alloresponse in organ transplant (including solid organ transplant or allograft), cell transplant, or the like.

"Pharmaceutically acceptable salt" refers to a salt of a binding domain polypeptide or fusion protein of this disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include the following: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, or the like.

In particular illustrative embodiments, a polypeptide or fusion protein of this disclosure is administered intravenously by, for example, bolus injection or infusion. Routes of administration in addition to intravenous include oral, topical, parenteral (*e.g.*, sublingually or buccally), sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal, intracavernous, intrathecal, intrameatal, intraurethral injection or infusion techniques. The pharmaceutical composition is formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of

the composition to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of one or more compounds of this disclosure in aerosol form may hold a plurality of dosage units.

For oral administration, an excipient and/or binder may be present, such as sucrose, kaolin, glycerin, starch dextrans, cyclodextrins, sodium alginate, ethyl cellulose, and carboxy methylcellulose. Sweetening agents, preservatives, dye/colorant, flavor enhancer, or any combination thereof may optionally be present. A coating shell may also optionally be used.

In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer, isotonic agent, or any combination thereof may optionally be included.

For nucleic acid-based formulations, or for formulations comprising expression products according to this disclosure, about 0.01 μg/kg to about 100 mg/kg body weight will be administered, for example, by the intradermal, subcutaneous, intramuscular, or intravenous route, or by any route known in the art to be suitable under a given set of circumstances. A preferred dosage, for example, is about 1 μg/kg to about 20 mg/kg, with about 5 μg/kg to about 10 mg/kg particularly preferred. It will be evident to those skilled in the art that the number and frequency of administration will be dependent upon the response of the host.

The pharmaceutical compositions of this disclosure may be in any form that allows for administration to a patient, such as, for example, in the form of a solid, liquid, or gas (aerosol). The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension, for administration by any route described herein.

A liquid pharmaceutical composition as used herein, whether in the form of a solution, suspension or other like form, may include one or more of the following components: sterile diluents such as water for injection, saline solution (*e.g.*, physiological saline), Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono- or digylcerides that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; buffers such as acetates, citrates or phosphates; chelating agents such as ethylenediaminetetraacetic

acid; and agents for the adjustment of tonicity such as sodium, chloride, or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred additive. An injectable pharmaceutical composition is preferably sterile.

It may also be desirable to include other components in the preparation, such as delivery vehicles including aluminum salts, water-in-oil emulsions, biodegradable oil vehicles, oil-in-water emulsions, biodegradable microcapsules, and liposomes. Examples of adjuvants for use in such vehicles include N-acetylmuramyl-L-alanine-D-isoglutamine (MDP), lipopolysaccharides (LPS), glucan, IL-12, GM-CSF, γ-interferon, and IL-15.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this disclosure, the type of carrier will vary depending on the mode of administration and whether a sustained release is desired. For parenteral administration, the carrier may comprise water, saline, alcohol, a fat, a wax, a buffer, or any combination thereof. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, magnesium carbonate, or any combination thereof, may be employed.

Also contemplated is the administration of multi-specific fusion protein compositions of this disclosure in combination with a second agent. A second agent may be one accepted in the art as a standard treatment for a particular disease state, such as inflammation, autoimmunity, and cancer. Exemplary second agents contemplated include cytokines, growth factors, steroids, NSAIDs, DMARDs, chemotherapeutics, radiotherapeutics, or other active and ancillary agents.

This disclosure contemplates a dosage unit comprising a pharmaceutical composition of this disclosure. Such dosage units include, for example, a single-dose or a multi-dose vial or syringe, including a two-compartment vial or syringe, one comprising the pharmaceutical composition of this disclosure in lyophilized form and the other a diluent for reconstitution. A multi-dose dosage unit can also be, *e.g.*, a bag or tube for connection to an intravenous infusion device.

This disclosure also contemplates a kit comprising a pharmaceutical composition in a unit dose or multi-dose container, *e.g.*, a vial,

and a set of instructions for administering the composition to patients suffering a disorder as described herein.

All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, non-patent publications, tables, sequences, webpages, or the like referred to in this specification, are incorporated herein by reference, in their entirety. The following examples are intended to illustrate, but not limit, this disclosure.

EXAMPLES

Xceptor Sequences

Nucleotide expression cassettes and amino acid sequences of exemplary multi-specific fusion proteins having a CTLA4 ectodomain are provided in SEQ ID NOS:8, 12, 16, 23, 27, 30, 34, 37 and 41 and SEQ ID NOS:9, 13, 17, 24, 28, 31, 35, 38, and 42, respectively. The activity of these exemplary multi-specific fusion proteins was tested as described in Examples 1-6 below. Abbreviations used in the following examples include the following terms: PBS-T: PBS, pH 7.2-7.4 and 0.1% Tween®20; Working buffer: PBS-T with 1% BSA; Blocking buffer: PBS-T with 3% BSA.

EXAMPLE 1

ANTI-CD86 BINDING DOMAINS

Hybridomas 3D1 and FUN1 were used to clone the anti-CD86 variable binding domains of these monoclonal antibodies. The sequences for the heavy chain, light chain, scFv linker, and CDRs from the FUN1 and 3D1 anti-CD86 monoclonal antibodies are found in SEQ NOS:305-313 and 318-326, respectively.

The following humanized FUN1 anti-CD86 monoclonal antibody variable binding domains were used to construct SMIP proteins and xceptors. The FUN1 CDRs were grafted into human germline sequences as follows: (1) FUN1-11 has Igkv4-1*01 FR for light chain and IgHV1-F*01 FR for heavy chain; (2) FUN1-21 has Igkv4-1*01 FR for light chain and IgHV1-2*02 FR for heavy chain; (3) FUN1-31 has Igkv4-1*01 FR for light chain and IgHV3-11*01 FR for heavy chain; (4) FUN1-12 has Igkv1-27*01 FR for light chain and IgHV1-F*01 FR for heavy chain; (5) FUN1-22 has Igkv1-27*01 FR for light chain and IgHV1-2*02 FR for heavy chain; and (6) FUN1-32 has Igkv1-27*01 FR for light chain and IgHV3-11*01 FR for heavy chain. The germline CDRs for the humanized molecules are similar to the original FUN1 molecules.

Consequently, six versions of humanized FUN1 SMIP proteins were also generated as follows: (1) FUN1-11 (SEQ ID NO:225); (2) FUN1-21 (SEQ ID NO:227); (3) FUN1-31 (SEQ ID NO:229); (4) FUN1-12 (SEQ ID NO:231); (5) FUN1-22 (SEQ ID NO:233); and (6) FUN1-32 (SEQ ID NO:235). Binding activity of these humanized FUN1 SMIP molecules is shown in Figure

7. In addition, the FUN1 variable domains (scFv) and humanized FUN1 scFv were used to make xceptors, such as IL10::FUN1 (SEQ ID NO:183); FUN1::IL10 (SEQ ID NO:187); FUN1-21::IL10 (SEQ ID NO:237); IL10::FUN1-21 (SEQ ID NO:254); IL10 I87A::FUN1-21 (SEQ ID NO:258); and monoIL10::FUN1-21 binding domain was also made using a short A2 hinge (SEQ ID NO:276) (wherein the A2 hinge amino acid sequence is set forth in SEQ ID NO:364).

These, and all the other constructs described herein, were cloned into appropriate mammalian expression vectors and expressed in various cell lines to produce protein for particular functional assays.

EXAMPLE 2

XCEPTOR BINDING TO IL10-R1 BY BIACORE™

IL10-R1 binding activity was examined for an Xceptor including a CTLA4 ectodomain and an IL10 domain (SEQ ID NO:9), substantially as follows.

Surface plasmon resonance (SPR) measurements were performed on a BIAcore™ T100 SPR (Pharmacia Biotech AB, Uppsala) using HBS-P+ (GE Healthcare) as a running buffer. IL-10R1 (25 μg/mL in 10 mM sodium acetate, pH 4.0; R&D Systems) was directly immobilized onto a CM5 chip using standard amine coupling chemistry (Biacore Amine Coupling Kit, GE Healthcare), with final immobilization levels of 867, 2687, and 6719 Ru (resonance units). IL-10-containing constructs were injected for 300 seconds, at a flow rate of 50 μl/min, in a series of concentrations from 100 pM to 10 nM. Dissociation was monitored for 1200 seconds, and the surface was regenerated by injecting 2 M magnesium chloride, pH 7.58, for 60 seconds, followed by injecting 20 mM EDTA (in HBS-P+) for 60 seconds. Binding interactions with the surface were stable through at least 30 regeneration cycles. Data were analyzed using BiaEvaluation for the T100, version 2.0 (GE Healthcare). Binding kinetics of the CTLA4/IL10 Xceptor to immobilized IL-10R1 could not be fit to a 1:1 Langmuir binding model, but could be fit with high accuracy to a bivalent analyte binding model. Equilibrium dissociation constants (K_D) could be calculated with high accuracy for each construct by fitting the observed response at saturation to a steady-state equilibrium model, and are provided below in Table 3. Inclusion of the CTLA4 ectodomain in the Xceptor fusion protein had no apparent effect on the IL10/IL10R1 interaction.

Table 3

Immobilized Protein	Analyte	First Site k_a ($M^{-1}s^{-1}$)	First Site k_d (s^{-1})	Second Site k_a (s^{-1})	Second Site k_d (s^{-1})	K_D (nM)
IL10-R1	IL10*	5.7×10^5	2.6×10^{-4}	-	-	0.46
IL10-R1	SEQ ID NO:9	7×10^5	2.9×10^{-4}	18×10^{-3}	8.6×10^{-3}	0.41**

* Literature value (Yoon et al. (2006) J. Biol. Chem 281:35088-35096)

** Calculated from k_a1 and k_d1

EXAMPLE 3

XCEPTOR BINDING TO CD80 AND BOTH CD80 AND IL10 BY ELISA

CD80 and IL10R binding activity was examined by ELISA for abatacept, a CTLA4-Ig construct referred to as CTLA4-N2 (SEQ ID NO: 10 and 11), and the CTLA4/IL10 Xceptor of SEQ ID NO: 9, substantially as follows.

CD80 Binding

Each well of a 96-well black Maxisorp CD80 plate (Nunc Catalog #437111) plate was coated with CD80-mIg (Ancell Catalog #510-020) at 2 µg/ml solution and incubated overnight at 4°C. The plate was then blocked with Blocking Buffer (PBS-T with 3% non-fat dry milk). Samples of the proteins to be tested serially diluted Blocking Buffer were added in duplicate wells to the CD80-mIg coated plate, the plate was covered, and incubated at room temperature for about 1 hour. After washing, 100 µl per well horse radish peroxidase goat anti-human IgG (gamma) diluted 1:1,000 in Blocking Buffer was added, the plate was covered, and incubated at room temperature for 60 minutes, followed by a 10 minute incubation at room temperature in QuantaBlu™ Fluorogenic Peroxidase Substrate (Thermo Scientific Catolog #15169). The absorbance of each well was read at 420 nm. The unrelated fusion protein TRU-015 was employed as a negative control.

The results of these experiments are shown in Figure 1. CTLA4-N2 was found to bind as well as abatacept to CD80-mIg in this ELISA format, while the CTLA4/IL10 Xceptor appeared to show weaker CD80 binding.

Xceptor Binding to both sIL10R1 and sCD80

Each well of a 96-well black Maxisorp CD80 plate (Nunc Catalog #437111) plate was coated with sIL10Ra (R&D Systems Catalog #510-020) at 2 µg/ml solution and incubated overnight at 4°C. The plate was then blocked with Blocking Buffer (PBS-T with 3% non-fat dry milk). Samples of the proteins to be tested serially diluted Blocking Buffer were added in duplicate wells to the sIL10Ra coated plate, the plate was covered, and incubated at room temperature for about 1 hour. After washing, anti-CD152 antibody (Ancell #359-020) at 10ng/ul or CD80-mIg (Ancell # 510-020) at 5 ug/ml was added followed by horse radish peroxidase goat anti-mouse IgG (Fc) (Pierce #31439) diluted 1:10,000 in Blocking Buffer was added, the plate was covered, and incubated at room temperature for 60 minutes, followed by a 10 minute incubation at room temperature in QuantaBlu™ Fluorogenic Peroxidase Substrate (Thermo Scientific Catolog #15169). The absorbance of each well was read at 420 nm. The unrelated fusion protein TRU-015 was employed as a negative control.

Figure 2 shows the results obtained for CTLA4-N2 and the CTLA4::IL10 xceptor of SEQ ID NO: 9. These results demonstrate that both the CTLA4 and IL10 domains of the CTLA4-Ig-IL10 Xceptor are able to bind to their ligand/receptor simultaneously.

EXAMPLE 4

XCEPTOR INDUCED STAT3 PHOSPHORYLATION

Binding of IL10 to IL10-R1 is known to activate Jak-1 and Tyk which in turn lead to activation of STAT3 (see, for example, Williams et al. (2007) J. Biol. Chem. 282:6965-6975). In addition, studies have demonstrated that flow cytometry may be employed to study the phosphorylation of STAT3 in PBMC (Lafarge et al. (2007) BMC Mol. Biol. 8:64). The ability of various IL10-containing constructs, including the CTLA4/IL10 Xceptor of SEQ ID NO: 9, to induce phosphorylation of STAT3 in human PBMC was examined substantially as follows.

PBMCs were isolated from a human donor and cultured overnight in complete media (RPMI, 10% FBS, pen/strep) at $2x10^6$ cells/ml. The following morning, the PBMCs were washed once, resuspended with pre-warmed RPMI 1640 (no supplements) at $4x10^6$ cells/ml and incubated at 37°C for 2.5hrs. Treatments were prepared at a 2X concentration in 0.25mL of RPMI 1640 and

mixed with $1x10^6$ PBMCs in 0.25mL of RPMI 1640. The samples were then incubated for 15min at 37°C. Upon completion of the 15min incubation, 0.5mL of ice cold BD Cytofix Buffer (BD Biosciences, cat #554655) was added to each tube. Cells were incubated on ice for 30min and then washed with 2mls of DPBS+2.5% FBS (FACS Buffer). After decanting and vortexing the samples, 0.5mL of ice cold BD PERM BUFFER III (BD Biosciences, cat # 558050) was added to each tube and the samples were then incubated on ice for 30min. Samples were washed 3X with 2mL of FACS Buffer, and resuspended in ~0.2mL of FACS buffer after the final wash. 20uL of FITC conjugated anti-Human STAT3 mAb (BD Biosciences, clone PY705) was added to each sample. Cells were incubated in the dark at room temperature for 30min. Samples were then washed 3X with FACS Buffer to remove any unbound antibody. Samples were analyzed on a LSRII flow cytometer. A gate was applied to live lymphocytes based on SSC and FSC profiles and MFI for FITC was determined.

As shown in Figure 3 and Figure 4, all IL-10 containing constructs increased STAT3 phosphorylation in a dose dependent fashion.

EXAMPLE 5

XCEPTOR BINDING TO CD86 AND BOTH CD86 AND IL10

A human B-lymphoblastoid cell line that expresses CD86 (WIL2-S) was used to examine CD86 binding, and a CHO cell line expressing CD86 (HuCD86-2A2 cells) on the surface was used in combination with soluble IL10 Receptor1 (IL10R1) fusion protein linked to a murine IgG Fc or an anti-IL10 antibody to examine the simultaneous binding of the CD86 antagonist and IL10 agonist found on xceptor molecules. Briefly, WIL2-S or HuCD86-2A2 cells were incubated with test molecules containing a CD86 antagonist at concentrations ranging from saturation to background levels. To the HuCD86-2A2 cells, an IL10R1-mulg fusion protein or a murine anti-IL10 antibody was further added to form a complex with the test molecules that had bound to the cell surface via CD86. After the incubation, cells were washed and a fluorophore (R-phycoerythrin) tagged $F(Ab')_2$ antibody specific for the Fc portion of the xceptor molecule, IL10R-Ig fusion protein, or anti-IL10 antibody. The tagged cells were then passed through a flow cytometer and data was analyzed by plotting median fluorescence intensity of each sample.

As shown in Figure 5, binding to CD86 on WIL2-S cells by xceptor molecules containing an anti-CD86 binding domain (*e.g.*, from hybridoma antibodies 3D1 and FUN1) showed higher affinity than binding of CTLA4 ectodomain containing xceptor molecules. More specifically, anti-CD86 3D1 containing xceptor 3D1::IL10 (SEQ ID NO:189) had slightly higher affinity to CD86 than anti-CD86 FUN1 containing xceptor FUN1::IL10 (SEQ ID NO:187), whereas CTLA4-Ig (SEQ ID NO:11) and a CTLA4 containing xceptor (SEQ ID NO:173) had much lower affinity for CD86 than the anti-CD86 binding domains from hybridoma antibodies 3D1 and FUN1.

As shown in Figure 6, xceptor molecules containing a CD86 antagonist and IL10 agonist could simultaneously bind CD86 on HuCD86-2A2 cells (CHO cells expressing CD86 on cell surface developed in house) and soluble IL10R1. Furthermore, Figure 6 shows that the IL10 variants had different binding affinities for IL10R1. For example, the xceptor molecules CTLA4::monoIL10 (SEQ ID NO:181) and (CTLA4::IL10)-75 (SEQ ID NO:173) had similar affinities for IL10R1, but the xceptors containing the viral mutated IL10 form, CTLA4::IL10I87A (SEQ ID NO:191) and CTLA4::IL10I87S (SEQ ID NO:193), showed much lower affinity for IL10R1.

In another experiment, different versions of humanized FUN1 SMIPs were tested for CD86 binding. Supernatants of HEK293 cells transiently transfected with the six different versions of humanized FUN1 SMIPs were examined for CD86 binding using HuCD86-2A2 cells. Figure 7 shows that that FUN1-21 (SEQ ID NO:227) had the best binding affinity to CD86 followed by FUN1-22 (SEQ ID NO:233) and then FUN1-11 (SEQ ID NO:225); the remaining humanized FUN1 SMIP proteins (FUN1-12, SEQ ID NO:229; FUN1-31, SEQ ID NO:231; FUN1-32, SEQ ID NO:235) did not show detectable binding.

EXAMPLE 6

VARYING BINDING DOMAIN LINKER LENGTHS IN XCEPTOR PROTEINS

Linker stability for CTLA4::IL10 molecules was examined. All linker variants were stably transfected in CHOK1SV cells and stable bulk populations were cultured at 37°C and shifted to 34°C on day 3. Proteins were purified by Protein A column and followed by second step SEC column. ELISA assays were performed to measure the IL10 binding to IL10R1-mIg fusion protein. The results in Figure 8 showed that xceptor (CTLA4::IL10)-65 (SEQ ID NO:9) had reduced IL10 binding due to instability of the linker, but

(CTLA4::IL10)-68 (SEQ ID NO:171), (CTLA4::IL10)-69 (SEQ ID NO:302), and (CTLA4::IL10)-75 (SEQ ID NO:173) were stable in these culture conditions.

Shorter linker variants were also tested in CTLA4::IL10 xceptor proteins for binding to IL10R1 by ELISA. The shorter linker variants were transiently transfected and proteins were Protein A column purified. ELISA assays were performed to measure the IL10 binding to IL10R1-mIg fusion protein. The results in Figure 9 showed that the shorter linker variants (CTLA4::IL10)-77 (SEQ ID NO:175), Q0033 (CTLA4::IL10)-78 (SEQ ID NO:177), and (CTLA4::IL10)-79 (SEQ ID NO:179) worked as well as the longer linkers for back end IL10 binding affinity (*e.g.*, compared to (CTLA4::IL10)-68; SEQ ID NO:171).

EXAMPLE 7

SERUM STABILITY AND PHARMACOKINETICS OF XCEPTOR PROTEINS

The serum stability of (CTLA4::IL10)-75 (SEQ ID NO:173) was tested. In this experiment, purified protein of SEQ ID NO:173 was treated in mouse serum at 37°C for 24 hours, 72 hours and F/T (freeze/thaw) and spike in at the time of assay (T0). All stability samples were tested for their binding to CD80 (using CD80 expressing 1F6 CHO cells) as well as for simultaneous binding to CD80 and anti-IL10 antibody binding to IL10 on the xceptor. The results showed that SEQ ID NO:173 was very stable and retained anti-IL10 binding after incubation in mouse serum at the tested concentrations (from about 0.01nM to about 10nM).

Pharmacokinetic (PK) studies for (CTLA4::IL10)-68 (SEQ ID NO:171) and (CTLA4::IL10)-75 (SEQ ID NO:173) were conducted in female Balb/c mice, using 3 mice per time point. Mice were injected intravenously with 200 µg/mouse. Mouse serum was collected at 15 minutes, 2 hours, 6 hours, 24 hours, 48 hours, 96 hours, 7 days and 14 days after treatment. Samples were tested for CD80 binding (CTLA4 assay) and simultaneous binding to CD80 and anti-IL10 antibody (IL10 assay). The results are summarized in Table 4 below.

Table 4. PK Study Summary

PK Estimates for Abatacept, (CTLA4::IL10)-68 and (CTLA4::IL10)-75		Abatacept Estimates	(CTLA4::IL10)-68 PK Parameter Estimates		(CTLA4::IL10)-75 PK Parameter Estimates	
Parameter	Units	CTLA4 Assay	CTLA4 Assay	IL-10 Assay	CTLA4 Assay	IL-10 Assay
HL_Lambda_z	hr	45.49	32.62	29.36	34.59	31.48
Vz_obs	mL/kg	117.30	84.571	158.57	206.48	285.30
Cl_obs	mL/hr/kg	1.79	1.797	3.74	4.14	6.28

EXAMPLE 8

XCEPTOR BINDING TO CD80, CD86 AND IL10R1

CD80 and IL10R1 binding was examined by ELISA, and/or CD86 and IL10R1 binding was examined using CD86-expressing CHO cells and either IL10R1-Ig or anti-IL10. Binding to mouse CD80 and CD86 was examined by ELISA using biotin-labeled mouse antibodies. The molecules examined included the control CTLA4-Ig (SEQ ID NO:11) fusion protein, and the following test xceptor molecules: (CTLA4::IL10)-65 (SEQ ID NO:9); (CTLA4::IL10)-68 (SEQ ID NO:171); (CTLA4::IL10)-69 (SEQ ID NO:302), (CTLA4::PDL2)-65 (SEQ ID NO:336), substantially as described in Examples 3 and 5.

As shown in Figures 10 and 11, the (CTLA4::IL10)-65, (CTLA4::IL10)-68, and (CTLA4::IL10)-69 xceptor molecules all bound CD80 by ELISA and CD86 on cells. The results in Figure 12 show that CTLA4::IL10 xceptor molecules can interact with huIL10R1. Further, as shown in Figure 13, CTLA4::IL10 xceptors can engage both BD1 (amino-terminal binding domain) and BD2 (carboxy-terminal binding domain) simultaneously to CD80 and IL10R1 by ELISA. Additionally, Figures 14 and 15 show that the (CTLA4::IL10)-65, (CTLA4::IL10)-68, and (CTLA4::IL10)-69 xceptor molecules, specific for human molecules, are capable of crossreacting with both mouse CD80 and mouse CD86.

EXAMPLE 9

XCEPTOR BINDING TO CD80 BY BIACORE™

CD80 binding activity was examined for abatacept (Orencia®, Bristol-Myers Squibb), a CTLA4-Fc fusion containing the L104E A29Y mutations, analogous to belatacept (SEQ ID NO:217), three CTLA4::IL10 xceptor linker variants each having a CTLA4 ectodomain and an IL10 domain: (CTLA4::IL10)-65 (SEQ ID NO:9), (CTLA4::IL10)-68 (SEQ ID NO:171), and (CTLA4::IL10)-75 (SEQ ID NO:173); an xceptor including a CTLA4 ectodomain with the L104E A29Y mutations and an IL10 domain (SEQ ID NO:219), and an xceptor containing a CTLA4 ectodomain and a PD-L1 domain (SEQ ID NO:13), substantially as described herein. Examination of binding of CTLA4-Fc to CD80/86 by BIAcore has been described previously (Greene et al. (1996) J. Biol. Chem. 271:26762-26771; van der Merwe et al. (1997) J. Exp. Med. 185:393-403; Collins et al. (2002) Immunity 17:201-210). Binding of CD80 by CTLA4 is of moderate affinity (K_d = ~200 nM), and is characterized by a fast on rate (4-8×10^5 $M^{-1}s^{-1}$) and a moderate off rate (0.090 s^{-1}). Binding of dimeric CTLA4-Fc to CD80 is biphasic, and has been reported with two off-rates (0.004, 0.086 s^{-1}). The L104E A29Y mutations on CTLA4-Fc have been reported to increase the affinity for CD80 two-fold over the wild type CTLA4-Fc (Larsen et al (2005) Am. J. Transplant. 5:443-453), primarily by decreasing the initial off-rate (reported as 0.00108 vs 0.00221 s^{-1}).

Surface plasmon resonance (SPR) measurements were performed on a BIAcore™ T100 SPR (Pharmacia Biotech AB, Uppsala) using HBS-EP+ (GE Healthcare) as a running buffer. CD80-mIgG (25 µg/mL in 10 mM sodium acetate, pH 4.0; Ancell, Inc) was directly immobilized onto a CM5 chip using standard amine coupling chemistry (Biacore Amine Coupling Kit, GE Healthcare), with final immobilization levels of 317, 973, and 1678 Ru (resonance units). CTLA4-containing constructs were injected for 150 seconds, at a flow rate of 10 µl/min, in a series of concentrations from 5 nM to 1 µM. Dissociation was monitored for 600 seconds, and the surface was regenerated by injecting 50 mM sodium citrate, 500 mM sodium chloride, pH 4.0, for 60 seconds. Binding interactions with the surface were stable through at least 75 regeneration cycles. Data were analyzed using BiaEvaluation for the T100 software (version 2.0.1, GE Healthcare).

Binding kinetics of the CTLA4 constructs to immobilized CD80 could not be fit to a 1:1 Langmuir binding model, but could be fit with high

accuracy to a bivalent analyte binding model. Increasing the association phase by increasing the length of injection did not alter the calculated kinetic parameters. Equilibrium dissociation constants (K_D) could be calculated with high accuracy for each construct by fitting the observed response at saturation to a steady-state equilibrium model. The results for all CD80 binding molecules are summarized in Table 5 below.

Table 5

Immobilized Protein	Analyte	First Site k_a ($M^{-1}s^{-1}$)	First Site k_d (s^{-1})	Second Site k_a (s^{-1})	Second Site k_d (s^{-1})	K_D (nM)
CD80	abatacept	$5.5 \pm 0.02 \times 10^5$	0.006	0.00019	$9.4 \pm 0.08 \times 10^{-4}$	130 ± 10
CD80	SEQ ID NO:9	$1.9 \pm 0.01 \times 10^5$	0.008	0.0045 ± 0.0001	0.015 ± 0.0003	233 ± 27
CD80	SEQ ID NO:13	$0.36 \pm 0.002 \times 10^5$	$7.4 \pm 0.047 \times 10^{-4}$	0.0057	0.064	176 ± 29
CD80	SEQ ID NO:171	$9.77 \pm 5.83 \times 10^5$	0.0145	0.0190	0.0434	37.5 ± 9.5
CD80	SEQ ID NO:173	$12.1 \pm 6.81 \times 10^5$	0.0124	0.0207	0.0431	28.0 ± 6.5
CD80	SEQ ID NO:217	$1.55 \pm 0.203 \times 10^5$	0.00373	0.00102	0.00332	13.3 ± 6.2
CD80	SEQ ID NO:219	$0.908 \pm 0.307 \times 10^5$	0.00235	0.00406	0.00706	19.1 ± 5.3

Equilibrium affinities for the Xceptors were determined to resemble that for abatacept and the reported affinity for CTLA4-Fc (200 nM; Greene et al. 1996, Ibid). Binding kinetics for the CTLA4::PDL1 xceptor were different from those for abatacept or the CTLA4::IL10 xceptor, although the on/off rate compensation gives a similar affinity. This may be due to the fact that PD-L1 binds CD80 with a weaker affinity than CTLA4 (K_D of 2.5 μM). Similar to previous studies, CTLA4 variants containing the L104E A29Y mutation (SEQ ID NOS:217 and 219) had a higher affinity for CD80, with a roughly two fold improvement in initial off rate (0.00373 s^{-1} for SEQ ID NO:217 as compared to 0.006 s^{-1} for abatacept).

EXAMPLE 10

XCEPTOR BINDING TO CD86 BY BIACORE™

CD86 binding activity was examined for abatacept, a CTLA4-Fc fusion containing the L104E A29Y mutations, analogous to belatacept (SEQ ID NO:217), an xceptor containing a CTLA4 ectodomain and an IL10 domain (SEQ ID NO: 9), an xceptor containing a CTLA4 ectodomain with the L104E A29Y mutations and an IL10 domain (SEQ ID NO:219), and different constructs (SMIP, PIMS, and xceptor) containing antibody variable domains from the 3D1 and FUN1 anti-CD86 antibodies, substantially as described herein. Binding of CD86 by CTLA4 is of low affinity (K_d = ~2.2 μM), and is characterized by a fast on rate (2-13×10^5 $M^{-1}s^{-1}$) and a moderate off rate (0.42 s^{-1}). The L104E A29Y mutations on CTLA4-Fc have been reported to increase the affinity for CD86 four-fold over the wild type CTLA4-Fc (Larsen et al (2005) Am. J. Transplant. 5:443-453), primarily by decreasing the initial off-rate (reported as 0.00206 vs 0.00816 s^{-1}). Apparently, no kinetic or equilibrium affinity data has been previously published for the 3D1 or FUN1 antibodies, so their relative affinities were determined.

Lower-affinity CD86 binding domains based on the CTLA4 ectodomain. SPR measurements were performed on a BIAcore™ T100 SPR (Pharmacia Biotech AB, Uppsala) using HBS-EP+ (GE Healthcare) as a running buffer. CD86-mIgG (25 μg/mL in 10 mM sodium acetate, pH 4.0, Ancell, Inc) was directly immobilized onto a CM5 chip using standard amine coupling chemistry (Biacore Amine Coupling Kit, GE Healthcare), with final immobilization levels of 37, 373, and 903 Ru. CTLA4-containing constructs were injected for 150 seconds, at a flow rate of 10 μl/min, in a series of

concentrations from 4 nM to 10 μM. Dissociation was monitored for 600 seconds, and the surface was either regenerated by injecting 50 mM sodium citrate, 500 mM sodium chloride, pH 5.0, for 60 seconds (wild type CTLA4) or 10 mM glycine, pH 1.7 (L104E A29Y CTLA4). Binding interactions with the surface, and immobilization levels, were stable through at least 100 regeneration cycles. Data were analyzed using BiaEvaluation for the T100 software (version 2.0.1, GE Healthcare). Owing to the low affinity of CTLA4 to CD86, and the very fast on and off rates (literature values are $0.2\text{-}1.3\times10^{6}$ $M^{-1}s^{-1}$ for k_a and 0.42 s^{-1} for k_d, at the limit of detection for the BIAcore™ T100 instrument) binding kinetics of abatacept to immobilized CD86 could not be determined. Binding kinetics of the constructs with the L104E A29Y CTLA4 domain (SEQ ID NO:217; SEQ ID NO:219) to immobilized CD86 could be determined with reasonable accuracy by fitting the observed response to the bivalent analyte model, however. Equilibrium dissociation constants (K_D) could be calculated with high accuracy for all constructs by fitting the observed response at saturation to a steady-state equilibrium model. The results are shown in Table 6, below.

Higher-affinity CD86 binding domains based on the 3D1 and FUN1 antibody variable domains. SPR measurements were performed as listed above, with the following exceptions: HBS-P+ (GE Healthcare) was used as a running buffer; dissociation was monitored for 1200 seconds; and the surface was regenerated by injecting 10 mM glycine, pH 1.7, for 60 seconds. Binding kinetics to immobilized CD86 could be determined in all cases. However, equilibrium dissociation constants (K_D) could be calculated with high accuracy for each construct by fitting the observed response at saturation to a steady-state equilibrium model. The results are shown in Table 6 below.

Table 6

Immobilized Protein	Analyte	First Site k_a ($M^{-1}s^{-1}$)	First Site k_d (s^{-1})	Second Site k_a (s^{-1})	Second Site k_d (s^{-1})	K_D (nM)
CD86	abatacept	--	--	--	--	3200 ± 1600
CD86	SEQ ID NO:217	0.847×10^5	0.01016	0.0298	0.0344	772 ± 300
CD86	SEQ ID NO:219	0.451×10^5	0.00910 ± 0.0001	0.011	0.0221	670 ± 180
CD86	3D1 SMIP	3.23×10^5	$4.40 \pm 0.05 \times 10^{-5}$	0.0055	0.0276	11.7 ± 1.2
CD86	SEQ ID NO:189	$9.74 \pm 0.066 \times 10^5$	$7.06 \pm 0.04 \times 10^{-5}$	0.0094	0.0462	26.5 ± 2.9
CD86	SEQ ID NO:328	1.12×10^5	$2.37 \pm 0.13 \times 10^{-5}$	0.00077	0.00377	28.0 ± 1.9
CD86	SEQ ID NO:185	$6.17 \pm 0.12 \times 10^5$	$8.30 \pm 0.12 \times 10^{-5}$	0.0124	0.102	35.7 ± 2.5
CD86	FUN1 mAb	$1.29 \pm 0.69 \times 10^5$	$2.28 \pm 0 \times 10^{-5}$	0.00278	0.0154	36.0 ± 5.5
CD86	SEQ ID NO:225	$0.139 \pm 0.556 \times 10^5$	35.0×10^{-5}	7.5×10^{-5}	$1.25 \pm 0.25 \times 10^{-6}$	119 ± 40
CD86	SEQ ID NO:227	$1.86 \pm 0.951 \times 10^5$	13.9×10^{-5}	0.00578	0.0127	26.9 ± 5.4
CD86	SEQ ID NO:402	0.5×10^5	9.1×10^{-5}	0.00113	0.00837	70.9 ± 5.9
CD86	mulL10-Ig	0.941×10^5	18×10^{-5}	0.0203	0.0722	50.6 ± 7
CD86	SEQ ID NO:254	1.58×10^5	12.8×10^{-5}	0.0064	0.0387	98.6 ± 10
CD86	SEQ ID NO:258	0.407×10^5	$43.3 \pm 1.2 \times 10^{-5}$	0.0198	0.0579	88.5 ± 19
CD86	SEQ ID NO:276	0.126×10^5	34.4×10^{-5}	0.011	0.0111	178 ± 18

Equilibrium affinities for abatacept (3.2 μM) resembled the reported affinity for CTLA4-Fc (2.2 μM; Greene et al. 1996, Ibid). Similar to previous studies, CTLA4 variants containing the L104E A29Y mutation (SEQ ID NO:217; SEQ ID NO:219) had a four-to-five fold higher affinity for CD86 (670 – 772 nM). Constructs containing 3D1 murine single-chain antibody fragments (scFvs) on the N-terminus (3D1 SMIP, SEQ ID NO: 317; 3D1::IL10, SEQ ID NO:189) had higher affinities (11.7, 26.5 nM) than the corresponding constructs with the 3D1 scFv on the C-terminus (3D1 PIMS, SEQ ID NO: 319; IL10::3D1, SEQ ID NO:185); examining the binding kinetics, this appeared to arise from both a higher initial on-rate and a lower initial-off rate, although in all cases, the affinity was at least 100-fold higher for CD86 than abatacept. For the FUN1 antibody, the parent murine monoclonal antibody was examined along with SMIP proteins containing two humanized single-chain FUN1 antibody fragments (SEQ ID NOS:225 and 227); the latter of the two (SEQ ID NO:227) showed similar binding kinetics and overall affinity to CD86 as the parent FUN1 mAb (26.9, 36 nM, respectively), which, again, was significantly higher than that of abatacept. Xceptor or PIMS molecules containing humanized FUN1 antibody fragments at the carboxy-terminus (IL10::FUN1-21, SEQ ID NO: 254; (IL10 I87A:: FUN1-21)-75, SEQ ID NO:258; (monoIL10-A2 hinge:: FUN1-21)-75, (SEQ ID NO:276); FUN1-21 PIMS, SEQ ID NO:402) had lower affinities than the xceptor containing the parent antibody sequence at the amino-terminus (FUN1::IL10, SEQ ID NO:187)) or the same FUN1-21 binding sequence on a SMIP protein (SEQ ID NO:227).

EXAMPLE 11

XCEPTOR BINDING TO MURINE CD86 BY BIACORE™

Murine CD86 binding activity was examined for abatacept, a CTLA4-Fc fusion containing the L104E A29Y mutations, analogous to belatacept (SEQ ID NO:217), two xceptors containing different BD2 linkers but the same CTLA4 and IL10 domains (SEQ ID NOS:171 and 173), an xceptor containing a CTLA4 ectodomain with the L104E A29Y mutations and an IL10 domain (SEQ ID NO:219), a murine CTLA4 fusion to human Fc domain (SEQ ID NO:404), and different constructs containing antibody variable domains from the rat GL1 anti-murine CD86 antibody, including two xceptors containing a GL1 antibody fragment and human IL10 domain (GL1::IL10, SEQ ID NO:252; and IL10::GL1, SEQ ID NO:256), substantially as described below. Human

CTLA4 is known to be cross-reactive to murine CD86, but, to the best of our knowledge, no kinetic or affinity measurements have been previously described. Similarly, the rat GL1 antibody has been described as being specific for murine CD86, but no kinetic or affinity measurements have been reported.

SPR measurements were performed on a BIAcore™ T100 SPR (Pharmacia Biotech AB, Uppsala) using HBS-EP+ (GE Healthcare) as a running buffer. Murine CD86-mIgG (25 µg/mL in 10 mM sodium acetate, pH 4.0, R&D Systems, Inc) was directly immobilized onto a CM5 chip using standard amine coupling chemistry (Biacore Amine Coupling Kit, GE Healthcare), with final immobilization levels of 150, 493, and 746 Ru. CTLA4-containing constructs were injected for 150 seconds, at a flow rate of 10 µl/min, in a series of concentrations from 4 nM to 8 µM. Dissociation was monitored for 600 seconds (CTLA4 constructs) or 1200 seconds (GL1 constructs), and the surface was regenerated by injecting 10 mM glycine, pH 1.7, for 60 seconds. Binding interactions with the surface, and immobilization levels, were stable through at least 100 regeneration cycles. Data were analyzed using BiaEvaluation for the T100 software (version 2.0.1, GE Healthcare). Binding kinetics to immobilized murine CD86 could be determined for all constructs, and fit with high accuracy to a bivalent analyte model (Table 7). Equilibrium dissociation constants (K_D) could also be calculated with high accuracy for each construct by fitting the observed response at saturation to a steady-state equilibrium model. For the CTLA4 variants (SEQ ID NOS:171, 173, 217, 219, and 404), simultaneous equilibrium fits across all three flow cells at three different immobilization densities gave more accurate results than fitting any one flow cell (a so-called 'multiple Rmax' fit), and so those affinities are listed. The results are shown in Table 7, below.

Table 7

Immobilized Protein	Analyte	First Site k_a ($M^{-1}s^{-1}$)	First Site k_d (s^{-1})	Second Site k_a (s^{-1})	Second Site k_d (s^{-1})	K_D (nM)
muCD86	SEQ ID NO:171	0.104×10^5	0.0241	0.0398	0.0627	1540 ± 210
muCD86	SEQ ID NO:173	0.132×10^5	0.0228	0.0405	0.0625	1810 ± 230
muCD86	SEQ ID NO:217	0.278×10^5	0.0787	0.0728 ± 0.0023	0.168	920 ± 88
muCD86	SEQ ID NO:219	0.321×10^5	0.0418	0.00026	0.00193	870 ± 160
muCD86	muCTLA4-Ig	0.278×10^5	0.0386	0.000659	0.00311	2250 ± 190
muCD86	GL1 mAb	$0.789 \pm 0.346 \times 10^5$	10.6×10^{-5}	0.00879	0.00635	37.7 ± 4.4
muCD86	GL1 SMIP	$1.18 \pm 0.427 \times 10^5$	6.2×10^{-5}	0.00964 ± 0.00031	0.0185	26.2 ± 5.4
muCD86	GL1 PIMS	1.77×10^5	1.25×10^{-4}	0.0431	0.0977	78.3 ± 20
muCD86	SEQ ID NO:252	2.19×10^5	1.9×10^{-4}	0.00943	0.0182	86.4 ± 8.3
muCD86	SEQ ID NO:256	6.73×10^4	4.4×10^{-5}	0.0271	0.088	95.1 ± 13

Xceptors containing human CTLA4 and human IL10 domains (SEQ ID NOS:171 and 173) had slightly higher affinities to murine CD86 (1.54, 1.81 μM) than the reported affinity for human CTLA4-Fc for human CD86 (2.2 μM; Greene et al. 1996). Human CTLA4 variants containing the L104E A29Y mutation (SEQ ID NOS:217 and 219) had only a two fold higher affinity for murine CD86 (870 – 920 nM); this seems to arise from a combination of a beneficial higher initial on-rate for murine CD86 and a detrimental higher initial off-rate. Murine CTLA4 seems to have an analogous, or slightly lower overall affinity for murine CD86 than human CTLA4. For the GL1 antibody, the parent rat monoclonal antibody was examined along with a SMIP containing a single-chain GL1 antibody fragment (GL1 SMIP, SEQ ID NO:239); both showed similar binding kinetics and overall affinity to murine CD86 (37.7, 26.2 nM, respectively), which, was significantly higher (~50 fold) than that of human or murine CTLA4-containing constructs. Xceptors containing IL-10 and the GL1 antibody fragment (SEQ ID NOS:252 and 256) showed a 3-fold lower affinity to murine CD86 compared to the parent antibody or SMIP, although this appeared to arise from either a reduced initial on-rate or off-rate in each case.

EXAMPLE 12

XCEPTOR BINDING TO PD1 BY BIACORE™

PD1 binding activity was examined for PDL1-Fc (SEQ ID NO:268) and PDL2-Fc (SEQ ID NO:270), as well as xceptors containing a CTLA4 ectodomain and either PDL1 (SEQ ID NO:13) or PDL2 (SEQ ID NO:336) domains, substantially as follows. Binding of PD1 by PDL2 has been generally reported to be higher affinity than the binding of PD1 by PDL1; a prior kinetic analysis (Youngnak et al, (2003) Biochem. Biophys. Res. Comm. 307, 672) suggested moderate affinities (112 nM for PDL1, 37 nM for PDL2), whereas a equilibrium analysis done in an alternate format (Butte et al, (2007) Immunity 27, 111) suggested weaker affinities (770 nM for PDL1, 590 nM for PDL2).

SPR measurements were performed on a BIAcore™ T100 SPR (Pharmacia Biotech AB, Uppsala) using HBS-P+ (GE Healthcare) as a running buffer. A construct with the PD1 ectodomain fused to a C-terminal AviTag™ (SEQ ID NO:406) was initially biotinylated using the *BirA* enzyme (Avidity, Inc., Aurora, CO) in 10 mM Tris, pH 8.0, and buffer exchanged into PBS. Neutravidin (100 μg/mL in 10 mM sodium acetate, pH 4.0, Thermo Scientific, Rockford, IL) was directly immobilized onto a CM5 chip using standard amine coupling

chemistry (Biacore Amine Coupling Kit, GE Healthcare), with final immobilization levels of 191, 771, and 1522 Ru, and used to capture biotinylated PD1 at levels of 171, 597, and 1244 Ru, respectively. PDL1/2-containing constructs were injected for 120 seconds, at a flow rate of 30 µl/min, in a series of concentrations from 6 nM to 2 µM. Dissociation was monitored for 1200 seconds, and the surface was regenerated by injecting 50 mM NaOH, 1M NaCl for 30 seconds. Binding interactions with the surface, and immobilization levels, were stable through at least 50 regeneration cycles.

Data were analyzed using BiaEvaluation for the T100 software (version 2.0.1, GE Healthcare). Binding kinetics to immobilized PD1 could be determined for all constructs, and fit either with high accuracy to a bivalent analyte model (SEQ ID NOS:268 and 270) or a 1:1 binding model (SEQ ID NOS:13 and 336) (Table 8). Equilibrium dissociation constants (K_D) could also be calculated with high accuracy for each construct by fitting the observed response at saturation to a steady-state equilibrium model. The results are shown in Table 8, below.

Table 8

Immobilized Protein	Analyte	First Site k_a ($M^{-1}s^{-1}$)	First Site k_d (s^{-1})	Second Site k_a (s^{-1})	Second Site k_d (s^{-1})	K_D (nM)
PD1	SEQ ID NO:13	0.699×10^5	0.165	n/a	n/a	2360**
PD1	SEQ ID NO:336	1.16×10^5	0.0395	n/a	n/a	340**
PD1	SEQ ID NO:268	$0.96 \pm 0.54 \times 10^5$	0.0544	3.18×10^{-6}	0.000191	246 ± 27
PD1	PDL1-Fc*	1.07×10^5	0.010	n/a	n/a	112**
PD1	SEQ ID NO:270	1.65×10^5	0.00724	0.0352	0.395	42 ± 4.4
PD1	PDL2-Fc*	1.22×10^5	0.0032	n/a	n/a	26**

* Literature value (Youngnak et al, (2003) Biochem. Biophys. Res. Comm. 307, 672)

** Kinetic K_D calculated from first site k_a and k_d

PDL1-Fc (SEQ ID NO:268) and PDL2-Fc (SEQ ID NO:270) showed similar binding kinetics and overall affinities to those reported in literature. Xceptors containing CTLA4 with PDL1 or PDL2 domains fused at the carboxy-terminus (SEQ ID NOS:13 and 336) had noticeably weaker (~10 fold) affinities to PD1 (2.36, 0.34 μM) than the amino-terminal PDL1/PDL2 fusions (246, 42 nM); this primarily arises from a noticeable increase in the initial off-rate (0.165, 0.0395 vs 0.0544, 0.00724), indicating the PDL1/2:PD1 complex may be destabilized when the binding domain is at the BD2 (carboxy-terminal) position.

EXAMPLE 13

XCEPTOR FUSION PROTEINS BLOCK HUMAN T CELL RESPONSES

This example demonstrates that xceptor fusion proteins of this disclosure can block a human T cell response. A mixed lymphocyte reaction (MLR) was used to test blocking by xceptor fusion proteins. In brief, human peripheral blood mononuclear cells (PBMC) from two donors were isolated using standard methods and kept separate. Based on previous studies, PBMC from one donor were designated as the "Responder" population and PBMC from the second donor were designated as the "Stimulator" population. Both donor PBMC were labeled with CFSE using standard methods. To prevent cell division, Stimulator PBMC were treated with mitomycin-C (MMC). MMC (Sigma #M4287-2mg) was reconstituted in sterile distilled water (Gibco #15230) at a concentration of 0.5mg/ml. Stimulator PBMC were suspended at a concentration of $1x10^6$/ml in complete culture media (CM), (RPMI-1640 containing 10% human B serum, 100 U/ml penicillin, 100ug/ml streptomycin, 2mM L-glutamine, NEAA, Na-pyruvate, CM 0.2um filtered) and MMC was added to a final concentration of 25 μg/ml. The Stimulator PBMC/MMC mixture was then incubated at 37°C, 5% CO_2, for 30 minutes after which cells were washed thrice with CM. Responder and Stimulator cells were suspended at a concentration of $4x10^6$/ml in CM and 0.05ml of each cell population was added per well of a 96 well-flat bottom tissue culture plate for a final $2x10^5$ cells/well/donor. All treatments at the designated concentrations shown in figures were added to the plate at the same time as the cells (note concentrations shown for antibodies and fusion proteins are at molar equivalents). MLR conditions (96 well plate PBMC treatment set-up) were then incubated at 37°c, 5% CO_2, for the duration of the experiment. MLR

experiments were harvested 7-8 days at which cells were stained with fluorescently tagged antibodies against CD5 (e-Bioscience) and CD25 (BD Biosciences) and run on a flow cytometer (LSR II, Becton Dickenson). Data was analyzed using FlowJo flow cytometry software (TreeStar). The gating strategy was as follows: cells that fell within a FSC:SSC lymphocyte gate were analyzed for CD5 expression, cells that then subsequently fell within the CD5+ gate were analyzed for CFSE dilution and CD25 up-regulation. Cells that were CD5+, $CFSE^{low}$ and $CD25^{high}$ were considered activated T cells.

Figures 16, 17, 21, and 22 show that many different kinds of xceptor fusion proteins containing a CD86 antagonist in combination with a heterologous binding domain are capable of blocking a T cell response to Responder/Stimulator MLR conditions.

EXAMPLE 14

CD86 ANTAGONIST XCEPTORS BLOCK A MOUSE T CELL RESPONSE

Mice splenocytes from two different mouse strains, C57BL/6 (or B6D2F1) and BALB/c, were isolated utilizing the scalpel/nylon mesh and RBC lyse method. Based on previous studies, splenocytes from mouse strain C57Bl/6 (or B6D2F1) were designated as the "Responder" population and splenocytes from mouse strain BALB/c were designated as the "Stimulator" population. Both mouse strain splenocytes were labeled with CFSE as previously described. To prevent cell division, Stimulator splenocytes were treated with mitomycin-C (MMC). MMC (Sigma #M4287-2mg) was reconstituted in sterile distilled water (Gibco #15230) at a concentration of 0.5 mg/ml. Stimulator splenocytes were suspended at a concentration of $5x10^7$/ml in complete culture media (CM), (RPMI-1640 containing 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin, 2mM L-glutamine, NEAA, Na-pyruvate, and 0.05 mM 2-mercaptoethanol) and MMC was added to a final concentration of 50 µg/ml. The Stimulator splenocyte/MMC mixture was then incubated at 37°C, 5% CO_2, for 20 minutes after which cells were washed thrice with CM. Responder and Stimulator cells were suspended at a concentration of $8x10^6$/ml in CM and 0.05ml of each cell population was added per well of a 96 well-flat bottom tissue culture plate for a final $4x10^5$cells/well/strain . All treatments at the designated concentrations shown in Figures 18-20 were added to the plate at the same time as the cells (note concentrations shown for antibodies and fusion proteins are at molar equivalents). MLR conditions (96

well plate with splenocyte/treatment set-up) were then incubated at 37°C, 5% CO_2, for the duration of the experiment. MLR experiments were harvested 4-5 days at which cells were stained with fluorescently tagged antibodies against CD5 (BD Biosciences) and CD25 (BD Biosciences) and run on a flow cytometer (LSR II, Becton Dickenson). Data was analyzed using FlowJo flow cytometry software (TreeStar). The gating strategy was as follows: cells that fell within a FSC:SSC lymphocyte gate were analyzed for CD5 expression, cells that then subsequently fell within the CD5+ gate were analyzed for CFSE dilution and CD25 up-regulation. Cells that were CD5+, $CFSE^{low}$ and $CD25^{high}$ were considered activated T cells.

Figures 18-20 show that many different kinds of xceptor fusion proteins containing a CD86 antagonist in combination with a heterologous binding domain are capable of blocking a mouse T cell response to Responder (B6D2F1)/Stimulator (BALB/c) MLR conditions.

EXAMPLE 15

IMMUNOSTIMULATORY ACTIVITY OF XCEPTOR MOLECULES CONTAINING IL10

The immunostimulatory activity of IL10 in various xceptor fusion proteins was tested in an *in vitro* cell proliferation assay. In particular, the MC/9 mouse mast liver cell line was used as follows: MC/9 cell line (American Type Culture Collection #CRL-8306) were grown in DMEM or RPMI plus 10% FBS and 5% Rat T-STIM (BD #354115). MC/9 cells were washed and rested in media without Rat T-STIM overnight (incubated at 37°C, 5% CO_2, in 96 well flat bottom plate at 1 x 10^5 cells/well, 100 µl/well). Various concentrations of IL10 protein and xceptor fusion proteins were incubated for 24 hours and proliferation was assessed by [^{3}H] thymidine incorporation after 6 hours.

The I87 variant of IL10 is known to be less immuno-stimulatory compared to wild-type IL10 (Ding *et al.*, *J. Exp. Med. 191*:213, 2000). IL10 normally forms a homodimer with the amino terminal domain of each monomer molecule binding to the carboxy terminal domain of the other monomer). The IL10 I87 variant (I87A and I87S), along with an IL10 molecule having a short linker (gggsgg; SEQ ID NO:379) that further separates the two subdomains of IL10 allowing these subdomains to form an intramolecular dimer, were examined in the xceptor format for immunostimulatory activity.

Figure 23 shows that mouse IL10 is capable of enhancing MC/9 cell proliferation to greater extent than CTLA4::IL10-I87A (SEQ ID NO:191)

xceptor, which contains a single mutation in amino acid 87 of IL10. Figure 24 shows that both human IL10 and (CTLA4::IL10)-75 (SEQ ID NO:173) are capable of enhancing MC/9 cell proliferation more than either CTLA4::IL10-I87A (SEQ ID NO:191) or CTLA4::monoIL-10 (SEQ ID NO:181).

EXAMPLE 16

ENGINEERING XCEPTOR MOLECULES TO TARGET SPECIFIC CELL TYPES

This Example describes the engineering of Xceptor fusion proteins to target specific cell types. This is achieved by engineering BD1 and BD2 affinities. Four Xceptor molecules were engineered with different affinity for CD86 and huIL10R1. Table 9 shows the different affinity ratios for these four molecules. By improving affinity for CD86 through the use of, for example, a CD86 binding domain (*e.g.*, 3D1 or humanized FUN1) and an engineered IL10 molecule (I87A) with lower affinity for huIL10R1, then such an arrangement can be used to favor targeting to a specific cell type of interest, such as APC.

Table 9.

		CD86	IL10R1	IL10R1/CD86
BD1	BD2	Affinity (nM)	Affinity (nM)	Affinity Ratio
CLTA4	IL10	2000*	0.1[&]	0.00005
CTLA4	IL10 I87A	2000*	10[#]	0.005
anti-CD86	IL10	40*	0.1[&]	0.0025
anti-CD86	IL10 I87A	40*	10[#]	0.25

* Approximate equilibrium affinity from in-house measurement of CTLA4, 3D1 and humanized FUN1 binding to CD86
& Approximate affinity based on Tan *et al.* (J. Biol. Chem. 268: 21053, 1993)
# Approximate affinity based on Ding *et al.* (J. Exp. Med. 191: 213, 2000)

EXAMPLE 17

XCEPTOR ACTIVITY IN *IN VIVO* RHEUMATOID ARTHRITIS ANIMAL MODELS

Rheumatoid Arthritis

The therapeutic efficacy of any of the xceptor molecules disclosed herein is examined in at least one of two murine models of rheumatoid arthritis

(RA), namely the collagen induced arthritis (CIA) and glucose-6-phosphate isomerase (G6PI) models. Each of these models has been shown to be useful for predicting efficacy of certain classes of therapeutic drugs in RA (*see* Holmdahl (2000) Arthritis Res. 2:169; Holmdahl (2006) Immunol. Lett. 103:86; Holmdahl (2007) Methods Mol. Med. 136:185; McDevitt, H. (2000) Arthritis Res. 2:85; Kamradt and Schubert (2005) Arthritis Res. Ther. 7:20).

(a) CIA Model

The CIA model is the best characterized mouse model of arthritis in terms of its pathogenesis and immunological basis. In addition, it is the most widely used model of RA and, although not perfect for predicting the ability of drugs to inhibit disease in patients, is considered by many to be the model of choice when investigating potential new therapeutics for RA (Jirholt et al. (2001) Arthritis Res. 3:87; Van den Berg, W.B. (2002) Curr. Rheumatol. Rep. 4:232; Rosloniec (2003) Collagen-Induced Arthritis. In Current Protocols in Immunology, eds. Coligan et al., John Wiley & Sons, Inc, Hoboken, NJ).

In the CIA model, arthritis is induced by immunization of male DBA/1 mice with collagen II (CII) in Complete Freund's Adjuvant (CFA). Specifically, mice are injected intradermally/ subcutaneously with CII in CFA on Day -21 and boosted with CII in Incomplete Freund's Adjuvant (IFA) on Day 0. Mice develop clinical signs of arthritis within days of the boost with CII/IFA. A subset of mice (0% to 10%) immunized with CII/CFA develop signs of arthritis on or around Day 0 without a boost and are excluded from the experiments. In some CIA experiments, the boost is omitted and mice are instead treated with Xceptor or control starting 21 days after immunization with CII/CFA (i.e. the day of first treatment is Day 0).

Mice are treated with Xceptor, vehicle (PBS), or negative or positive control in a preventative and/or therapeutic regimen. Preventative treatment starts on Day 0 and continues through the peak of disease in control (untreated) mice. Therapeutic treatment starts when the majority of mice show mild signs of arthritis. Enbrel®, which has been shown to have good efficacy in both the CIA and G6PI-induced models of arthritis, is used as a positive control. Data collected in every experiment includes clinical scores and cumulative incidence of arthritis. Clinical signs of arthritis in the CIA model are scored using a scale from 0 to 4 as shown in Table 10 below.

Table 10

Score	Observations
0	No apparent swelling or redness
1	Swelling/redness in one to three digits
2	Redness and/or swelling in more than three digits, mild swelling extending into the paw, swollen or red ankle, or mild swelling/redness of forepaw
3	Swollen paw with mild to moderate redness
4	Extreme redness and swelling in entire paw

(b) G6PI Model

In the G6PI model, arthritis is induced by immunization of DBA/1 mice with G6PI in adjuvant (Kamradt and Schubert (2005) Arthritis Res. Ther. 7:20; Schubert et al., (2004) J. Immunol. 172:4503; Bockermann, R. et al. (2005) Arthritis Res. Ther. 7:R1316; Iwanami et al., (2008) Arthritis Rheum. 58:754; Matsumoto et al., (2008) Arthritis Res. Ther. 10:R66). G6PI is an enzyme present in virtually all cells in the body and it is not known why immunization induces a joint specific disease. A number of agents, such as CTLA4-Ig, TNF antagonists (e.g. Enbrel®) and anti-IL6 receptor monoclonal antibody, have been shown to inhibit development of arthritis in the G6PI model.

Male DBA/1 mice are immunized with G6PI in Complete Freund's Adjuvant (CFA) in order to induce arthritis. Specifically, mice are injected intradermally/ subcutaneously with G6PI in CFA on Day 0 and develop clinical signs of arthritis within days of the immunization. As with the CIA model discussed above, mice are treated with xceptor, vehicle (PBS), or negative or positive control in a preventative and/or therapeutic regimen. Preventative treatment starts on Day 0 and continues through the peak of disease in control mice. Therapeutic treatment starts when the majority of mice show mild signs of arthritis. Enbrel®, which has been shown to have good efficacy in both the CIA and G6PI-induced models of arthritis, is used as a positive control. Data collected in every experiment includes clinical scores and cumulative incidence of arthritis. Clinical signs of arthritis in the G6PI model are scored using a scale similar to that employed for the CIA model.

All of the patents, patent application publications, patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

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CLAIMS

What is claimed is:

1. A multi-specific fusion protein, comprising a CD86 binding domain linked to a heterologous binding domain by an intervening domain, wherein the heterologous binding domain is an IL-10 agonist, and wherein the IL-10 agonist binding domain comprises an IL-10 or a functional region thereof.

2. A multi-specific fusion protein, comprising a CD86 binding domain linked to a heterologous binding domain by an intervening domain, wherein the heterologous binding domain comprises an IL-10 agonist, and wherein the IL-10 agonist is an IL-10 or a functional region thereof.

3. The multi-specific fusion protein of claim 1 or 2, wherein the CD86 binding domain is a CTLA4 ectodomain or a sub-domain of a CTLA4 ectodomain.

4. The multi-specific fusion protein of claim 1 or 2, wherein the CD86 binding domain is a Fab, scFv, a domain antibody, or a heavy chain-only antibody specific for CD86.

5. The multi-specific fusion protein of claim 4, wherein the CD86 binding domain comprises light and heavy chain variable domains of FUN1 anti-CD86 antibody or a humanized variant thereof.

6. The multi-specific fusion protein of claim 5, wherein the CD86 binding domain comprises amino acids 1-258 of SEQ ID NO:187 or 237.

7. The multi-specific fusion protein of claim 1 or 2, wherein the CD86 binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:3-6, 410, and 412.

8. The multi-specific fusion protein according to any one of claims 1-7, wherein the heterologous binding domain comprises an amino acid sequence of SEQ ID NO:7.

9. The multi-specific fusion protein of any one of claims 1-7, wherein the IL-10 agonist comprises the amino acid sequence provided in SEQ ID NO:7 or a variant thereof comprising a point mutation at position 87.

10. The multi-specific fusion protein according to any one of claims 1-9, wherein the intervening domain comprises an immunoglobulin constant region or constant sub-region disposed between the CD86 binding domain and the heterologous binding domain.

11. The multi-specific fusion protein of claim 10, wherein the immunoglobulin constant region or constant sub-region comprises IgG1 CH2 and CH3 domains.

12. The multi-specific fusion protein according to any one of claims 1-9, wherein the intervening domain comprises an immunoglobulin constant region disposed between a first and a second linker.

13. The multi-specific fusion protein of claim 12, wherein the first and second linkers are independently selected from the linkers provided in SEQ ID NOs:43-166, 244, 307, 320, 355-379 and 383-398.

14. The multi-specific fusion protein of claim 13, wherein the intervening domain comprises a human immunoglobulin Fc region, albumin, transferrin, a scaffold domain that binds a serum protein, or a combination thereof.

15. The multi-specific fusion protein according to any one of claims 1-9, wherein the intervening domain comprises a structure, from amino-terminus to carboxy-terminus, as follows:

-L1-X-L2-

wherein:

L1 and L2 are each independently a linker comprising from about two to about 150 amino acids; and

X is selected from the group consisting of: an immunoglobulin constant region, an immunoglobulin constant sub-region, albumin, and transferrin.

16. The multi-specific fusion protein of claim 15, wherein the immunoglobulin constant region or constant sub-region comprises IgG1 CH2 and CH3 domains.

17. The multi-specific fusion protein according to claim 15 or 16, wherein L1 is a human immunoglobulin hinge region, and zero, one, or more cysteine residues in the human immunoglobulin hinge region is each substituted with another amino acid.

18. The multi-specific fusion protein according to any one of claims 15-17, wherein X is a human IgG1 Fc domain or at least one CH domain thereof, optionally mutated to eliminate FcγRI-III interaction while retaining FcRn interaction.

19. The multi-specific fusion protein according to any one of claims 1-9, wherein the intervening domain can dimerize.

20. The multi-specific fusion protein of claim 1 or 2, having the following structure:

N-BD1-X-L2-BD2-C

wherein:

BD1 is the CD86 binding domain, wherein the CD86 binding domain is at least about 90% identical to CTLA4 ectodomain;

-X- is -L1-CH2CH3-, wherein L1 is an IgG1 hinge region, optionally mutated by substituting the first cysteine and wherein -CH2CH3- is the CH2CH3 region of an IgG1 Fc domain, optionally mutated to eliminate FcγRI-III interaction while retaining FcRn interaction;

L2 is a linker selected from the group consisting of: SEQ ID NOs:43-166, 244, 307, 320, 355-379, and 383-398; and

BD2 is the heterologous binding domain.

21. The multi-specific fusion protein of claim 1 or 2, wherein the fusion protein comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs:

9, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, 195, 197, 209, 211, 213, 215, 217, 219, 221, 223, 237, 239, 252, 254, 256, 258, 260, 262, 276, 302, 330, 334, 350, 352, and 354.

22. The multi-specific fusion protein of claim 1 or 2 or 4, wherein the CD86 binding domain comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain comprises a CDR1 of SEQ ID NO:308, a CDR2 of SEQ ID NO:309, and a CDR3 of SEQ ID NO:310, and wherein the light chain comprises a CDR1 of SEQ ID NO:311, a CDR2 of SEQ ID NO:312, and a CDR3 of SEQ ID NO:313.

23. The multi-specific fusion protein of claim 1 or 2, wherein the IL-10 molecule is a monoIL10.

24. The multi-specific fusion protein of claim 1 or 2 or 23, wherein the IL-10 agonist binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:380-382.

25. The multi-specific fusion protein according to any one of claims 1-9, 14, or 20 wherein the intervening domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:409 and 415-417.

26. The multi-specific fusion protein of claim 13, wherein the first linker is selected from the group consisting of SEQ ID NOS:89, 100, and 159-164.

27. A composition comprising one or more multi-specific fusion proteins according to any one of claims 1-26 and a pharmaceutically acceptable carrier, diluent, or excipient.

28. A polynucleotide encoding the multi-specific fusion protein according to any one of claims 1-26.

29. The polynucleotide of claim 28, wherein the polynucleotide comprises a nucleic acid sequence selected from the group consisting of: SEQ ID NOs: 8, 170, 172, 174, 176,

178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 208, 210, 212, 214, 216, 218, 220, 222, 236, 238, 251, 253, 255, 257, 259, 261, 275, 301, 329, 333, 349, 351, and 353.

30. An expression vector comprising the polynucleotide according to claim 28 or 29 operably linked to an expression control sequence.

31. A host cell comprising the expression vector according to claim 30.

32. Use of the fusion protein of any one of claims 1-26 or the composition of claim 27 in the manufacture of the medicament for treating a subject with a disorder associated with CD86, IL-10, or a combination thereof.

33. Use of the fusion protein of any one of claims 1-26 or the composition of claim 27 in the manufacture of the medicament for treating a subject with an autoimmune disease selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, asthma, systemic lupus erythematosus (SLE), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), graft versus host disease, psoriasis, multiple sclerosis, dermatomyositis, polymyositis, pernicious anaemia, primary biliary cirrhosis, acute disseminated encephalomyelitis (ADEM), Addison's disease, ankylosing spondylitis, antiphospholipid antibody syndrome (APS) autoimmune hepatitis, diabetes mellitus type 1, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, idiopathic thrombocytopenic purpura, lupus erythematosus, pemphigus vulgaris, Sjögren's syndrome, temporal arthritis (also known as "giant cell arthritis"), autoimmune hemolytic anemia, bullous pemphigoid, vasculitis, celiac disease, endometriosis, hidradenitis suppurativa, interstitial cystitis, morphea, scleroderma, narcolepsy, neuromyotonia, vitiligo and autoimmune inner ear disease or for suppressing a detrimental alloresponse to an organ transplant.

SEQUENCE LISTING

<110> Thompson, Peter A.
Baum, Peter R.
Tan, Phillip
Blankenship, John W.
Natarajan, Sateesh

<120> CD86 ANTAGONIST MULTI-TARGET BINDING PROTEINS

<130> 910180.421PC

<140> PCT
<141> 2009-10-02

<160> 422

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 161
<212> PRT
<213> Homo sapiens

<400> 1
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Thr Arg Thr Trp Pro Cys Thr Leu Leu Phe Phe Leu Leu Phe Ile Pro
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Val Phe Cys Lys Ala Met His Val Ala Gln Pro Ala Val Val Leu Ala
35 40 45
Ser Ser Arg Gly Ile Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly
50 55 60
Lys Ala Thr Glu Val Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln
65 70 75 80
Val Thr Glu Val Cys Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr
85 90 95
Phe Leu Asp Asp Ser Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val
100 105 110
Asn Leu Thr Ile Gln Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile
115 120 125
Cys Lys Val Glu Leu Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly
130 135 140
Asn Gly Thr Gln Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser
145 150 155 160
Asp

<210> 2
<211> 152
<212> PRT
<213> Homo sapiens

<400> 2
Met Leu Arg Leu Leu Leu Ala Leu Asn Leu Phe Pro Ser Ile Gln Val
1 5 10 15
Thr Gly Asn Lys Ile Leu Val Lys Gln Ser Pro Met Leu Val Ala Tyr
20 25 30
Asp Asn Ala Val Asn Leu Ser Cys Lys Tyr Ser Tyr Asn Leu Phe Ser
35 40 45
Arg Glu Phe Arg Ala Ser Leu His Lys Gly Leu Asp Ser Ala Val Glu
50 55 60
Val Cys Val Val Tyr Gly Asn Tyr Ser Gln Gln Leu Gln Val Tyr Ser
65 70 75 80
Lys Thr Gly Phe Asn Cys Asp Gly Lys Leu Gly Asn Glu Ser Val Thr

```
                85                  90                  95
Phe Tyr Leu Gln Asn Leu Tyr Val Asn Gln Thr Asp Ile Tyr Phe Cys
            100                 105                 110
Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser
        115                 120                 125
Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro
    130                 135                 140
Leu Phe Pro Gly Pro Ser Lys Pro
145                 150
```

<210> 3
<211> 115
<212> PRT
<213> Homo sapiens

<400> 3

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

<210> 4
<211> 7
<212> PRT
<213> Homo sapiens

<400> 4

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Ser Pro Gly Lys Ala Thr Glu
 1               5
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<210> 5
<211> 9
<212> PRT
<213> Homo sapiens

<400> 5

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Tyr Met Met Gly Asn Glu Leu Thr Phe
 1               5
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<210> 6
<211> 9
<212> PRT
<213> Homo sapiens

<400> 6

```
Leu Met Tyr Pro Pro Pro Tyr Tyr Leu
 1               5
```

<210> 7
<211> 178
<212> PRT

<213> Homo sapiens

<400> 7

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

<210> 8
<211> 1700
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide coding fusion protein having a CTLA4 ectodomain and an IL10 domain

<400> 8

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aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca agggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tctagcccag gccagggcac ccagtctgag aacagctgca cccacttccc aggcaacctg 1260
cctaacatgc ttcgagatct ccgagatgcc ttcagcagag tgaagacttt ctttcaaatg 1320
aaggatcagc tggacaactt gttgttaaag gagtccttgc tggaggactt taagggttac 1380
ctgggttgcc aagccttgtc tgagatgatc cagttttacc tggaggaggt gatgccccaa 1440
gctgagaacc aagacccaga catcaaggcg catgtgaact ccctggggga gaacctgaag 1500
accctcaggc tgaggctacg gcgctgtcat cgatttcttc cctgtgaaaa caagagcaag 1560
gccgtggagc aggtgaagaa tgcctttaat aagctccaag agaaaggcat ctacaaagcc 1620
atgagtgagt ttgacatctt catcaactac atagaagcct acatgacaat gaagatacga 1680
aactaatcta gagcggccgc                                             1700
```

<210> 9
<211> 537
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an IL10 domain

<400> 9

```
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1               5                  10                  15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln
    370                 375                 380
Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu
385                 390                 395                 400
Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met
                405                 410                 415
Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp
            420                 425                 430
Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe
        435                 440                 445
Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile
```

450 455 460
Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu
465 470 475 480
Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys
485 490 495
Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly
500 505 510
Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu
515 520 525
Ala Tyr Met Thr Met Lys Ile Arg Asn
530 535

<210> 10
<211> 1158
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide coding CTLA4-Ig construct

<400> 10
aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagccgg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
taatctagag cggccgcc 1158

<210> 11
<211> 356
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4-Ig construct

<400> 11
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1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125

```
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly
        355
```

<210> 12
<211> 1880
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein
having a CTLA4 ectodomain and a PDL1 domain

<400> 12

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aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt ccccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tcttttactg tcacggttcc caaggaccta tatgtggtag agtatggtag caatatgaca 1260
attgaatgca aattcccagt agaaaaacaa ttagacctgg ctgcactaat tgtctattgg 1320
gaaatggagg ataagaacat tattcaattt gtgcatggag aggaagacct gaaggttcag 1380
catagtagct acagacagag ggcccggctg ttgaaggacc agctctccct gggaaatgct 1440
gcacttcaga tcacagatgt gaaattgcag gatgcagggg tgtaccgctg catgatcagc 1500
tatggtggtg ccgactacaa gcgaattact gtgaaagtca atgccccata caacaaaatc 1560
```

aaccaaagaa ttttggttgt ggatccagtc acctctgaac atgaactgac atgtcaggct 1620
gagggctacc ccaaggccga agtcatctgg acaagcagtg accatcaagt cctgagtggt 1680
aagaccacca ccaccaattc caagagagag gagaagcttt tcaatgtgac cagcacactg 1740
agaatcaaca caacaactaa tgagattttc tactgcactt ttaggagatt agatcctgag 1800
gaaaaccata cagctgaatt ggtcatccca gaactacctc tggcacatcc tccaaatgaa 1860
aggtaatcta gagcggccgc 1880

<210> 13
<211> 597
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and a PDL1 domain

<400> 13

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

405 410 415
Glu Met Glu Asp Lys Asn Ile Ile Gln Phe Val His Gly Glu Glu Asp
420 425 430
Leu Lys Val Gln His Ser Ser Tyr Arg Gln Arg Ala Arg Leu Leu Lys
435 440 445
Asp Gln Leu Ser Leu Gly Asn Ala Ala Leu Gln Ile Thr Asp Val Lys
450 455 460
Leu Gln Asp Ala Gly Val Tyr Arg Cys Met Ile Ser Tyr Gly Gly Ala
465 470 475 480
Asp Tyr Lys Arg Ile Thr Val Lys Val Asn Ala Pro Tyr Asn Lys Ile
485 490 495
Asn Gln Arg Ile Leu Val Val Asp Pro Val Thr Ser Glu His Glu Leu
500 505 510
Thr Cys Gln Ala Glu Gly Tyr Pro Lys Ala Glu Val Ile Trp Thr Ser
515 520 525
Ser Asp His Gln Val Leu Ser Gly Lys Thr Thr Thr Thr Asn Ser Lys
530 535 540
Arg Glu Glu Lys Leu Phe Asn Val Thr Ser Thr Leu Arg Ile Asn Thr
545 550 555 560
Thr Thr Asn Glu Ile Phe Tyr Cys Thr Phe Arg Arg Leu Asp Pro Glu
565 570 575
Glu Asn His Thr Ala Glu Leu Val Ile Pro Glu Leu Pro Leu Ala His
580 585 590
Pro Pro Asn Glu Arg
595

<210> 14
<211> 338
<212> PRT
<213> Homo sapiens

<400> 14
Met Val Val Met Ala Pro Arg Thr Leu Phe Leu Leu Leu Ser Gly Ala
1 5 10 15
Leu Thr Leu Thr Glu Thr Trp Ala Gly Ser His Ser Met Arg Tyr Phe
20 25 30
Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala
35 40 45
Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser
50 55 60
Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly
65 70 75 80
Pro Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln
85 90 95
Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser
100 105 110
Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly
115 120 125
Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly
130 135 140
Lys Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala
145 150 155 160
Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val
165 170 175
Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu
180 185 190
His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro
195 200 205
Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr
210 215 220
Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr
225 230 235 240
Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu
245 250 255
Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val
260 265 270
Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu

275 280 285
Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Lys Gln Ser Ser Leu Pro
290 295 300
Thr Ile Pro Ile Met Gly Ile Val Ala Gly Leu Val Val Leu Ala Ala
305 310 315 320
Val Val Thr Gly Ala Ala Val Ala Ala Val Leu Trp Arg Lys Lys Ser
325 330 335
Ser Asp

<210> 15
<211> 318
<212> PRT
<213> Homo sapiens

<400> 15
Met Val Val Met Ala Pro Arg Thr Leu Phe Leu Leu Leu Ser Gly Ala
1 5 10 15
Leu Thr Leu Thr Glu Thr Trp Gly Ser His Ser Met Arg Tyr Phe Ser
20 25 30
Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile Ala Met
35 40 45
Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ser Ala
50 55 60
Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu Gly Pro
65 70 75 80
Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala Gln Thr
85 90 95
Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu
100 105 110
Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu Gly Ser
115 120 125
Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp Gly Lys
130 135 140
Asp Tyr Leu Ala Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala Ala Asp
145 150 155 160
Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn Val Ala
165 170 175
Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp Leu His
180 185 190
Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp Pro Pro
195 200 205
Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala Thr Leu
210 215 220
Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu Thr Trp
225 230 235 240
Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val Glu Thr
245 250 255
Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val
260 265 270
Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His Glu Gly
275 280 285
Leu Pro Glu Pro Leu Met Leu Arg Trp Ser Lys Glu Gly Asp Gly Gly
290 295 300
Ile Met Ser Val Arg Glu Ser Arg Ser Leu Ser Glu Asp Leu
305 310 315

<210> 16
<211> 2105
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein
having a CTLA4 ectodomain and an HLA-G5 domain

<400> 16
aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tctggctccc actccatgag gtatttcagc gccgccgtgt cccggcccgg ccgcggggag 1260
ccccgcttca tcgccatggg ctacgtggac gacacgcagt tcgtgcggtt cgacagcgac 1320
tcggcgtgtc cgaggatgga gccgcgggcg ccgtgggtgg agcaggaggg gccggagtat 1380
tgggaagagg agacacggaa caccaaggcc cacgcacaga ctgacagaat gaacctgcag 1440
accctgcgcg gctactacaa ccagagcgag gccagttctc acaccctcca gtggatgatt 1500
ggctgcgacc tggggtccga cggacgcctc ctccgcgggt atgaacagta tgcctacgat 1560
ggcaaggatt acctcaccct gaacgaggac ctgcgctcct ggaccgcagc ggacactgcg 1620
gctcagatct ccaagcgcaa gtgtgaggcg gccaatgtgg ctgaacaaag gagagcctac 1680
ctggagggca cgtgcgtgga gtggctccac agatacctgg agaacgggaa ggagatgctg 1740
cagcgcgcgg acccccccaa gacacacgtg acccaccacc ctgtctttga ctatgaggcc 1800
accctgaggt gctgggccct gggcttctac cctgcggaga tcatactgac ctggcagcgg 1860
gatggggagg accagaccca ggacgtggag ctcgtggaga ccaggcctgc aggggatgga 1920
accttccaga agtgggcagc tgtggtggtg ccttctggag aggagcagag atacacgtgc 1980
catgtgcagc atgaggggct gccggagccc ctcatgctga gatggagtaa ggagggagat 2040
ggaggcatca tgtctgttag ggaaagcagg agcctctctg aagaccttta atctagagcg 2100
gccgc 2105

<210> 17
<211> 672
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an
HLA-G5 domain

<400> 17
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Gly Ser His Ser Met Arg Tyr
    370                 375                 380
Phe Ser Ala Ala Val Ser Arg Pro Gly Arg Gly Glu Pro Arg Phe Ile
385                 390                 395                 400
Ala Met Gly Tyr Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp
                405                 410                 415
Ser Ala Cys Pro Arg Met Glu Pro Arg Ala Pro Trp Val Glu Gln Glu
            420                 425                 430
Gly Pro Glu Tyr Trp Glu Glu Glu Thr Arg Asn Thr Lys Ala His Ala
        435                 440                 445
Gln Thr Asp Arg Met Asn Leu Gln Thr Leu Arg Gly Tyr Tyr Asn Gln
    450                 455                 460
Ser Glu Ala Ser Ser His Thr Leu Gln Trp Met Ile Gly Cys Asp Leu
465                 470                 475                 480
Gly Ser Asp Gly Arg Leu Leu Arg Gly Tyr Glu Gln Tyr Ala Tyr Asp
                485                 490                 495
Gly Lys Asp Tyr Leu Thr Leu Asn Glu Asp Leu Arg Ser Trp Thr Ala
            500                 505                 510
Ala Asp Thr Ala Ala Gln Ile Ser Lys Arg Lys Cys Glu Ala Ala Asn
        515                 520                 525
Val Ala Glu Gln Arg Arg Ala Tyr Leu Glu Gly Thr Cys Val Glu Trp
    530                 535                 540
Leu His Arg Tyr Leu Glu Asn Gly Lys Glu Met Leu Gln Arg Ala Asp
545                 550                 555                 560
Pro Pro Lys Thr His Val Thr His His Pro Val Phe Asp Tyr Glu Ala
                565                 570                 575
Thr Leu Arg Cys Trp Ala Leu Gly Phe Tyr Pro Ala Glu Ile Ile Leu
            580                 585                 590
Thr Trp Gln Arg Asp Gly Glu Asp Gln Thr Gln Asp Val Glu Leu Val
        595                 600                 605
Glu Thr Arg Pro Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val
    610                 615                 620
Val Val Pro Ser Gly Glu Glu Gln Arg Tyr Thr Cys His Val Gln His
625                 630                 635                 640
Glu Gly Leu Pro Glu Pro Leu Met Leu Arg Trp Ser Lys Glu Gly Asp
                645                 650                 655
Gly Gly Ile Met Ser Val Arg Glu Ser Arg Ser Leu Ser Glu Asp Leu
            660                 665                 670
```

<210> 18
<211> 728

<212> PRT
<213> Homo sapiens

<400> 18

```
Met Trp Val Thr Lys Leu Leu Pro Ala Leu Leu Leu Gln His Val Leu
 1               5                  10                  15
Leu His Leu Leu Leu Leu Pro Ile Ala Ile Pro Tyr Ala Glu Gly Gln
            20                  25                  30
Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser Ala Lys Thr
        35                  40                  45
Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr Lys Lys Val
    50                  55                  60
Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu
65                  70                  75                  80
Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg Lys Gln Cys
                85                  90                  95
Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys Lys Glu Phe
            100                 105                 110
Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys
        115                 120                 125
Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys
    130                 135                 140
Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro His Glu His
145                 150                 155                 160
Ser Phe Leu Pro Ser Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr
                165                 170                 175
Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser
            180                 185                 190
Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu
        195                 200                 205
Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp
    210                 215                 220
His Thr Glu Ser Gly Lys Ile Cys Gln Arg Trp Asp His Gln Thr Pro
225                 230                 235                 240
His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp
                245                 250                 255
Asp Asn Tyr Cys Arg Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr
            260                 265                 270
Thr Leu Asp Pro His Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys
        275                 280                 285
Ala Asp Asn Thr Met Asn Asp Thr Asp Val Pro Leu Glu Thr Thr Glu
    290                 295                 300
Cys Ile Gln Gly Gln Gly Glu Gly Tyr Arg Gly Thr Val Asn Thr Ile
305                 310                 315                 320
Trp Asn Gly Ile Pro Cys Gln Arg Trp Asp Ser Gln Tyr Pro His Glu
                325                 330                 335
His Asp Met Thr Pro Glu Asn Phe Lys Cys Lys Asp Leu Arg Glu Asn
            340                 345                 350
Tyr Cys Arg Asn Pro Asp Gly Ser Glu Ser Pro Trp Cys Phe Thr Thr
        355                 360                 365
Asp Pro Asn Ile Arg Val Gly Tyr Cys Ser Gln Ile Pro Asn Cys Asp
    370                 375                 380
Met Ser His Gly Gln Asp Cys Tyr Arg Gly Asn Gly Lys Asn Tyr Met
385                 390                 395                 400
Gly Asn Leu Ser Gln Thr Arg Ser Gly Leu Thr Cys Ser Met Trp Asp
                405                 410                 415
Lys Asn Met Glu Asp Leu His Arg His Ile Phe Trp Glu Pro Asp Ala
            420                 425                 430
Ser Lys Leu Asn Glu Asn Tyr Cys Arg Asn Pro Asp Asp Asp Ala His
        435                 440                 445
Gly Pro Trp Cys Tyr Thr Gly Asn Pro Leu Ile Pro Trp Asp Tyr Cys
    450                 455                 460
Pro Ile Ser Arg Cys Glu Gly Asp Thr Thr Pro Thr Ile Val Asn Leu
465                 470                 475                 480
Asp His Pro Val Ile Ser Cys Ala Lys Thr Lys Gln Leu Arg Val Val
                485                 490                 495
Asn Gly Ile Pro Thr Arg Thr Asn Ile Gly Trp Met Val Ser Leu Arg
            500                 505                 510
```

```
Tyr Arg Asn Lys His Ile Cys Gly Gly Ser Leu Ile Lys Glu Ser Trp
        515                 520                 525
Val Leu Thr Ala Arg Gln Cys Phe Pro Ser Arg Asp Leu Lys Asp Tyr
    530                 535                 540
Glu Ala Trp Leu Gly Ile His Asp Val His Gly Arg Gly Asp Glu Lys
545                 550                 555                 560
Cys Lys Gln Val Leu Asn Val Ser Gln Leu Val Tyr Gly Pro Glu Gly
                565                 570                 575
Ser Asp Leu Val Leu Met Lys Leu Ala Arg Pro Ala Val Leu Asp Asp
            580                 585                 590
Phe Val Ser Thr Ile Asp Leu Pro Asn Tyr Gly Cys Thr Ile Pro Glu
        595                 600                 605
Lys Thr Ser Cys Ser Val Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn
    610                 615                 620
Tyr Asp Gly Leu Leu Arg Val Ala His Leu Tyr Ile Met Gly Asn Glu
625                 630                 635                 640
Lys Cys Ser Gln His His Arg Gly Lys Val Thr Leu Asn Glu Ser Glu
                645                 650                 655
Ile Cys Ala Gly Ala Glu Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp
            660                 665                 670
Tyr Gly Gly Pro Leu Val Cys Glu Gln His Lys Met Arg Met Val Leu
        675                 680                 685
Gly Val Ile Val Pro Gly Arg Gly Cys Ala Ile Pro Asn Arg Pro Gly
    690                 695                 700
Ile Phe Val Arg Val Ala Tyr Tyr Ala Lys Trp Ile His Lys Ile Ile
705                 710                 715                 720
Leu Thr Tyr Lys Val Pro Gln Ser
                725
```

<210> 19
<211> 290
<212> PRT
<213> Homo sapiens

<400> 19

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

```
Asp Asn Tyr Cys Arg Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr
            260                 265                 270
Thr Leu Asp Pro His Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys
        275                 280                 285
Glu Thr
    290
```

<210> 20
<211> 723
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Trp Val Thr Lys Leu Leu Pro Ala Leu Leu Leu Gln His Val Leu
 1               5                  10                  15
Leu His Leu Leu Leu Leu Pro Ile Ala Ile Pro Tyr Ala Glu Gly Gln
            20                  25                  30
Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser Ala Lys Thr
        35                  40                  45
Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr Lys Lys Val
    50                  55                  60
Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu
65                  70                  75                  80
Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg Lys Gln Cys
                85                  90                  95
Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys Lys Glu Phe
            100                 105                 110
Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys
        115                 120                 125
Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys
    130                 135                 140
Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro His Glu His
145                 150                 155                 160
Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg
                165                 170                 175
Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg
            180                 185                 190
Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr
        195                 200                 205
Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr Glu Ser Gly
    210                 215                 220
Lys Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg His Lys Phe
225                 230                 235                 240
Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg
                245                 250                 255
Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His
            260                 265                 270
Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala Asp Asn Thr Met
        275                 280                 285
Asn Asp Thr Asp Val Pro Leu Glu Thr Thr Glu Cys Ile Gln Gly Gln
    290                 295                 300
Gly Glu Gly Tyr Arg Gly Thr Val Asn Thr Ile Trp Asn Gly Ile Pro
305                 310                 315                 320
Cys Gln Arg Trp Asp Ser Gln Tyr Pro His Glu His Asp Met Thr Pro
                325                 330                 335
Glu Asn Phe Lys Cys Lys Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro
            340                 345                 350
Asp Gly Ser Glu Ser Pro Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg
        355                 360                 365
Val Gly Tyr Cys Ser Gln Ile Pro Asn Cys Asp Met Ser His Gly Gln
    370                 375                 380
Asp Cys Tyr Arg Gly Asn Gly Lys Asn Tyr Met Gly Asn Leu Ser Gln
385                 390                 395                 400
Thr Arg Ser Gly Leu Thr Cys Ser Met Trp Asp Lys Asn Met Glu Asp
                405                 410                 415
Leu His Arg His Ile Phe Trp Glu Pro Asp Ala Ser Lys Leu Asn Glu
            420                 425                 430
```

```
Asn Tyr Cys Arg Asn Pro Asp Asp Asp Ala His Gly Pro Trp Cys Tyr
        435                 440                 445
Thr Gly Asn Pro Leu Ile Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys
    450                 455                 460
Glu Gly Asp Thr Thr Pro Thr Ile Val Asn Leu Asp His Pro Val Ile
465                 470                 475                 480
Ser Cys Ala Lys Thr Lys Gln Leu Arg Val Val Asn Gly Ile Pro Thr
                485                 490                 495
Arg Thr Asn Ile Gly Trp Met Val Ser Leu Arg Tyr Arg Asn Lys His
            500                 505                 510
Ile Cys Gly Gly Ser Leu Ile Lys Glu Ser Trp Val Leu Thr Ala Arg
        515                 520                 525
Gln Cys Phe Pro Ser Arg Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly
    530                 535                 540
Ile His Asp Val His Gly Arg Gly Asp Glu Lys Cys Lys Gln Val Leu
545                 550                 555                 560
Asn Val Ser Gln Leu Val Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu
                565                 570                 575
Met Lys Leu Ala Arg Pro Ala Val Leu Asp Asp Phe Val Ser Thr Ile
            580                 585                 590
Asp Leu Pro Asn Tyr Gly Cys Thr Ile Pro Glu Lys Thr Ser Cys Ser
        595                 600                 605
Val Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn Tyr Asp Gly Leu Leu
    610                 615                 620
Arg Val Ala His Leu Tyr Ile Met Gly Asn Glu Lys Cys Ser Gln His
625                 630                 635                 640
His Arg Gly Lys Val Thr Leu Asn Glu Ser Glu Ile Cys Ala Gly Ala
                645                 650                 655
Glu Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu
            660                 665                 670
Val Cys Glu Gln His Lys Met Arg Met Val Leu Gly Val Ile Val Pro
        675                 680                 685
Gly Arg Gly Cys Ala Ile Pro Asn Arg Pro Gly Ile Phe Val Arg Val
    690                 695                 700
Ala Tyr Tyr Ala Lys Trp Ile His Lys Ile Ile Leu Thr Tyr Lys Val
705                 710                 715                 720
Pro Gln Ser
```

<210> 21
<211> 285
<212> PRT
<213> Homo sapiens

<400> 21

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

```
Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg
            180                 185                 190
Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr
        195                 200                 205
Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr Glu Ser Gly
    210                 215                 220
Lys Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg His Lys Phe
225                 230                 235                 240
Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg
                245                 250                 255
Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His
            260                 265                 270
Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Glu Thr
        275                 280                 285


<210> 22
<211> 210
<212> PRT
<213> Hoomo sapiens

<400> 22
Met Trp Val Thr Lys Leu Leu Pro Ala Leu Leu Leu Gln His Val Leu
 1                5                  10                  15
Leu His Leu Leu Leu Leu Pro Ile Ala Ile Pro Tyr Ala Glu Gly Gln
            20                  25                  30
Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser Ala Lys Thr
        35                  40                  45
Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr Lys Lys Val
    50                  55                  60
Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu
65                  70                  75                  80
Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg Lys Gln Cys
                85                  90                  95
Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys Lys Glu Phe
            100                 105                 110
Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys
        115                 120                 125
Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys
    130                 135                 140
Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro His Glu His
145                 150                 155                 160
Ser Phe Leu Pro Ser Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr
                165                 170                 175
Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser
            180                 185                 190
Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu
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Gly Lys
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<210> 23
<211> 3794
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein
      having a CTLA4 ectodomain and an HGF domain

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gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
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gatcaggacc atgtgagggg gattatggtg gcccacttgt ttgtgagcaa cataaaatga 3660
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taccacagtc atag 3794

<210> 24
<211> 1074
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an
HGF domain

<400> 24

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20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
355 360 365
Gln Lys Ala Arg His Ser Pro Asn Ser Gln Arg Lys Arg Arg Asn Thr
370 375 380
Ile His Glu Phe Lys Lys Ser Ala Lys Thr Thr Leu Ile Lys Ile Asp
385 390 395 400
Pro Ala Leu Lys Ile Lys Thr Lys Lys Val Asn Thr Ala Asp Gln Cys
405 410 415
Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu Pro Phe Thr Cys Lys Ala
420 425 430
Phe Val Phe Asp Lys Ala Arg Lys Gln Cys Leu Trp Phe Pro Phe Asn
435 440 445
Ser Met Ser Ser Gly Val Lys Lys Glu Phe Gly His Glu Phe Asp Leu
450 455 460
Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Arg
465 470 475 480
Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln
485 490 495
Pro Trp Ser Ser Met Ile Pro His Glu His Ser Phe Leu Pro Ser Ser
500 505 510
Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg Gly
515 520 525
Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg Tyr

530 535 540
Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr Cys
545 550 555 560
Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr Glu Ser Gly Lys
565 570 575
Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg His Lys Phe Leu
580 585 590
Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg Asn
595 600 605
Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His Thr
610 615 620
Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala Asp Asn Thr Met Asn
625 630 635 640
Asp Thr Asp Val Pro Leu Glu Thr Thr Glu Cys Ile Gln Gly Gln Gly
645 650 655
Glu Gly Tyr Arg Gly Thr Val Asn Thr Ile Trp Asn Gly Ile Pro Cys
660 665 670
Gln Arg Trp Asp Ser Gln Tyr Pro His Glu His Asp Met Thr Pro Glu
675 680 685
Asn Phe Lys Cys Lys Asp Leu Arg Glu Asn Tyr Cys Arg Asn Pro Asp
690 695 700
Gly Ser Glu Ser Pro Trp Cys Phe Thr Thr Asp Pro Asn Ile Arg Val
705 710 715 720
Gly Tyr Cys Ser Gln Ile Pro Asn Cys Asp Met Ser His Gly Gln Asp
725 730 735
Cys Tyr Arg Gly Asn Gly Lys Asn Tyr Met Gly Asn Leu Ser Gln Thr
740 745 750
Arg Ser Gly Leu Thr Cys Ser Met Trp Asp Lys Asn Met Glu Asp Leu
755 760 765
His Arg His Ile Phe Trp Glu Pro Asp Ala Ser Lys Leu Asn Glu Asn
770 775 780
Tyr Cys Arg Asn Pro Asp Asp Asp Ala His Gly Pro Trp Cys Tyr Thr
785 790 795 800
Gly Asn Pro Leu Ile Pro Trp Asp Tyr Cys Pro Ile Ser Arg Cys Glu
805 810 815
Gly Asp Thr Thr Pro Thr Ile Val Asn Leu Asp His Pro Val Ile Ser
820 825 830
Cys Ala Lys Thr Lys Gln Leu Arg Val Val Asn Gly Ile Pro Thr Arg
835 840 845
Thr Asn Ile Gly Trp Met Val Ser Leu Arg Tyr Arg Asn Lys His Ile
850 855 860
Cys Gly Gly Ser Leu Ile Lys Glu Ser Trp Val Leu Thr Ala Arg Gln
865 870 875 880
Cys Phe Pro Ser Arg Asp Leu Lys Asp Tyr Glu Ala Trp Leu Gly Ile
885 890 895
His Asp Val His Gly Arg Gly Asp Glu Lys Cys Lys Gln Val Leu Asn
900 905 910
Val Ser Gln Leu Val Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu Met
915 920 925
Lys Leu Ala Arg Pro Ala Val Leu Asp Asp Phe Val Ser Thr Ile Asp
930 935 940
Leu Pro Asn Tyr Gly Cys Thr Ile Pro Glu Lys Thr Ser Cys Ser Val
945 950 955 960
Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn Tyr Asp Gly Leu Leu Arg
965 970 975
Val Ala His Leu Tyr Ile Met Gly Asn Glu Lys Cys Ser Gln His His
980 985 990
Arg Gly Lys Val Thr Leu Asn Glu Ser Glu Ile Cys Ala Gly Ala Glu
995 1000 1005
Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu Val
1010 1015 1020
Cys Glu Gln His Lys Met Arg Met Val Leu Gly Val Ile Val Pro Gly
1025 1030 1035 1040
Arg Gly Cys Ala Ile Pro Asn Arg Pro Gly Ile Phe Val Arg Val Ala
1045 1050 1055
Tyr Tyr Ala Lys Trp Ile His Lys Ile Ile Leu Thr Tyr Lys Val Pro
1060 1065 1070
Gln Ser

<210> 25
<211> 229
<212> PRT
<213> Homo sapiens

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

<210> 26
<211> 253
<212> PRT
<213> Homo sapiens

<400> 26
Met Trp Pro Pro Gly Ser Ala Ser Gln Pro Pro Pro Ser Pro Ala Ala
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Ala Thr Gly Leu His Pro Ala Ala Arg Pro Val Ser Leu Gln Cys Arg
            20   25   30
Leu Ser Met Cys Pro Ala Arg Ser Leu Leu Leu Val Ala Thr Leu Val
        35   40   45
Leu Leu Asp His Leu Ser Leu Ala Arg Asn Leu Pro Val Ala Thr Pro
    50   55   60
Asp Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu Leu Arg
65   70   75   80
Ala Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu Phe Tyr
                85   90   95
Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys Asp Lys
            100   105   110
Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys Asn Glu
        115   120   125
Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly Ser Cys
    130   135   140
Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu Ser Ser
145   150   155   160
Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr Met Asn

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                165                 170                 175
Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp Gln Asn
            180                 185                 190
Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe Asn Ser
        195                 200                 205
Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe Tyr Lys
    210                 215                 220
Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile Arg Ala
225                 230                 235                 240
Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
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<210> 27
<211> 2486
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein having a CTLA4 ectodomain and an IL35 domain

<400> 27

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gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
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atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
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cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
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gagttcaaga ccatgaatgc aaagcttctg atggatccta agaggcagat ctttctagat 2280
caaaacatgc tggcagttat tgatgagctg atgcaggccc tgaatttcaa cagtgagact 2340
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aatgcttcct aatctagagc ggccgc                                      2486
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<210> 28
<211> 799

<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an IL35 domain

<400> 28

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            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Arg Lys Gly Pro Pro Ala Ala
    370                 375                 380
Leu Thr Leu Pro Arg Val Gln Cys Arg Ala Ser Arg Tyr Pro Ile Ala
385                 390                 395                 400
Val Asp Cys Ser Trp Thr Leu Pro Pro Ala Pro Asn Ser Thr Ser Pro
                405                 410                 415
Val Ser Phe Ile Ala Thr Tyr Arg Leu Gly Met Ala Ala Arg Gly His
            420                 425                 430
Ser Trp Pro Cys Leu Gln Gln Thr Pro Thr Ser Thr Ser Cys Thr Ile
        435                 440                 445
Thr Asp Val Gln Leu Phe Ser Met Ala Pro Tyr Val Leu Asn Val Thr
    450                 455                 460
Ala Val His Pro Trp Gly Ser Ser Ser Ser Phe Val Pro Phe Ile Thr
465                 470                 475                 480
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Glu His Ile Ile Lys Pro Asp Pro Pro Glu Gly Val Arg Leu Ser Pro
                485                 490                 495
Leu Ala Glu Arg Gln Leu Gln Val Gln Trp Glu Pro Pro Gly Ser Trp
            500                 505                 510
Pro Phe Pro Glu Ile Phe Ser Leu Lys Tyr Trp Ile Arg Tyr Lys Arg
        515                 520                 525
Gln Gly Ala Ala Arg Phe His Arg Val Gly Pro Ile Glu Ala Thr Ser
    530                 535                 540
Phe Ile Leu Arg Ala Val Arg Pro Arg Ala Arg Tyr Tyr Val Gln Val
545                 550                 555                 560
Ala Ala Gln Asp Leu Thr Asp Tyr Gly Glu Leu Ser Asp Trp Ser Leu
                565                 570                 575
Pro Ala Thr Ala Thr Met Ser Leu Gly Lys Gly Gly Gly Ser Gly Gly
            580                 585                 590
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Arg Asn Leu Pro Val Ala
        595                 600                 605
Thr Pro Asp Pro Gly Met Phe Pro Cys Leu His His Ser Gln Asn Leu
    610                 615                 620
Leu Arg Ala Val Ser Asn Met Leu Gln Lys Ala Arg Gln Thr Leu Glu
625                 630                 635                 640
Phe Tyr Pro Cys Thr Ser Glu Glu Ile Asp His Glu Asp Ile Thr Lys
                645                 650                 655
Asp Lys Thr Ser Thr Val Glu Ala Cys Leu Pro Leu Glu Leu Thr Lys
            660                 665                 670
Asn Glu Ser Cys Leu Asn Ser Arg Glu Thr Ser Phe Ile Thr Asn Gly
        675                 680                 685
Ser Cys Leu Ala Ser Arg Lys Thr Ser Phe Met Met Ala Leu Cys Leu
    690                 695                 700
Ser Ser Ile Tyr Glu Asp Leu Lys Met Tyr Gln Val Glu Phe Lys Thr
705                 710                 715                 720
Met Asn Ala Lys Leu Leu Met Asp Pro Lys Arg Gln Ile Phe Leu Asp
                725                 730                 735
Gln Asn Met Leu Ala Val Ile Asp Glu Leu Met Gln Ala Leu Asn Phe
            740                 745                 750
Asn Ser Glu Thr Val Pro Gln Lys Ser Ser Leu Glu Glu Pro Asp Phe
        755                 760                 765
Tyr Lys Thr Lys Ile Lys Leu Cys Ile Leu Leu His Ala Phe Arg Ile
    770                 775                 780
Arg Ala Val Thr Ile Asp Arg Val Met Ser Tyr Leu Asn Ala Ser
785                 790                 795


<210> 29
<211> 200
<212> PRT
<213> Homo sapiens

<400> 29
Met Glu Pro Pro Gly Asp Trp Gly Pro Pro Pro Trp Arg Ser Thr Pro
 1                5                  10                  15
Lys Thr Asp Val Leu Arg Leu Val Leu Tyr Leu Thr Phe Leu Gly Ala
            20                  25                  30
Pro Cys Tyr Ala Pro Ala Leu Pro Ser Cys Lys Glu Asp Glu Tyr Pro
        35                  40                  45
Val Gly Ser Glu Cys Cys Pro Lys Cys Ser Pro Gly Tyr Arg Val Lys
    50                  55                  60
Glu Ala Cys Gly Glu Leu Thr Gly Thr Val Cys Glu Pro Cys Pro Pro
65                  70                  75                  80
Gly Thr Tyr Ile Ala His Leu Asn Gly Leu Ser Lys Cys Leu Gln Cys
                85                  90                  95
Gln Met Cys Asp Pro Ala Met Gly Leu Arg Ala Ser Arg Asn Cys Ser
            100                 105                 110
Arg Thr Glu Asn Ala Val Cys Gly Cys Ser Pro Gly His Phe Cys Ile
        115                 120                 125
Val Gln Asp Gly Asp His Cys Ala Ala Cys Arg Ala Tyr Ala Thr Ser
    130                 135                 140
Ser Pro Gly Gln Arg Val Gln Lys Gly Gly Thr Glu Ser Gln Asp Thr
145                 150                 155                 160
```

Leu Cys Gln Asn Cys Pro Pro Gly Thr Phe Ser Pro Asn Gly Thr Leu
165 170 175
Glu Glu Cys Gln His Gln Thr Lys Cys Ser Trp Leu Val Thr Lys Ala
180 185 190
Gly Ala Gly Thr Ser Ser Ser His
195 200

<210> 30
<211> 1707
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein having a CTLA4 ectodomain and an HVEM ectodomain

<400> 30
aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tctctgccgt cctgcaagga ggacgagtac ccagtgggct ccgagtgctg ccccaagtgc 1260
agtccaggtt atcgtgtgaa ggaggcctgc ggggagctga cgggcacagt gtgtgaaccc 1320
tgccctccag gcacctacat tgcccacctc aatggcctaa gcaagtgtct gcagtgccaa 1380
atgtgtgacc cagccatggg cctgcgcgcg agccggaact gctccaggac agagaacgcc 1440
gtgtgtggct gcagcccagg ccacttctgc atcgtccagg acggggacca ctgcgccgcg 1500
tgccgcgctt acgccacctc cagcccgggc cagagggtgc agaagggagg caccgagagt 1560
caggacaccc tgtgtcagaa ctgccccccg gggaccttct ctcccaatgg gaccctggag 1620
gaatgtcagc accagaccaa gtgcagctgg ctggtgacga aggccggagc tgggaccagc 1680
agctcccact aaatctagag cggccgc 1707

<210> 31
<211> 539
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an HVEM ectodomain

<400> 31
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80

Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
355 360 365
Gln Lys Ala Arg His Ser Pro Asn Ser Leu Pro Ser Cys Lys Glu Asp
370 375 380
Glu Tyr Pro Val Gly Ser Glu Cys Cys Pro Lys Cys Ser Pro Gly Tyr
385 390 395 400
Arg Val Lys Glu Ala Cys Gly Glu Leu Thr Gly Thr Val Cys Glu Pro
405 410 415
Cys Pro Pro Gly Thr Tyr Ile Ala His Leu Asn Gly Leu Ser Lys Cys
420 425 430
Leu Gln Cys Gln Met Cys Asp Pro Ala Met Gly Leu Arg Ala Ser Arg
435 440 445
Asn Cys Ser Arg Thr Glu Asn Ala Val Cys Gly Cys Ser Pro Gly His
450 455 460
Phe Cys Ile Val Gln Asp Gly Asp His Cys Ala Ala Cys Arg Ala Tyr
465 470 475 480
Ala Thr Ser Ser Pro Gly Gln Arg Val Gln Lys Gly Gly Thr Glu Ser
485 490 495
Gln Asp Thr Leu Cys Gln Asn Cys Pro Pro Gly Thr Phe Ser Pro Asn
500 505 510
Gly Thr Leu Glu Glu Cys Gln His Gln Thr Lys Cys Ser Trp Leu Val
515 520 525
Thr Lys Ala Gly Ala Gly Thr Ser Ser Ser His
530 535

<210> 32
<211> 238
<212> PRT
<213> Homo sapiens

<400> 32
Met Arg Ile Phe Ala Val Phe Ile Phe Met Thr Tyr Trp His Leu Leu
1 5 10 15

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

<210> 33
<211> 230
<212> PRT
<213> Homo sapiens

<400> 33

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

<210> 34
<211> 1823
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein having a CTLA4 ectodomain and an PDL2 domain

<400> 34
aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tctttattca cagtgacagt ccctaaggaa ctgtacataa tagagcatgg cagcaatgtg 1260
accctggaat gcaactttga cactggaagt catgtgaacc ttggagcaat aacagccagt 1320
ttgcaaaagg tggaaaatga tacatcccca caccgtgaaa gagccacttt gctggaggag 1380
cagctgcccc tagggaaggc ctcgttccac atacctcaag tccaagtgag ggacgaagga 1440
cagtaccaat gcataatcat ctatggggtc gcctgggact acaagtacct gaccctgaaa 1500
gtcaaagctt cctacaggaa aataaacact cacatcctaa aggttccaga aacagatgag 1560
gtagagctca cctgccaggc tacaggttat cctctggcag aagtatcctg gccaaacgtc 1620
agcgttcctg ccaacaccag ccactccagg acccctgaag gcctctacca ggtcaccagt 1680
gttctgcgcc taaagccacc ccctggcaga aacttcagct gtgtgttctg gaatactcac 1740
gtgagggaac ttactttggc cagcattgac cttcaaagtc agatggaacc caggacccat 1800
ccaacttaat ctagagcggc cgc 1823

<210> 35
<211> 578
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an PDL2 domain

<400> 35
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125

```
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Leu Phe Thr Val Thr Val Pro
    370                 375                 380
Lys Glu Leu Tyr Ile Ile Glu His Gly Ser Asn Val Thr Leu Glu Cys
385                 390                 395                 400
Asn Phe Asp Thr Gly Ser His Val Asn Leu Gly Ala Ile Thr Ala Ser
                405                 410                 415
Leu Gln Lys Val Glu Asn Asp Thr Ser Pro His Arg Glu Arg Ala Thr
            420                 425                 430
Leu Leu Glu Glu Gln Leu Pro Leu Gly Lys Ala Ser Phe His Ile Pro
        435                 440                 445
Gln Val Gln Val Arg Asp Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr
    450                 455                 460
Gly Val Ala Trp Asp Tyr Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser
465                 470                 475                 480
Tyr Arg Lys Ile Asn Thr His Ile Leu Lys Val Pro Glu Thr Asp Glu
                485                 490                 495
Val Glu Leu Thr Cys Gln Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser
            500                 505                 510
Trp Pro Asn Val Ser Val Pro Ala Asn Thr Ser His Ser Arg Thr Pro
        515                 520                 525
Glu Gly Leu Tyr Gln Val Thr Ser Val Leu Arg Leu Lys Pro Pro Pro
    530                 535                 540
Gly Arg Asn Phe Ser Cys Val Phe Trp Asn Thr His Val Arg Glu Leu
545                 550                 555                 560
Thr Leu Ala Ser Ile Asp Leu Gln Ser Gln Met Glu Pro Arg Thr His
                565                 570                 575
Pro Thr
```

<210> 36

<400> 36
000

<210> 37

<220>

<223> Nucleotide expression cassette of a fusion protein having a CTLA4 ectodomain and an HVEM ectodomain

<400> 37
000

<210> 38

<220>
<223> Fusion protein having a CTLA4 ectodomain and an HVEM ectodomain

<400> 38
000

<210> 39
<211> 164
<212> PRT
<213> Homo sapiens

<400> 39
Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1 5 10 15
Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
20 25 30
Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
35 40 45
Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
50 55 60
Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65 70 75 80
Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
85 90 95
Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
100 105 110
Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
115 120 125
Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
130 135 140
Gly Asn Lys Thr His Asn Ala Val Cys Val Pro Gly Ser Pro Pro Ala
145 150 155 160
Glu Pro Leu Gly

<210> 40
<211> 255
<212> PRT
<213> Homo sapiens

<400> 40
Met Ala Gln His Gly Ala Met Gly Ala Phe Arg Ala Leu Cys Gly Leu
1 5 10 15
Ala Leu Leu Cys Ala Leu Ser Leu Gly Gln Arg Pro Thr Gly Gly Pro
20 25 30
Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
35 40 45
Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
50 55 60
Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
65 70 75 80
Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
85 90 95
Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
100 105 110
Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
115 120 125
Lys Pro Trp Thr Asp Cys Cys Trp Arg Cys Arg Arg Arg Pro Lys Thr

130 135 140
Pro Glu Ala Ala Ser Ser Pro Arg Lys Ser Gly Ala Ser Asp Arg Gln
145 150 155 160
Arg Arg Arg Gly Gly Trp Glu Thr Cys Gly Cys Glu Pro Gly Arg Pro
165 170 175
Pro Gly Pro Pro Thr Ala Ala Ser Pro Ser Pro Gly Ala Pro Gln Ala
180 185 190
Ala Gly Ala Leu Arg Ser Ala Leu Gly Arg Ala Leu Leu Pro Trp Gln
195 200 205
Gln Lys Trp Val Gln Glu Gly Gly Ser Asp Gln Arg Pro Gly Pro Cys
210 215 220
Ser Ser Ala Ala Ala Ala Gly Pro Cys Arg Arg Glu Arg Glu Thr Gln
225 230 235 240
Ser Trp Pro Pro Ser Ser Leu Ala Gly Pro Asp Gly Val Gly Ser
245 250 255

<210> 41
<211> 1631
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide expression cassette of a fusion protein having a CTLA4 ectodomain and an GITR domain

<400> 41
aagcttgccg ccatggaagc accagcgcag cttctcttcc tcctgctact ctggctccca 60
gataccaccg gtatgcacgt ggcccagcct gctgtggtac tggccagcag ccgaggcatc 120
gccagctttg tgtgtgagta tgcatctcca ggcaaagcca ctgaggtccg ggtgacagtg 180
cttcggcagg ctgacagcca ggtgactgaa gtctgtgcgg caacctacat gatggggaat 240
gagttgacct tcctagatga ttccatctgc acgggcacct ccagtggaaa tcaagtgaac 300
ctcactatcc aaggactgag ggccatggac acgggactct acatctgcaa ggtggagctc 360
atgtacccac cgccatacta cctgggcata ggcaacggaa cccagattta tgtaattgat 420
ccagaaccgt gcccagattc tgacctcgag cccaaatctt ctgacaaaac tcacacatgc 480
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 540
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 600
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 660
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 720
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 780
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 840
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 900
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 960
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1020
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1080
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1140
cagaggcaca acaattcttc cctgaataca agaactcaga aagcacgtca ttctccgaat 1200
tctcagcgcc ccaccggggg tcccgggtgc ggccctgggc gcctcctgct tgggacggga 1260
acggacgcgc gctgctgccg ggttcacacg acgcgctgct gccgcgatta cccgggcgag 1320
gagtgctgtt ccgagtggga ctgcatgtgt gtccagcctg aattccactg cggagaccct 1380
tgctgcacga cctgccggca ccacccttgt cccccaggcc aggggtaca gtcccagggg 1440
aaattcagtt ttggcttcca gtgtatcgac tgtgcctcgg ggaccttctc cgggggccac 1500
gaaggccact gcaaaccttg gacagactgc acccagttcg ggtttctcac tgtgttccct 1560
gggaacaaga cccacaacgc tgtgtgcgtc ccagggtccc ccccggcaga gccgcttggg 1620
taagcggccg c 1631

<210> 42
<211> 516
<212> PRT
<213> Artificial Sequence

<220>
<223> Fusion protein having a CTLA4 ectodomain and an GITR domain

<400> 42
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15

```
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Gln Arg Pro Thr Gly Gly Pro
    370                 375                 380
Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
385                 390                 395                 400
Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
                405                 410                 415
Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
            420                 425                 430
Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
        435                 440                 445
Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
    450                 455                 460
Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
465                 470                 475                 480
Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
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Cys Pro Asn Ser
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Pro Cys Pro Asn Ser
            20

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Pro Cys Pro Asn Ser
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<223> Linker

<400> 145
Leu Pro Pro Glu Thr Gln Glu Ser Gln Glu Val Thr Leu Ser Cys Pro
 1   5   10   15
Pro Cys Pro Asn Ser
            20

<210> 146
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 146
Glu Pro Ala Phe Thr Pro Gly Pro Asn Ile Glu Leu Gln Lys Asp Ser
 1   5   10   15
Asp Cys Pro Asn Ser
            20

<210> 147
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 147
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Arg
 1   5   10   15
His Cys Pro Asn Ser
            20

<210> 148
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 148
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Arg
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 149
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 149
Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 1   5   10   15
Ser Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            20   25   30
Gly Ser Asn Ser
        35

<210> 150
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 150
Arg Thr Arg Tyr Leu Gln Val Ser Gln Gln Leu Gln Gln Thr Asn Arg
 1   5   10   15
Val Leu Glu Val Thr Asn Ser Ser Leu Arg Gln Gln Leu Arg Leu Lys
            20   25   30
Ile Thr Gln Leu Gly Gln Ser Ala Glu Asp Leu Gln Gly Ser Arg Arg
        35   40   45
Glu Leu Ala Gln Ser Gln Glu Ala Leu Gln Val Glu Gln Arg Ala His
    50   55   60
Gln Ala Ala Glu Gly Gln Leu Gln Ala Cys Gln Ala Asp Arg Gln Lys
65   70   75   80
Thr Lys Glu Thr Leu Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu
                85   90   95
Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys
            100   105   110
Gly Ser Ala Asp Thr Cys Cys Pro Asn Ser
        115   120

<210> 151
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 151
Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Gly Asn Ser
 1   5   10

<210> 152
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 152

Asn Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
1 5 10 15
Gly Ser Gly Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
20 25 30
Gly Gly Gly Ser Gly Asn Ser
35

<210> 153
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 153
Asn Tyr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
1 5 10 15
Ser Gly Asn Ser
20

<210> 154
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 154
Ser Pro Pro Ser Pro Asn Ser
1 5

<210> 155
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 155
Glu Pro Thr Ser Thr Asp Lys Thr His Thr Ser Pro Pro Ser Pro Asn
1 5 10 15
Ser

<210> 156
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 156
Glu Pro Thr Ser Thr Asp Lys Thr His Thr Cys Pro Pro Cys Pro Asn
1 5 10 15
Ser

<210> 157
<211> 19

<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 157
Leu Ser Val Lys Ala Asp Phe Leu Thr Pro Ser Ile Ser Pro Pro Cys
 1   5   10   15
Pro Asn Ser

<210> 158
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 158
Gly Gly Gly Ala Ser Cys Pro Pro Cys Ala Asn Ser
 1   5   10

<210> 159
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 159
Arg Thr Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys
 1   5   10   15
Ala Arg His Ser Gly His
            20

<210> 160
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 160
Arg Thr Arg Tyr Leu Gln Val Ser Gln Gln Leu Gln Gln Thr Asn Arg
 1   5   10   15
Val Leu Glu Val Thr Asn Ser Ser Leu Arg Gln Gln Leu Arg Leu Lys
            20   25   30
Ile Thr Gln Leu Gly Gln Ser Ala Glu Asp Leu Gln Gly Ser Arg Arg
        35   40   45
Glu Leu Ala Gln Ser Gln Glu Ala Leu Gln Val Glu Gln Arg Ala His
    50   55   60
Gln Ala Ala Glu Gly Gln Leu Gln Ala Cys Gln Ala Asp Arg Gln Lys
65   70   75   80
Thr Lys Glu Thr Leu Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu
                85   90   95
Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys
            100   105   110
Gly Ser Ala Asp Thr Cys
        115

<210> 161
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 161
Arg Thr Gln Ser Glu Glu Gln Gln Arg Arg Ala Leu Glu Gln Lys Leu
 1   5   10   15
Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr Cys Gly Ser Ala
            20   25   30
Asp Thr Cys
        35

<210> 162
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 162
Arg Thr Glu Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe
 1   5   10   15
Phe Thr Cys Gly Ser Ala Asp Thr Cys
            20   25

<210> 163
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 163
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
 1   5   10   15
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            20   25

<210> 164
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 164
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ala Ser
 1   5   10   15

<210> 165
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 165
Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
 1   5   10   15

<210> 166
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 166
Gly Asp Gln Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro
 1   5   10   15
Cys Pro

<210> 167
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterologous leader sequence

<400> 167
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
 1   5   10   15
Val Ile Met Ser Arg Gly
            20

<210> 168
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterologous leader sequence

<400> 168
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1   5   10   15
Asp Thr Thr Gly
            20

<210> 169
<211> 60
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide coding a heterologous leader
      sequence

<400> 169
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60

<210> 170
<211> 1611
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::IL10 fusion protein with H68 linker

<400> 170
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa agttacagcc cgaattctag cccaggccag 1140
ggcacccagt ctgagaacag ctgcacccac ttcccaggca acctgcctaa catgcttcga 1200
gatctccgag atgccttcag cagagtgaag actttctttc aaatgaagga tcagctggac 1260
aacttgttgt taaaggagtc cttgctggag gactttaagg gttacctggg ttgccaagcc 1320
ttgtctgaga tgatccagtt ttacctggag gaggtgatgc cccaagctga gaaccaagac 1380
ccagacatca aggcgcatgt gaactccctg ggggagaacc tgaagaccct caggctgagg 1440
ctacggcgct gtcatcgatt tcttccctgt gaaaacaaga gcaaggccgt ggagcaggtg 1500
aagaatgcct ttaataagct ccaagagaaa ggcatctaca aagccatgag tgagtttgac 1560
atcttcatca actacataga agcctacatg acaatgaaga tacgaaacta a 1611

<210> 171
<211> 536
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::IL10 fusion protein with H68 linker

<400> 171
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205

```
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
        355                 360                 365
Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser
    370                 375                 380
Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg
385                 390                 395                 400
Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys
                405                 410                 415
Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe
            420                 425                 430
Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr
        435                 440                 445
Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys
    450                 455                 460
Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg
465                 470                 475                 480
Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala
                485                 490                 495
Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile
            500                 505                 510
Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala
        515                 520                 525
Tyr Met Thr Met Lys Ile Arg Asn
    530                 535
```

<210> 172
<211> 1614
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::IL10 fusion protein with H75 linker

<400> 172
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840

ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacagg aactcagatg gcaggtcatt ctccgaattc tagcccaggc 1140
cagggcaccc agtctgagaa cagctgcacc cacttcccag gcaacctgcc taacatgctt 1200
cgagatctcc gagatgcctt cagcagagtg aagactttct ttcaaatgaa ggatcagctg 1260
gacaacttgt tgttaaagga gtccttgctg gaggacttta agggttacct gggttgccaa 1320
gccttgtctg agatgatcca gttttacctg gaggaggtga tgccccaagc tgagaaccaa 1380
gacccagaca tcaaggcgca tgtgaactcc ctgggggaga acctgaagac cctcaggctg 1440
aggctacggc gctgtcatcg atttcttccc tgtgaaaaca agagcaaggc cgtggagcag 1500
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1560
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1614

<210> 173
<211> 537
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::IL10 fusion protein with H75 linker

<400> 173
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225   230   235   240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245   250   255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260   265   270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290   295   300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305   310   315   320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325   330   335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340   345   350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr

```
        355                 360                 365
Gln Met Ala Gly His Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln
    370                 375                 380
Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu
385                 390                 395                 400
Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met
                405                 410                 415
Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp
            420                 425                 430
Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe
        435                 440                 445
Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile
    450                 455                 460
Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu
465                 470                 475                 480
Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys
                485                 490                 495
Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly
            500                 505                 510
Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu
        515                 520                 525
Ala Tyr Met Thr Met Lys Ile Arg Asn
    530                 535
```

<210> 174
<211> 1602
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::IL10 fusion protein with H77 linker

<400> 174

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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa ccgaattcta gcccaggcca gggcacccag 1140
tctgagaaca gctgcaccca cttcccaggc aacctgccta acatgcttcg agatctccga 1200
gatgccttca gcagagtgaa gactttcttt caaatgaagg atcagctgga caacttgttg 1260
ttaaaggagt ccttgctgga ggactttaag ggttacctgg gttgccaagc cttgtctgag 1320
atgatccagt tttacctgga ggaggtgatg ccccaagctg agaaccaaga cccagacatc 1380
aaggcgcatg tgaactccct gggggagaac ctgaagaccc tcaggctgag gctacggcgc 1440
tgtcatcgat ttcttccctg tgaaaacaag agcaaggccg tggagcaggt gaagaatgcc 1500
tttaataagc tccaagagaa aggcatctac aaagccatga gtgagtttga catcttcatc 1560
aactacatag aagcctacat gacaatgaag atacgaaact aa                    1602
```

<210> 175
<211> 533
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::IL10 fusion protein with H77 linker

<400> 175

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Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1               5                  10                  15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
        355                 360                 365
Thr Glu Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser
    370                 375                 380
Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg
385                 390                 395                 400
Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu
                405                 410                 415
Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr
            420                 425                 430
Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu
        435                 440                 445
Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val
    450                 455                 460
Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg
465                 470                 475                 480
Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln
                485                 490                 495
Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala
            500                 505                 510
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Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr
515 520 525
Met Lys Ile Arg Asn
530

<210> 176
<211> 1593
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::IL10 fusion protein with H78 linker

<400> 176
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cccgaattct agcccaggcc agggcaccca gtctgagaac 1140
agctgcaccc acttcccagg caacctgcct aacatgcttc gagatctccg agatgccttc 1200
agcagagtga agactttctt tcaaatgaag gatcagctgg acaacttgtt gttaaaggag 1260
tccttgctgg aggactttaa gggttacctg ggttgccaag ccttgtctga gatgatccag 1320
ttttacctgg aggaggtgat gccccaagct gagaaccaag acccagacat caaggcgcat 1380
gtgaactccc tgggggagaa cctgaagacc ctcaggctga ggctacggcg ctgtcatcga 1440
tttcttccct gtgaaaacaa gagcaaggcc gtggagcagg tgaagaatgc ctttaataag 1500
ctccaagaga aaggcatcta caaagccatg agtgagtttg acatcttcat caactacata 1560
gaagcctaca tgacaatgaa gatacgaaac taa 1593

<210> 177
<211> 530
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::IL10 fusion protein with H78 linker

<400> 177
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys

```
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Pro
        355                 360                 365
Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His
    370                 375                 380
Phe Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe
385                 390                 395                 400
Ser Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu
                405                 410                 415
Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys
            420                 425                 430
Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro
        435                 440                 445
Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu
    450                 455                 460
Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg
465                 470                 475                 480
Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn
                485                 490                 495
Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu
            500                 505                 510
Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile
        515                 520                 525
Arg Asn
    530
```

<210> 178
<211> 1584
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::IL10 fusion
protein with H79 linker

<400> 178
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180

```
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttccgaattc tagcccaggc cagggcaccc agtctgagaa cagctgcacc 1140
cacttcccag gcaacctgcc taacatgctt cgagatctcc gagatgcctt cagcagagtg 1200
aagactttct ttcaaatgaa ggatcagctg gacaacttgt tgttaaagga gtccttgctg 1260
gaggacttta agggttacct gggttgccaa gccttgtctg agatgatcca gttttacctg 1320
gaggaggtga tgccccaagc tgagaaccaa gacccagaca tcaaggcgca tgtgaactcc 1380
ctgggggaga acctgaagac cctcaggctg aggctacggc gctgtcatcg atttcttccc 1440
tgtgaaaaca agagcaaggc cgtggagcag gtgaagaatg cctttaataa gctccaagag 1500
aaaggcatct acaaagccat gagtgagttt gacatcttca tcaactacat agaagcctac 1560
atgacaatga agatacgaaa ctaa                                        1584
```

<210> 179
<211> 527
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::IL10 fusion protein with H79 linker

<400> 179

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

```
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Pro Asn Ser Ser
        355                 360                 365
Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly
    370                 375                 380
Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val
385                 390                 395                 400
Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys
                405                 410                 415
Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu
            420                 425                 430
Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu
        435                 440                 445
Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn
    450                 455                 460
Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro
465                 470                 475                 480
Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn
                485                 490                 495
Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile
            500                 505                 510
Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
        515                 520                 525
```

<210> 180
<211> 1629
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding a CTLA4::monoIL10
fusion protein

<400> 180

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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa agttacagcc cgaattctag cccaggccag 1140
ggcacccagt ctgagaacag ctgcacccac ttcccaggca acctgcctaa catgcttcga 1200
gatctccgag atgccttcag cagagtgaag actttctttc aaatgaagga tcagctggac 1260
aacttgttgt taaaggagtc cttgctggag gactttaagg gttacctggg ttgccaagcc 1320
ttgtctgaga tgatccagtt ttacctggag gaggtgatgc cccaagctga gaaccaagac 1380
ccagacatca aggcgcatgt gaactccctg ggggagaacc tgaagaccct caggctgagg 1440
```

ctacggcgct gtcatcgatt tcttccctgt gaaaacggtg gtggatccgg cggtaagagc 1500
aaggccgtgg agcaggtgaa gaatgccttt aataagctcc aagagaaagg catctacaaa 1560
gccatgagtg agtttgacat cttcatcaac tacatagaag cctacatgac aatgaagata 1620
cgaaactaa 1629

<210> 181
<211> 542
<212> PRT
<213> Artificial Sequence

<220>
<223> A CTLA4::monoIL10 fusion protein

<400> 181
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
355 360 365
Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser
370 375 380
Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg
385 390 395 400
Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys
405 410 415
Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe
420 425 430

```
Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr
        435                 440                 445
Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys
    450                 455                 460
Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg
465                 470                 475                 480
Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Gly Gly Gly Ser
                485                 490                 495
Gly Gly Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys
            500                 505                 510
Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe
        515                 520                 525
Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
    530                 535                 540
```

<210> 182
<211> 2013
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10::FUN1 fusion protein

<400> 182

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agcccaggcc agggcaccca gtctgagaac agctgcaccc acttcccagg caacctgcct 60
aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggaccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggtaact cattattcaa ccaagaagtt 1200
caaattccct tgaccgaaag ttacagcccg aattctgagg tccaactgca gcagtctgga 1260
cctgagctgg agaagcctgg cgcttcagtg aagatatcct gcaaggcttc tggttactca 1320
ttcactgact acaacatgaa ctgggtgaag cagagcaatg gaaagagcct tgagtggatt 1380
ggaaatattg atccttacta tggtggtact agttacaatc agaagttcaa gggcaaggcc 1440
acattgactg tagacaaatc ctccagcaca gcctacatgc agctcaacag cctgacatct 1500
gaagactctg cagtctattt ctgtgcaaga tgggactata ggtacgacga cgggagggct 1560
tactatgtta tggacttctg gggtcaagga acctcagtca ccgtctcctc agggggtgga 1620
ggctctggtg gcggtggctc tggcggaggt ggatccggtg gcggcggatc tgagctccag 1680
atgacccagt ctccatcatc tctggctgcg tctgcaggag aaaaggtcac tatgagctgt 1740
aagtccagtc aaagtgtttt atacagttca aatcagaaga actacttggc ctggtaccag 1800
cagaaaccag ggcagtctcc taaactgctg atctactggg catccactag ggaatctggt 1860
gtccctgatc gcttcacagg cagtggatct gggacacatt ttactctgac cgtcagcagt 1920
gtgcaagctg aagacctggc agtttattac tgtcatcaat acctctactc gtggacgttc 1980
ggtggaggca ccaacctgga aatcaaacgg taa                                2013
```

<210> 183
<211> 670
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10::FUN1 fusion protein

<400> 183
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145 150 155 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
260 265 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
290 295 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
370 375 380
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
385 390 395 400
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Glu Val Gln Leu
405 410 415
Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala Ser Val Lys Ile
420 425 430
Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Asn Met Asn Trp
435 440 445
Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile Gly Asn Ile Asp
450 455 460
Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala
465 470 475 480
Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Asn
485 490 495
Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Trp Asp
500 505 510
Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly
515 520 525

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Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    530                 535                 540
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln
545                 550                 555                 560
Met Thr Gln Ser Pro Ser Ser Leu Ala Ala Ser Ala Gly Glu Lys Val
                565                 570                 575
Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln
            580                 585                 590
Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
        595                 600                 605
Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
    610                 615                 620
Phe Thr Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr Val Ser Ser
625                 630                 635                 640
Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr
                645                 650                 655
Ser Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg
            660                 665                 670
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<210> 184
<211> 1983
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10::3D1 fusion protein

<400> 184

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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
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gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
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agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggtaact cattattcaa ccaagaagtt 1200
caaattccct tgaccgaaag ttacagcccg aattctcagg tccagctgca gcagtctggg 1260
cctgagctgg tgaggcctgg ggaatcagtg aagatttcct gcaagggttc cggctacaca 1320
ttcactgatt atgctataca gtgggtgaag cagagtcatg caaagagtct agagtggatt 1380
ggagttatta atatttacta tgataataca aactacaacc agaagtttaa gggcaaggcc 1440
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gaggattctg ccatctatta ctgtgcaaga gcggcctggt atatggacta ctggggtcaa 1560
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gtgtcagcag gagagaaggt cactatgagc tgcaaatcca gtcagagtct gctcaacagt 1740
agaacccgag agaactactt ggcttggtac cagcagaaac cagggcagtc tcctaaactg 1800
ctgatctact gggcatccac tagggaatct ggggtccctg atcgcttcac aggcagtgga 1860
tctgggacag atttcactct caccatcagc agtgtgcagg ctgaagacct ggcagtttat 1920
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taa                                                                 1983
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<210> 185
<211> 660
<212> PRT

<213> Artificial Sequence

<220>
<223> IL10::3D1 fusion protein

<400> 185
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1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145 150 155 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
260 265 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
290 295 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
370 375 380
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
385 390 395 400
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu
405 410 415
Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu Ser Val Lys Ile
420 425 430
Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr Ala Ile Gln Trp
435 440 445
Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile Gly Val Ile Asn
450 455 460
Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala
465 470 475 480
Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ala
485 490 495

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Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Ala Ala
            500                 505                 510
Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        515                 520                 525
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    530                 535                 540
Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala
545                 550                 555                 560
Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
                565                 570                 575
Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln
            580                 585                 590
Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
        595                 600                 605
Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
    610                 615                 620
Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr
625                 630                 635                 640
Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys
                645                 650                 655
Leu Glu Ile Lys
            660
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<210> 186
<211> 2013
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding FUN1::IL10 fusion protein

<400> 186

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aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240
atgcagctca acagcctgac atctgaagac tctgcagtct atttctgtgc aagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggtca aggaacctca 360
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ggtggcggcg gatctgagct ccagatgacc cagtctccat catctctggc tgcgtctgca 480
ggagaaaagg tcactatgag ctgtaagtcc agtcaaagtg ttttatacag ttcaaatcag 540
aagaactact tggcctggta ccagcagaaa ccagggcagt ctcctaaact gctgatctac 600
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cattttactc tgaccgtcag cagtgtgcaa gctgaagacc tggcagttta ttactgtcat 720
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cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
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cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
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aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
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tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
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cccttgaccg aaagttacag cccgaattct agcccaggcc agggcaccca gtctgagaac 1560
agctgcaccc acttcccagg caacctgcct aacatgcttc gagatctccg agatgccttc 1620
agcagagtga agactttctt tcaaatgaag gatcagctgg acaacttgtt gttaaaggag 1680
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gtgaactccc tgggggagaa cctgaagacc ctcaggctga ggctacggcg ctgtcatcga 1860
tttcttccct gtgaaaacaa gagcaaggcc gtggagcagg tgaagaatgc ctttaataag 1920
ctccaagaga aaggcatcta caaagccatg agtgagtttg acatcttcat caactacata 1980
gaagcctaca tgacaatgaa gatacgaaac taa                              2013
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<210> 187
<211> 670
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1::IL10 fusion protein

<400> 187
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
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Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
            20   25   30
Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile
        35   40   45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100   105   110
Asp Phe Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
        115   120   125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130   135   140
Ser Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ala Ala Ser Ala
145   150   155   160
Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165   170   175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180   185   190
Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195   200   205
Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr His Phe Thr Leu
    210   215   220
Thr Val Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His
225   230   235   240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile
                245   250   255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260   265   270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275   280   285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290   295   300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305   310   315   320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325   330   335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340   345   350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355   360   365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370   375   380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385   390   395   400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405   410   415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420   425   430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435   440   445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450   455   460

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Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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                485                 490                 495
Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro
            500                 505                 510
Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn
        515                 520                 525
Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys
    530                 535                 540
Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu
545                 550                 555                 560
Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser
                565                 570                 575
Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn
            580                 585                 590
Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu
        595                 600                 605
Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys
    610                 615                 620
Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys
625                 630                 635                 640
Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe
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Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
            660                 665                 670
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<210> 188
<211> 1983
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding 3D1::IL10 fusion protein

<400> 188

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catgcaaaga gtctagagtg gattggagtt attaatattt actatgataa tacaaactac 180
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caggctgaag acctggcagt ttattactgc acgcaatctt ataatcttta cacgttcgga 720
gggggggacca agctggaaat aaaactcgag cccaaatctt ctgacaaaac tcacacatgc 780
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt ccccccaaaa 840
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 900
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 960
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1020
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 1080
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1140
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1200
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 1260
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1320
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1380
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 1680
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 1740
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 1800
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gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 1920
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taa 1983

<210> 189
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1::IL10 fusion protein

<400> 189

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

```
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480
Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
                485                 490                 495
Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys
            500                 505                 510
Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp
        515                 520                 525
Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp
    530                 535                 540
Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu
545                 550                 555                 560
Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val
                565                 570                 575
Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn
            580                 585                 590
Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys
        595                 600                 605
His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val
    610                 615                 620
Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met
625                 630                 635                 640
Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met
                645                 650                 655
Lys Ile Arg Asn
            660
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<210> 190
<211> 1611
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::IL10 I87A
fusion protein

<400> 190

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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa agttacagcc cgaattctag cccaggccag 1140
ggcacccagt ctgagaacag ctgcacccac ttcccaggca acctgcctaa catgcttcga 1200
gatctccgag atgccttcag cagagtgaag actttctttc aaatgaagga tcagctggac 1260
aacttgttgt taaaggagtc cttgctggag gactttaagg gttacctggg ttgccaagcc 1320
ttgtctgaga tgatccagtt ttacctggag gaggtgatgc cccaagctga gaaccaagac 1380
ccagacgcca aggcgcatgt gaactccctg ggggagaacc tgaagaccct caggctgagg 1440
ctacggcgct gtcatcgatt tcttccctgt gaaaacaaga gcaaggccgt ggagcaggtg 1500
aagaatgcct ttaataagct ccaagagaaa ggcatctaca aagccatgag tgagtttgac 1560
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atcttcatca actacataga agcctacatg acaatgaaga tacgaaacta a 1611

<210> 191
<211> 536
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::IL10 I87A fusion protein

<400> 191
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
355 360 365
Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser
370 375 380
Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg
385 390 395 400
Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys
405 410 415
Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe
420 425 430
Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr
435 440 445
Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ala Lys

450 455 460
Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg
465 470 475 480
Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala
485 490 495
Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile
500 505 510
Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala
515 520 525
Tyr Met Thr Met Lys Ile Arg Asn
530 535

<210> 192
<211> 1611
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::IL10 I87S
fusion protein

<400> 192
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa agttacagcc cgaattctag cccaggccag 1140
ggcacccagt ctgagaacag ctgcacccac ttcccaggca acctgcctaa catgcttcga 1200
gatctccgag atgccttcag cagagtgaag actttctttc aaatgaagga tcagctggac 1260
aacttgttgt taaaggagtc cttgctggag gactttaagg gttacctggg ttgccaagcc 1320
ttgtctgaga tgatccagtt ttacctggag gaggtgatgc cccaagctga gaaccaagac 1380
ccagacagca aggcgcatgt gaactccctg ggggagaacc tgaagaccct caggctgagg 1440
ctacggcgct gtcatcgatt tcttccctgt gaaaacaaga gcaaggccgt ggagcaggtg 1500
aagaatgcct ttaataagct ccaagagaaa ggcatctaca aagccatgag tgagtttgac 1560
atcttcatca actacataga agcctacatg acaatgaaga tacgaaacta a 1611

<210> 193
<211> 536
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::IL10 I87S fusion protein

<400> 193
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60

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Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
        355                 360                 365
Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser
    370                 375                 380
Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg
385                 390                 395                 400
Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys
                405                 410                 415
Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe
            420                 425                 430
Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr
        435                 440                 445
Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ser Lys
    450                 455                 460
Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg
465                 470                 475                 480
Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala
                485                 490                 495
Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile
            500                 505                 510
Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala
        515                 520                 525
Tyr Met Thr Met Lys Ile Arg Asn
    530                 535
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<210> 194
<211> 1635
<212> DNA
<213> Artificial Sequence

<220>

<223> Nucleotide sequence encoding mouse CTLA4::mouse
IL10 fusion protein with H68 linker

<400> 194
gccatacagg tgacccaacc ttcagtggtg ttggctagca gccatggtgt cgccagcttt 60
ccatgtgaat attcaccatc acacaacact gatgaggtcc gggtgactgt gctgcggcag 120
acaaatgacc aaatgactga ggtctgtgcc acgacattca cagagaagaa tacagtgggc 180
ttcctagatt acccccttctg cagtggtacc tttaatgaaa gcagagtgaa cctcaccatc 240
caaggactga gagctgttga cacgggactg tacctctgca aggtggaact catgtaccca 300
ccgccatact ttgtgggcat gggcaacggg acgcagattt atgtcattga tccagaacca 360
tgcccggatt ctgacctcga gcccagagtg cccataacac agaacccctg tcctccactc 420
aaagagtgtc ccccatgcgc agctccagac gcagcgggtg cgccatccgt cttcatcttc 480
cctccaaaga tcaaggatgt actcatgatc tccctgagcc ccatggtcac atgtgtggtg 540
gtggatgtga gcgaggatga cccagacgtc cagatcagct ggtttgtgaa caacgtggaa 600
gtacacacag ctcagacaca aacccataga gaggattaca acagtactct ccgggtggtc 660
agtgccctcc ccatccagca ccaggactgg atgagtggca aggcgttcgc atgcgcggtc 720
aacaacagag ccctcccatc ccccatcgag aaaaccatct caaaacccag agggccagta 780
agagctccac aggtatatgt cttgcctcca ccagcagaag agatgactaa gaaagagttc 840
agtctgacct gcatgatcgc aggcttctta cctgccgaaa ttgctgtgga ctggaccagc 900
aatgggcgta cagagcaaaa ctacaagaac accgcaacag tcctggactc tgatggttct 960
tacttcatgt acagcaagct cagagtacaa aagagcactt gggaaagagg aagtctttc 1020
gcctgctcag tggtccacga gggtctgcac aatcacctta cgactaagac catctcccgg 1080
tctctgggta aaaactcatt attcaaccaa gaagttcaaa ttcccttgac cgaaagttac 1140
agcccgaatt ctagcagggg ccagtacagc cgggaagaca ataactgcac ccacttccca 1200
gtcggccaga gccacatgct cctagagctg cggactgcct tcagccaggt gaagactttc 1260
tttcaaacaa aggaccagct ggacaacata ctgctaaccg actccttaat gcaggacttt 1320
aagggttact tgggttgcca agccttatcg gaaatgatcc agttttacct ggtagaagtg 1380
atgccccagg cagagaagca tggcccagaa atcaaggagc atttgaactc cctgggtgag 1440
aagctgaaga ccctcaggat gcggctgagg cgctgtcatc gatttctccc ctgtgaaaat 1500
aagagcaagg cagtggagca ggtgaagagt gattttaata agctccaaga ccaaggtgtc 1560
tacaaggcca tgaatgaatt tgacatcttc atcaactgca tagaagcata catgatgatc 1620
aaaatgaaaa gctaa 1635

<210> 195
<211> 544
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse CTLA4::mouse IL10 fusion protein with H68
linker

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

```
        195                 200                 205
His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro
    210                 215                 220
Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val
225                 230                 235                 240
Asn Asn Arg Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro
                245                 250                 255
Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala
            260                 265                 270
Glu Glu Met Thr Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Ala Gly
        275                 280                 285
Phe Leu Pro Ala Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr
    290                 295                 300
Glu Gln Asn Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser
305                 310                 315                 320
Tyr Phe Met Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg
                325                 330                 335
Gly Ser Leu Phe Ala Cys Ser Val Val His Glu Gly Leu His Asn His
            340                 345                 350
Leu Thr Thr Lys Thr Ile Ser Arg Ser Leu Gly Lys Asn Ser Leu Phe
        355                 360                 365
Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
    370                 375                 380
Ser Arg Gly Gln Tyr Ser Arg Glu Asp Asn Asn Cys Thr His Phe Pro
385                 390                 395                 400
Val Gly Gln Ser His Met Leu Leu Glu Leu Arg Thr Ala Phe Ser Gln
                405                 410                 415
Val Lys Thr Phe Phe Gln Thr Lys Asp Gln Leu Asp Asn Ile Leu Leu
            420                 425                 430
Thr Asp Ser Leu Met Gln Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
        435                 440                 445
Leu Ser Glu Met Ile Gln Phe Tyr Leu Val Glu Val Met Pro Gln Ala
    450                 455                 460
Glu Lys His Gly Pro Glu Ile Lys Glu His Leu Asn Ser Leu Gly Glu
465                 470                 475                 480
Lys Leu Lys Thr Leu Arg Met Arg Leu Arg Arg Cys His Arg Phe Leu
                485                 490                 495
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Ser Asp Phe
            500                 505                 510
Asn Lys Leu Gln Asp Gln Gly Val Tyr Lys Ala Met Asn Glu Phe Asp
        515                 520                 525
Ile Phe Ile Asn Cys Ile Glu Ala Tyr Met Met Ile Lys Met Lys Ser
    530                 535                 540
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<210> 196
<211> 1638
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding mouse CTLA4::mouse IL10 fusion protein with H75 linker

<400> 196

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gccatacagg tgacccaacc ttcagtggtg ttggctagca gccatggtgt cgccagcttt 60
ccatgtgaat attcaccatc acacaacact gatgaggtcc gggtgactgt gctgcggcag 120
acaaatgacc aaatgactga ggtctgtgcc acgacattca cagagaagaa tacagtgggc 180
ttcctagatt acccccttctg cagtggtacc tttaatgaaa gcagagtgaa cctcaccatc 240
caaggactga gagctgttga cacgggactg tacctctgca aggtggaact catgtaccca 300
ccgccatact ttgtgggcat gggcaacggg acgcagattt atgtcattga tccagaacca 360
tgcccggatt ctgacctcga gcccagagtg cccataacac agaaccctg tcctccactc 420
aaagagtgtc ccccatgcgc agctccagac gcagcgggtg cgccatccgt cttcatcttc 480
cctccaaaga tcaaggatgt actcatgatc tccctgagcc ccatggtcac atgtgtggtg 540
gtggatgtga gcgaggatga cccagacgtc cagatcagct ggtttgtgaa caacgtggaa 600
gtacacacag ctcagacaca aacccataga gaggattaca acagtactct ccgggtggtc 660
agtgccctcc ccatccagca ccaggactgg atgagtggca aggcgttcgc atgcgcggtc 720
aacaacagag ccctcccatc ccccatcgag aaaaccatct caaaacccag agggccagta 780
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agagctccac aggtatatgt cttgcctcca ccagcagaag agatgactaa gaaagagttc 840
agtctgacct gcatgatcac aggcttctta cctgccgaaa ttgctgtgga ctggaccagc 900
aatgggcgta cagagcaaaa ctacaagaac accgcaacag tcctggactc tgatggttct 960
tacttcatgt acagcaagct cagagtacaa aagagcactt gggaaagagg aagtcttttc 1020
gcctgctcag tggtccacga gggtctgcac aatcacctta cgactaagac catctcccgg 1080
tctctgggta aacagaggca caacaattct tccctgaata caggaactca gatggcaggt 1140
cattctccga attctagcag gggccagtac agccgggaag acaataactg cacccacttc 1200
ccagtcggcc agagccacat gctcctagag ctgcggactg ccttcagcca ggtgaagact 1260
ttctttcaaa caaaggacca gctggacaac atactgctaa ccgactcctt aatgcaggac 1320
tttaagggtt acttgggttg ccaagcctta tcggaaatga tccagtttta cctggtagaa 1380
gtgatgcccc aggcagagaa gcatggccca gaaatcaagg agcatttgaa ctccctgggt 1440
gagaagctga agaccctcag gatgcggctg aggcgctgtc atcgatttct cccctgtgaa 1500
aataagagca aggcagtgga gcaggtgaag agtgatttta ataagctcca agaccaaggt 1560
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atcaaaatga aaagctaa 1638

<210> 197
<211> 545
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse CTLA4::mouse IL10 fusion protein with H75
linker

<400> 197
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35 40 45
Cys Ala Thr Thr Phe Thr Glu Lys Asn Thr Val Gly Phe Leu Asp Tyr
50 55 60
Pro Phe Cys Ser Gly Thr Phe Asn Glu Ser Arg Val Asn Leu Thr Ile
65 70 75 80
Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Leu Cys Lys Val Glu
85 90 95
Leu Met Tyr Pro Pro Pro Tyr Phe Val Gly Met Gly Asn Gly Thr Gln
100 105 110
Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro
115 120 125
Arg Val Pro Ile Thr Gln Asn Pro Cys Pro Pro Leu Lys Glu Cys Pro
130 135 140
Pro Cys Ala Ala Pro Asp Ala Ala Gly Ala Pro Ser Val Phe Ile Phe
145 150 155 160
Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val
165 170 175
Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile
180 185 190
Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr
195 200 205
His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro
210 215 220
Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val
225 230 235 240
Asn Asn Arg Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro
245 250 255
Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala
260 265 270
Glu Glu Met Thr Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Thr Gly
275 280 285
Phe Leu Pro Ala Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr
290 295 300
Glu Gln Asn Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser
305 310 315 320
Tyr Phe Met Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg
325 330 335

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Gly Ser Leu Phe Ala Cys Ser Val Val His Glu Gly Leu His Asn His
            340                 345                 350
Leu Thr Thr Lys Thr Ile Ser Arg Ser Leu Gly Lys Gln Arg His Asn
        355                 360                 365
Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn
    370                 375                 380
Ser Ser Arg Gly Gln Tyr Ser Arg Glu Asp Asn Asn Cys Thr His Phe
385                 390                 395                 400
Pro Val Gly Gln Ser His Met Leu Leu Glu Leu Arg Thr Ala Phe Ser
                405                 410                 415
Gln Val Lys Thr Phe Phe Gln Thr Lys Asp Gln Leu Asp Asn Ile Leu
            420                 425                 430
Leu Thr Asp Ser Leu Met Gln Asp Phe Lys Gly Tyr Leu Gly Cys Gln
        435                 440                 445
Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Val Glu Val Met Pro Gln
    450                 455                 460
Ala Glu Lys His Gly Pro Glu Ile Lys Glu His Leu Asn Ser Leu Gly
465                 470                 475                 480
Glu Lys Leu Lys Thr Leu Arg Met Arg Leu Arg Arg Cys His Arg Phe
                485                 490                 495
Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Ser Asp
            500                 505                 510
Phe Asn Lys Leu Gln Asp Gln Gly Val Tyr Lys Ala Met Asn Glu Phe
        515                 520                 525
Asp Ile Phe Ile Asn Cys Ile Glu Ala Tyr Met Met Ile Lys Met Lys
    530                 535                 540
Ser
545
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<210> 198
<211> 1920
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding GITR::3D1 fusion protein

<400> 198

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tgctgttccg agtgggactg catgtgtgtc cagcctgaat tccactgcgg agacccttgc 180
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aacaagaccc acaacgctgt gtgcgtccca gggtccccgc cggcagagcc gcttgggctc 420
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 480
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 540
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aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 660
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 720
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 780
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 840
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 900
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 960
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gattctgcca tctattactg tgcaagagcg gcctggtata tggactactg gggtcaagga 1500
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acccgagaga actacttggc ttggtaccag cagaaaccag ggcagtctcc taaactgctg 1740
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gggacagatt tcactctcac catcagcagt gtgcaggctg aagacctggc agtttattac 1860
tgcacgcaat cttataatct ttacacgttc ggaggggggga ccaagctgga aataaaataa 1920

<210> 199
<211> 639
<212> PRT
<213> Artificial Sequence

<220>
<223> GITR::3D1 fusion protein

<400> 199
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20 25 30
Cys Arg Asp Tyr Pro Gly Glu Glu Cys Cys Ser Glu Trp Asp Cys Met
35 40 45
Cys Val Gln Pro Glu Phe His Cys Gly Asp Pro Cys Cys Thr Thr Cys
50 55 60
Arg His His Pro Cys Pro Pro Gly Gln Gly Val Gln Ser Gln Gly Lys
65 70 75 80
Phe Ser Phe Gly Phe Gln Cys Ile Asp Cys Ala Ser Gly Thr Phe Ser
85 90 95
Gly Gly His Glu Gly His Cys Lys Pro Trp Thr Asp Cys Thr Gln Phe
100 105 110
Gly Phe Leu Thr Val Phe Pro Gly Asn Lys Thr His Asn Ala Val Cys
115 120 125
Val Pro Gly Ser Pro Pro Ala Glu Pro Leu Gly Leu Glu Pro Lys Ser
130 135 140
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
145 150 155 160
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
165 170 175
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
180 185 190
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
195 200 205
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
210 215 220
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
225 230 235 240
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
245 250 255
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
260 265 270
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
275 280 285
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
290 295 300
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
305 310 315 320
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
325 330 335
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
340 345 350
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
355 360 365
Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr
370 375 380
Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Gln Gln Ser Gly Pro
385 390 395 400
Glu Leu Val Arg Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser
405 410 415
Gly Tyr Thr Phe Thr Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser His

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            420                 425                 430
Ala Lys Ser Leu Glu Trp Ile Gly Val Ile Asn Ile Tyr Tyr Asp Asn
        435                 440                 445
Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Met Thr Val Asp
    450                 455                 460
Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ala Arg Leu Thr Ser Glu
465                 470                 475                 480
Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Ala Ala Trp Tyr Met Asp Tyr
                485                 490                 495
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser
            500                 505                 510
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
        515                 520                 525
Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly Glu
    530                 535                 540
Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg
545                 550                 555                 560
Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser
                565                 570                 575
Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro
            580                 585                 590
Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        595                 600                 605
Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln Ser
    610                 615                 620
Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
625                 630                 635
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<210> 200
<211> 1989
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding HVEM::3D1 fusion protein

<400> 200

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tgtgacccag ccatgggcct gcgcgcgagc cggaactgct ccaggacaga gaacgccgtg 240
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cgcgcttacg ccacctccag cccgggccag agggtgcaga agggaggcac cgagagtcag 360
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tgtcagcacc agaccaagtg cagctggctg gtgacgaagg ccggagctgg gaccagcagc 480
tcccacctcg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct 540
gaagccgcgg gtgcaccgtc agtcttcctc ttcccccccaa aacccaagga caccctcatg 600
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ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 960
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ggtcaaggaa cctcagtcac cgtctcctca gggggtggag gctctggtgg cggtggctct 1620
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ctggctgtgt cagcaggaga gaaggtcact atgagctgca aatccagtca gagtctgctc 1740
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aaactgctga tctactgggc atccactagg gaatctgggg tccctgatcg cttcacaggc 1860
agtggatctg ggacagattt cactctcacc atcagcagtg tgcaggctga agacctggca 1920
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<210> 201
<211> 662
<212> PRT
<213> Artificial Sequence

<220>
<223> HVEM::3D1 fusion protein

<400> 201
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Thr Gly Thr Val Cys Glu Pro Cys Pro Pro Gly Thr Tyr Ile Ala His
35 40 45
Leu Asn Gly Leu Ser Lys Cys Leu Gln Cys Gln Met Cys Asp Pro Ala
50 55 60
Met Gly Leu Arg Ala Ser Arg Asn Cys Ser Arg Thr Glu Asn Ala Val
65 70 75 80
Cys Gly Cys Ser Pro Gly His Phe Cys Ile Val Gln Asp Gly Asp His
85 90 95
Cys Ala Ala Cys Arg Ala Tyr Ala Thr Ser Ser Pro Gly Gln Arg Val
100 105 110
Gln Lys Gly Gly Thr Glu Ser Gln Asp Thr Leu Cys Gln Asn Cys Pro
115 120 125
Pro Gly Thr Phe Ser Pro Asn Gly Thr Leu Glu Glu Cys Gln His Gln
130 135 140
Thr Lys Cys Ser Trp Leu Val Thr Lys Ala Gly Ala Gly Thr Ser Ser
145 150 155 160
Ser His Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
165 170 175
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
180 185 190
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
195 200 205
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
210 215 220
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
225 230 235 240
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
245 250 255
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
260 265 270
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
275 280 285
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
290 295 300
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
305 310 315 320
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
325 330 335
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
340 345 350
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
355 360 365
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
370 375 380
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln
385 390 395 400
Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val
405 410 415
Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu Ser Val

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            420                 425                 430
Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr Ala Ile
        435                 440                 445
Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile Gly Val
    450                 455                 460
Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe Lys Gly
465                 470                 475                 480
Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu
                485                 490                 495
Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg
            500                 505                 510
Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val
        515                 520                 525
Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    530                 535                 540
Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro Ser Ser
545                 550                 555                 560
Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser
                565                 570                 575
Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr
            580                 585                 590
Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser
        595                 600                 605
Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly
    610                 615                 620
Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala
625                 630                 635                 640
Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly
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<210> 202
<211> 2163
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding PDL1::3D1 fusion protein

<400> 202

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gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 780
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cctgagctgg tgaggcctgg ggaatcagtg aagatttcct gcaagggttc cggctacaca 1500
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<210> 203
<211> 720
<212> PRT
<213> Artificial Sequence

<220>
<223> PDL1::3D1 fusion protein

<400> 203

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        35                  40                  45
Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg
    50                  55                  60
Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala
65                  70                  75                  80
Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys
                85                  90                  95
Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val
            100                 105                 110
Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
        115                 120                 125
Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
    130                 135                 140
Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
145                 150                 155                 160
Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
                165                 170                 175
Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
            180                 185                 190
Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
        195                 200                 205
Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Leu Glu Pro Lys
    210                 215                 220
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
225                 230                 235                 240
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        355                 360                 365
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Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
    450                 455                 460
Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Gln Gln Ser Gly
465                 470                 475                 480
Pro Glu Leu Val Arg Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly
                485                 490                 495
Ser Gly Tyr Thr Phe Thr Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser
            500                 505                 510
His Ala Lys Ser Leu Glu Trp Ile Gly Val Ile Asn Ile Tyr Tyr Asp
        515                 520                 525
Asn Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Met Thr Val
    530                 535                 540
Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ala Arg Leu Thr Ser
545                 550                 555                 560
Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Ala Ala Trp Tyr Met Asp
                565                 570                 575
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly
            580                 585                 590
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        595                 600                 605
Asp Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly
    610                 615                 620
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
625                 630                 635                 640
Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                645                 650                 655
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
            660                 665                 670
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        675                 680                 685
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln
    690                 695                 700
Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
705                 710                 715                 720
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<210> 204
<211> 2106
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding PDL2::3D1 fusion protein

<400> 204

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caaaaggtgg aaaatgatac atccccacac cgtgaaagag ccactttgct ggaggagcag 180
ctgcccttag ggaaggcctc gttccacata cctcaagtcc aagtgaggga cgaaggacag 240
taccaatgca taatcatcta tggggtcgcc tgggactaca agtacctgac tctgaaagtc 300
aaagcttcct acaggaaaat aaacactcac atcctaaagg ttccagaaac agatgaggta 360
gagctcacct gccaggctac aggttatcct ctggcagaag tatcctggcc aaacgtcagc 420
gttcctgcca acaccagcca ctccaggacc cctgaaggcc tctaccaggt caccagtgtt 480
ctgcgcctaa agccaccccc tggcagaaac ttcagctgtg tgttctggaa tactcacgtg 540
agggaactta ctttggccag cattgacctt caaagtcaga tggaacccag gacccatcca 600
actctcgagc ccaaatcttc tgacaaaact cacacatgcc caccgtgccc agcacctgaa 660
gccgcgggtg caccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 720
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tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 780
aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 840
gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 900
ctgaatggca aggcgtacgc gtgcgcggtc tccaacaaag ccctcccagc ccccatcgag 960
aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca 1020
tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1080
ccaagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1140
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac 1200
aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 1260
aaccactaca cgcagaagag cctctccctg tctccgggta actcattatt caaccaagaa 1320
gttcaaattc ccttgaccga aagttacagc ccgaattctc aggtccagct gcagcagtct 1380
gggcctgagc tggtgaggcc tggggaatca gtgaagattt cctgcaaggg ttccggctac 1440
acattcactg attatgctat acagtgggtg aagcagagtc atgcaaagag tctagagtgg 1500
attggagtta ttaatattta ctatgataat acaaactaca accagaagtt taagggcaag 1560
gccacaatga ctgtagacaa atcctccagc acagcctata tggaacttgc cagattgaca 1620
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caaggaacct cagtcaccgt ctcctcaggg ggtggaggct ctggtggcgg tggctctggc 1740
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gctgtgtcag caggagagaa ggtcactatg agctgcaaat ccagtcagag tctgctcaac 1860
agtagaaccc gagagaacta cttggcttgg taccagcaga aaccagggca gtctcctaaa 1920
ctgctgatct actgggcatc cactagggaa tctggggtcc ctgatcgctt cacaggcagt 1980
ggatctggga cagatttcac tctcaccatc agcagtgtgc aggctgaaga cctggcagtt 2040
tattactgca cgcaatctta taatctttac acgttcggag gggggaccaa gctggaaata 2100
aaataa 2106

<210> 205
<211> 701
<212> PRT
<213> Artificial Sequence

<220>
<223> PDL2::3D1 fusion protein

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

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
275 280 285
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
290 295 300
Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
305 310 315 320
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
325 330 335
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
340 345 350
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
355 360 365
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
370 375 380
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
385 390 395 400
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
405 410 415
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
420 425 430
Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser
435 440 445
Tyr Ser Pro Asn Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu
450 455 460
Val Arg Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr
465 470 475 480
Thr Phe Thr Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys
485 490 495
Ser Leu Glu Trp Ile Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn
500 505 510
Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser
515 520 525
Ser Ser Thr Ala Tyr Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser
530 535 540
Ala Ile Tyr Tyr Cys Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly
545 550 555 560
Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
565 570 575
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
580 585 590
Leu Ser Gln Ser Pro Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val
595 600 605
Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg
610 615 620
Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
625 630 635 640
Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
645 650 655
Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
660 665 670
Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn
675 680 685
Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
690 695 700

<210> 206
<211> 1806
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding TGFBetaR1::3D1 fusion protein

<400> 206
gcggcgctgc tcccgggggc gacggcgtta cagtgtttct gccacctctg tacaaaagac 60
aattttactt gtgtgacaga tgggctctgc tttgtctctg tcacagagac cacagacaaa 120

gttatacaca acagcatgtg tatagctgaa attgacttaa ttccgcgaga taggccgttt 180
gtatgtgcac cctcttcaaa aactgggtct gtgactacaa catattgctg caatcaggac 240
cattgcaata aaatagaact tccaactact gtaaagtcat cacctggcct tggtcctgtg 300
gaactcgagc ccaaatcttc tgacaaaact cacacatgcc caccgtgccc agcacctgaa 360
gccgcgggtg caccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 420
tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 480
aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 540
gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 600
ctgaatggca aggcgtacgc gtgcgcggtc tccaacaaag ccctcccagc ccccatcgag 660
aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca 720
tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 780
ccaagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 840
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac 900
aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 960
aaccactaca cgcagaagag cctctccctg tctccgggta actcattatt caaccaagaa 1020
gttcaaattc ccttgaccga aagttacagc ccgaattctc aggtccagct gcagcagtct 1080
gggcctgagc tggtgaggcc tggggaatca gtgaagattt cctgcaaggg ttccggctac 1140
acattcactg attatgctat acagtgggtg aagcagagtc atgcaaagag tctagagtgg 1200
attggagtta ttaatattta ctatgataat acaaactaca accagaagtt taagggcaag 1260
gccacaatga ctgtagacaa atcctccagc acagcctata tggaacttgc cagattgaca 1320
tctgaggatt ctgccatcta ttactgtgca agagcggcct ggtatatgga ctactggggt 1380
caaggaacct cagtcaccgt ctcctcaggg ggtggaggct ctggtggcgg tggctctggc 1440
ggaggtggat ccggtggcgg cggatctgac attgtgctgt cacagtctcc atcctccctg 1500
gctgtgtcag caggagagaa ggtcactatg agctgcaaat ccagtcagag tctgctcaac 1560
agtagaaccc gagagaacta cttggcttgg taccagcaga aaccagggca gtctcctaaa 1620
ctgctgatct actgggcatc cactagggaa tctggggtcc ctgatcgctt cacaggcagt 1680
ggatctggga cagatttcac tctcaccatc agcagtgtgc aggctgaaga cctggcagtt 1740
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aaataa 1806

<210> 207
<211> 601
<212> PRT
<213> Artificial Sequence

<220>
<223> TGFBetaR1::3D1 fusion protein

<400> 207
Ala Ala Leu Leu Pro Gly Ala Thr Ala Leu Gln Cys Phe Cys His Leu
 1   5   10   15
Cys Thr Lys Asp Asn Phe Thr Cys Val Thr Asp Gly Leu Cys Phe Val
            20   25   30
Ser Val Thr Glu Thr Thr Asp Lys Val Ile His Asn Ser Met Cys Ile
        35   40   45
Ala Glu Ile Asp Leu Ile Pro Arg Asp Arg Pro Phe Val Cys Ala Pro
    50   55   60
Ser Ser Lys Thr Gly Ser Val Thr Thr Thr Tyr Cys Cys Asn Gln Asp
65   70   75   80
His Cys Asn Lys Ile Glu Leu Pro Thr Thr Val Lys Ser Ser Pro Gly
                85   90   95
Leu Gly Pro Val Glu Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr
            100   105   110
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe
        115   120   125
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    130   135   140
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
145   150   155   160
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
                165   170   175
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            180   185   190
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys
        195   200   205
Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    210   215   220
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

225 230 235 240
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
245 250 255
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
260 265 270
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
275 280 285
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
290 295 300
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
305 310 315 320
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu
325 330 335
Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn
340 345 350
Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly
355 360 365
Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp
370 375 380
Tyr Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp
385 390 395 400
Ile Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys
405 410 415
Phe Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala
420 425 430
Tyr Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr
435 440 445
Cys Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser
450 455 460
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
465 470 475 480
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser
485 490 495
Pro Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys
500 505 510
Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu
515 520 525
Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
530 535 540
Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser
545 550 555 560
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu
565 570 575
Asp Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe
580 585 590
Gly Gly Gly Thr Lys Leu Glu Ile Lys
595 600

<210> 208
<211> 1629
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::monoIL10 I87A
fusion protein

<400> 208
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tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540

cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttcaaattcc cttgaccgaa agttacagcc cgaattctag cccaggccag 1140
ggcacccagt ctgagaacag ctgcacccac ttcccaggca acctgcctaa catgcttcga 1200
gatctccgag atgccttcag cagagtgaag actttctttc aaatgaagga tcagctggac 1260
aacttgttgt taaaggagtc cttgctggag gactttaagg gttacctggg ttgccaagcc 1320
ttgtctgaga tgatccagtt ttacctggag gaggtgatgc cccaagctga gaaccaagac 1380
ccagacgcca aggcgcatgt gaactccctg ggggagaacc tgaagaccct caggctgagg 1440
ctacggcgct gtcatcgatt tcttccctgt gaaaacggtg gtggatccgg cggtaagagc 1500
aaggccgtgg agcaggtgaa gaatgccttt aataagctcc aagagaaagg catctacaaa 1560
gccatgagtg agtttgacat cttcatcaac tacatagaag cctacatgac aatgaagata 1620
cgaaactaa 1629

<210> 209
<211> 542
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::monoIL10 I87A fusion protein

<400> 209
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
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Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225   230   235   240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245   250   255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260   265   270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290   295   300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu

305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu
355 360 365
Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser
370 375 380
Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg
385 390 395 400
Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys
405 410 415
Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe
420 425 430
Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr
435 440 445
Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ala Lys
450 455 460
Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg
465 470 475 480
Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Gly Gly Gly Ser
485 490 495
Gly Gly Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys
500 505 510
Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe
515 520 525
Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
530 535 540

<210> 210
<211> 2001
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding monoIL10::3D1 fusion protein

<400> 210
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacgg tggtggatcc 360
ggcggtaaga gcaaggccgt ggagcaggtg aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaacct cgagcccaaa tcttctgaca aaactcacac atgcccaccg 540
tgcccagcac ctgaagccgc gggtgcaccg tcagtcttcc tcttcccccc aaaacccaag 600
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 660
gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 720
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tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg 960
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ttattcaacc aagaagttca aattcccttg accgaaagtt acagcccgaa ttctcaggtc 1260
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cttgccagat tgacatctga ggattctgcc atctattact gtgcaagagc ggcctggtat 1560
atggactact ggggtcaagg aacctcagtc accgtctcct caggggtgg aggctctggt 1620

ggcggtggct ctggcggagg tggatccggt ggcggcggat ctgacattgt gctgtcacag 1680
tctccatcct ccctggctgt gtcagcagga gagaaggtca ctatgagctg caaatccagt 1740
cagagtctgc tcaacagtag aacccgagag aactacttgg cttggtacca gcagaaacca 1800
gggcagtctc ctaaactgct gatctactgg gcatccacta gggaatctgg ggtccctgat 1860
cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcag tgtgcaggct 1920
gaagacctgg cagtttatta ctgcacgcaa tcttataatc tttacacgtt cggaggggg 1980
accaagctgg aaataaaata a 2001

<210> 211
<211> 666
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10::3D1 fusion protein

<400> 211
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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115 120 125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130 135 140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145 150 155 160
Thr Met Lys Ile Arg Asn Leu Glu Pro Lys Ser Ser Asp Lys Thr His
165 170 175
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
180 185 190
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
195 200 205
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
210 215 220
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225 230 235 240
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
245 250 255
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
260 265 270
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
275 280 285
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
290 295 300
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
305 310 315 320
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
325 330 335
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
340 345 350
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
355 360 365
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
370 375 380
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser
385 390 395 400
Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro

405 410 415
Asn Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro
420 425 430
Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr
435 440 445
Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu
450 455 460
Trp Ile Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln
465 470 475 480
Lys Phe Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr
485 490 495
Ala Tyr Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr
500 505 510
Tyr Cys Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr
515 520 525
Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
530 535 540
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln
545 550 555 560
Ser Pro Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser
565 570 575
Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr
580 585 590
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
595 600 605
Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
610 615 620
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
625 630 635 640
Glu Asp Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr
645 650 655
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
660 665

<210> 212
<211> 1983
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::3D1 fusion protein

<400> 212
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
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cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
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cactacacgc agaagagcct ctccctgtct ccgggtaact cattattcaa ccaagaagtt 1200
caaattccct tgaccgaaag ttacagcccg aattctcagg tccagctgca gcagtctggg 1260
cctgagctgg tgaggcctgg ggaatcagtg aagatttcct gcaagggttc cggctacaca 1320
ttcactgatt atgctataca gtgggtgaag cagagtcatg caaagagtct agagtggatt 1380

ggagttatta atatttacta tgataataca aactacaacc agaagtttaa gggcaaggcc 1440
acaatgactg tagacaaatc ctccagcaca gcctatatgg aacttgccag attgacatct 1500
gaggattctg ccatctatta ctgtgcaaga gcggcctggt atatggacta ctggggtcaa 1560
ggaacctcag tcaccgtctc ctcaggggt ggaggctctg gtggcggtgg ctctggcgga 1620
ggtggatccg gtggcggcgg atctgacatt gtgctgtcac agtctccatc ctccctggct 1680
gtgtcagcag gagagaaggt cactatgagc tgcaaatcca gtcagagtct gctcaacagt 1740
agaacccgag agaactactt ggcttggtac cagcagaaac cagggcagtc tcctaaactg 1800
ctgatctact gggcatccac tagggaatct ggggtccctg atcgcttcac aggcagtgga 1860
tctgggacag atttcactct caccatcagc agtgtgcagg ctgaagacct ggcagtttat 1920
tactgcacgc aatcttataa tctttacacg ttcggagggg ggaccaagct ggaaataaaa 1980
taa 1983

<210> 213
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A::3D1 fusion protein

<400> 213
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1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145 150 155 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
260 265 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
290 295 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

370 375 380
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
385 390 395 400
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu
405 410 415
Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu Ser Val Lys Ile
420 425 430
Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr Ala Ile Gln Trp
435 440 445
Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile Gly Val Ile Asn
450 455 460
Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala
465 470 475 480
Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ala
485 490 495
Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Ala Ala
500 505 510
Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
515 520 525
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
530 535 540
Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala
545 550 555 560
Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
565 570 575
Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln
580 585 590
Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
595 600 605
Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
610 615 620
Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr
625 630 635 640
Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys
645 650 655
Leu Glu Ile Lys
660

<210> 214
<211> 2001
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding monoIL10 I87A::3D1
fusion protein

<400> 214
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
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ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaacct cgagcccaaa tcttctgaca aaactcacac atgcccaccg 540
tgcccagcac ctgaagccgc gggtgcaccg tcagtcttcc tcttcccccc aaaacccaag 600
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 660
gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 720
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aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1080
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg 1140

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aagggttccg gctacacatt cactgattat gctatacagt gggtgaagca gagtcatgca 1380
aagagtctag agtggattgg agttattaat atttactatg ataatacaaa ctacaaccag 1440
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cttgccagat tgacatctga ggattctgcc atctattact gtgcaagagc ggcctggtat 1560
atggactact ggggtcaagg aacctcagtc accgtctcct caggggtgg aggctctggt 1620
ggcggtggct ctggcggagg tggatccggt ggcggcggat ctgacattgt gctgtcacag 1680
tctccatcct ccctggctgt gtcagcagga gagaaggtca ctatgagctg caaatccagt 1740
cagagtctgc tcaacagtag aacccgagag aactacttgg cttggtacca gcagaaacca 1800
gggcagtctc ctaaactgct gatctactgg gcatccacta gggaatctgg ggtccctgat 1860
cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcag tgtgcaggct 1920
gaagacctgg cagtttatta ctgcacgcaa tcttataatc tttacacgtt cggaggggg 1980
accaagctgg aaataaaata a 2001

<210> 215
<211> 666
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10 I87A::3D1 fusion protein

<400> 215
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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115 120 125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130 135 140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145 150 155 160
Thr Met Lys Ile Arg Asn Leu Glu Pro Lys Ser Ser Asp Lys Thr His
165 170 175
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
180 185 190
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
195 200 205
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
210 215 220
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225 230 235 240
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
245 250 255
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
260 265 270
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
275 280 285
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
290 295 300
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
305 310 315 320
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
325 330 335
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

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            340                 345                 350
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        355                 360                 365
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    370                 375                 380
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser
385                 390                 395                 400
Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro
                405                 410                 415
Asn Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro
            420                 425                 430
Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr
        435                 440                 445
Asp Tyr Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu
    450                 455                 460
Trp Ile Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln
465                 470                 475                 480
Lys Phe Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr
                485                 490                 495
Ala Tyr Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr
            500                 505                 510
Tyr Cys Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr
        515                 520                 525
Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    530                 535                 540
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln
545                 550                 555                 560
Ser Pro Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser
                565                 570                 575
Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr
            580                 585                 590
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        595                 600                 605
Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly
    610                 615                 620
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
625                 630                 635                 640
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Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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<210> 216
<211> 1071
<212> DNA
<213> Artificial Sequence

<220>
<223> LEA29-Fc - a CTLA4 variant

<400> 216

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ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacg agggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
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ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
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cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgcccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
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accgtggaca agagccggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtta a 1071

<210> 217
<211> 356
<212> PRT
<213> Artificial Sequence

<220>
<223> LEA29-Fc - a CTLA4 variant

<400> 217
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20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Glu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly
355

<210> 218
<211> 1614
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding LEA29Y::IL10 fusion
protein with H75 linker

<400> 218
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaatacact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacg agggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacagg aactcagatg gcaggtcatt ctccgaattc tagcccaggc 1140
cagggcaccc agtctgagaa cagctgcacc cacttcccag gcaacctgcc taacatgctt 1200
cgagatctcc gagatgcctt cagcagagtg aagactttct ttcaaatgaa ggatcagctg 1260
gacaacttgt tgttaaagga gtccttgctg gaggacttta agggttacct gggttgccaa 1320
gccttgtctg agatgatcca gttttacctg gaggaggtga tgccccaagc tgagaaccaa 1380
gacccagacg ccaaggcgca tgtgaactcc ctgggggaga acctgaagac cctcaggctg 1440
aggctacggc gctgtcatcg atttcttccc tgtgaaaaca agagcaaggc cgtggagcag 1500
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1560
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1614

<210> 219
<211> 537
<212> PRT
<213> Artificial Sequence

<220>
<223> LEA29Y::IL10 fusion protein with H75 linker

<400> 219
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Tyr Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Glu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala

```
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr
        355                 360                 365
Gln Met Ala Gly His Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln
    370                 375                 380
Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu
385                 390                 395                 400
Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met
                405                 410                 415
Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp
            420                 425                 430
Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe
        435                 440                 445
Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ala
    450                 455                 460
Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu
465                 470                 475                 480
Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys
                485                 490                 495
Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly
            500                 505                 510
Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu
        515                 520                 525
Ala Tyr Met Thr Met Lys Ile Arg Asn
    530                 535
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<210> 220
<211> 1602
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::monoIL10
fusion protein with H79 linker

<400> 220

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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
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gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtaa ctcattattc 1080
aaccaagaag ttccgaattc tagcccaggc cagggcaccc agtctgagaa cagctgcacc 1140
cacttcccag gcaacctgcc taacatgctt cgagatctcc gagatgcctt cagcagagtg 1200
aagactttct ttcaaatgaa ggatcagctg gacaacttgt tgttaaagga gtccttgctg 1260
gaggacttta agggttacct gggttgccaa gccttgtctg agatgatcca gttttacctg 1320
gaggaggtga tgccccaagc tgagaaccaa gacccagaca tcaaggcgca tgtgaactcc 1380
ctgggggaga acctgaagac cctcaggctg aggctacggc gctgtcatcg atttcttccc 1440
tgtgaaaacg gtggtggatc cggcggtaag agcaaggccg tggagcaggt gaagaatgcc 1500
tttaataagc tccaagagaa aggcatctac aaagccatga gtgagtttga catcttcatc 1560
aactacatag aagcctacat gacaatgaag atacgaaact aa 1602

<210> 221
<211> 533
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::monoIL10 fusion protein with H79 linker

<400> 221
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225   230   235   240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245   250   255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260   265   270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290   295   300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305   310   315   320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325   330   335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340   345   350
Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Pro Asn Ser Ser
        355   360   365
Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly
    370   375   380

Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val
385 390 395 400
Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys
405 410 415
Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu
420 425 430
Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu
435 440 445
Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn
450 455 460
Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro
465 470 475 480
Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu Gln
485 490 495
Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala
500 505 510
Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr
515 520 525
Met Lys Ile Arg Asn
530

<210> 222
<211> 1608
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::monoIL10
fusion protein with H80 linker

<400> 222
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacacc gaattctagc ccaggccagg gcacccagtc tgagaacagc 1140
tgcacccact tcccaggcaa cctgcctaac atgcttcgag atctccgaga tgccttcagc 1200
agagtgaaga ctttctttca aatgaaggat cagctggaca acttgttgtt aaaggagtcc 1260
ttgctggagg actttaaggg ttacctgggt tgccaagcct tgtctgagat gatccagttt 1320
tacctggagg aggtgatgcc ccaagctgag aaccaagacc cagacatcaa ggcgcatgtg 1380
aactccctgg gggagaacct gaagacgctc aggctgaggc tacggcgctg tcatcgattt 1440
cttccctgtg aaaacggtgg tggatccggc ggtaagagca aggccgtgga gcaggtgaag 1500
aatgccttta ataagctcca agagaaaggc atctacaaag ccatgagtga gtttgacatc 1560
ttcatcaact acatagaagc ctacatgaca atgaagatac gaaactaa 1608

<210> 223
<211> 535
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::monoIL10 fusion protein with H80 linker

<400> 223

Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Pro Asn
355 360 365
Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe
370 375 380
Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser
385 390 395 400
Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu
405 410 415
Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln
420 425 430
Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln
435 440 445
Ala Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly
450 455 460
Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe
465 470 475 480
Leu Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val
485 490 495
Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr
500 505 510
Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr
515 520 525
Met Thr Met Lys Ile Arg Asn

530 535

<210> 224
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0114 - a generated variant of humanized FUN1

<400> 224
gaggtccagc tggtacagtc tggggctgag gtgaagaagc ctggggctac agtgaaaatc 60
tcctgcaagg tttctggata caccttcacc gactacaaca tgaactgggt gcaacaggcc 120
cctggaaaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag agtcaccata accgcggaca cgtctacaga cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 480
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 600
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 660
gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa 1473

<210> 225
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0114 - a generated variant of humanized FUN1

<400> 225
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
100 105 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu

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145                 150                 155                 160
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165                 170                 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180                 185                 190
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195                 200                 205
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 226
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0115 - a generated variant of humanized FUN1

<400> 226

```
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc gactacaaca tgaactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 480
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 600
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 660
gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
```

```
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa                               1473

<210> 227
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0115 - a generated variant of
      humanized FUN1

<400> 227
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1               5                  10                  15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100                 105                 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
145                 150                 155                 160
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165                 170                 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180                 185                 190
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195                 200                 205
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
```

```
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 228
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0116 - a generated variant of humanized FUN1

<400> 228

```
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactacaaca tgaactggat acgccaggct 120
ccagggaagg ggctggagtg ggtttcaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 480
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 600
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 660
gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa                               1473
```

<210> 229
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0116 - a generated variant of humanized FUN1

<400> 229

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
```

```
            20                  25                  30
Asn Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100                 105                 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
145                 150                 155                 160
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165                 170                 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180                 185                 190
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195                 200                 205
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 230
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0117 - a generated variant of

humanized FUN1

<400> 230
gaggtccagc tggtacagtc tggggctgag gtgaagaagc ctggggctac agtgaaaatc 60
tcctgcaagg tttctggata caccttcacc gactacaaca tgaactgggt gcaacaggcc 120
cctggaaaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag agtcaccata accgcggaca cgtctacaga cacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc aacatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat ccagatgacc cagtctccat cctccctgtc tgcatctgta 480
ggagacagag tcaccatcac ttgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta tcagcagaaa ccagggaaag ttcctaagct cctgatctat 600
tgggcatcca ctagggaatc tggggtccca tctcggttca gtggcagtgg atctgggaca 660
gatttcactc tcaccatcag cagcctgcag cctgaagatg ttgcaactta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa 1473

<210> 231
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0117 - a generated variant of
humanized FUN1

<400> 231
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met Asn Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Thr Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
100 105 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
145 150 155 160
Gly Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Val Leu Tyr
165 170 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
180 185 190
Lys Val Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
195 200 205
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
210 215 220
Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys His

```
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 232
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0118 - a generated variant of humanized FUN1

<400> 232

```
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc gactacaaca tgaactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat ccagatgacc cagtctccat cctccctgtc tgcatctgta 480
ggagacagag tcaccatcac ttgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta tcagcagaaa ccagggaaag ttcctaagct cctgatctat 600
tgggcatcca ctagggaatc tggggtccca tctcggttca gtggcagtgg atctgggaca 660
gatttcactc tcaccatcag cagcctgcag cctgaagatg ttgcaactta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
```

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa 1473

<210> 233
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0118 - a generated variant of humanized FUN1

<400> 233
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
100 105 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
145 150 155 160
Gly Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Val Leu Tyr
165 170 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
180 185 190
Lys Val Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
195 200 205
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
210 215 220
Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys His
225 230 235 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
245 250 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
260 265 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
275 280 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
290 295 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305 310 315 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
325 330 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
340 345 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
355 360 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
370 375 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385 390 395 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
405 410 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
420 425 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe

```
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 234
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0119 - a generated variant of humanized FUN1

<400> 234

```
caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gactacaaca tgaactggat acgccaggct 120
ccagggaagg ggctggagtg ggtttcaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat ccagatgacc cagtctccat cctccctgtc tgcatctgta 480
ggagacagag tcaccatcac ttgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta tcagcagaaa ccagggaaag ttcctaagct cctgatctat 600
tgggcatcca ctagggaatc tggggtccca tctcggttca gtggcagtgg atctgggaca 660
gatttcactc tcaccatcag cagcctgcag cctgaagatg ttgcaactta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa                              1473
```

<210> 235
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized FUN1 SMIP M0119 - a generated variant of humanized FUN1

<400> 235

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

```
            100                 105                 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140
Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
145                 150                 155                 160
Gly Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165                 170                 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180                 185                 190
Lys Val Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195                 200                 205
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys His
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 236
<211> 2013
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding humanized FUN1
M0115::IL10 fusion protein

<400> 236
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc gactacaaca tgaactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420

ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 480
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 600
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 660
gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt aactcattat tcaaccaaga agttcaaatt 1500
cccttgaccg aaagttacag cccgaattct agcccaggcc agggcaccca gtctgagaac 1560
agctgcaccc acttcccagg caacctgcct aacatgcttc gagatctccg agatgccttc 1620
agcagagtga agactttctt tcaaatgaag gatcagctgg acaacttgtt gttaaaggag 1680
tccttgctgg aggactttaa gggttacctg ggttgccaag ccttgtctga gatgatccag 1740
ttttacctgg aggaggtgat gccccaagct gagaaccaag acccagacat caaggcgcat 1800
gtgaactccc tgggggagaa cctgaagacc ctcaggctga ggctacggcg ctgtcatcga 1860
tttcttccct gtgaaaacaa gagcaaggcc gtggagcagg tgaagaatgc ctttaataag 1920
ctccaagaga aaggcatcta caaagccatg agtgagtttg acatcttcat caactacata 1980
gaagcctaca tgacaatgaa gatacgaaac taa 2013

<210> 237
<211> 670
<212> PRT
<213> Artificial Sequence

<220>
<223> humanized FUN1 M0115::IL10 fusion protein

<400> 237
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
100 105 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
145 150 155 160
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
165 170 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
180 185 190
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
195 200 205
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
210 215 220
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
225 230 235 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile

245 250 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
260 265 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
275 280 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
290 295 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305 310 315 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
325 330 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
340 345 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
355 360 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
370 375 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385 390 395 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
405 410 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
420 425 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
435 440 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
450 455 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465 470 475 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln
485 490 495
Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro
500 505 510
Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn
515 520 525
Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys
530 535 540
Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu
545 550 555 560
Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser
565 570 575
Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn
580 585 590
Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu
595 600 605
Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys
610 615 620
Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys
625 630 635 640
Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe
645 650 655
Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
660 665 670

<210> 238
<211> 1443
<212> DNA
<213> Artificial Sequence

<220>
<223> anti-mouse CD86 (GL1) SMIP

<400> 238
gaggtgcagc tggtggagtc tgctggaggt ttagtgcagc ctggaaggtc cctaaaactc 60
tcctgtgcag cctcaggatt cactttcagt gactattaca tggcctgggt ccgccaggct 120
ccaacgaagg ggctggagtg ggtcgcaacc attagtcatg acggtagtag tacttactat 180
cgagactccg tgaagggccg attcacaatc tccagagata atgcaaaaac catcctatac 240

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ctgcaaatgg acagtctgag gtctgaggac acggccactt atttctgtgc aagacagaat 300
attatggatt attggggcca aggagtcatg gtcacagtct cctcaggggg tggaggctct 360
ggtggcggtg gctctggcgg aggtggatcc ggtggcggcg gatctgacat tgtgatgacc 420
cagactccat cctcccaggc tgtgtcagca ggggagaagg tcactatgag ctgcaagtcc 480
agtcagagtc ttttgtacag tagagaccag agtaactact tggcctggta ccagcagaaa 540
cctgggcagt ctcctaaact acttatctac ttggcatcca ctagggaatc aggggtccct 600
gatcgcttca taggcagtgg ctctgggaca gacttcactc tgaccatcag cagtgtgcag 660
gctgaagatc tggcagatta ttactgtcag cagcattaca actatccgct cacgttcggt 720
tctgggacca agctagaaat caaactcgag cccaaatctt ctgacaaaac tcacacatgc 780
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt ccccccaaaa 840
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 900
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 960
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1020
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 1080
gccctcccag ccccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1140
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1200
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 1260
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1320
tacagcaagc tcaccgtgga caagagccgg tggcagcagg ggaacgtctt ctcatgctcc 1380
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1440
taa                                                               1443
```

<210> 239
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> anti-mouse CD86 (GL1) SMIP

<400> 239

```
Glu Val Gln Leu Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30
Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
        35                  40                  45
Ala Thr Ile Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr
65                  70                  75                  80
Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95
Ala Arg Gln Asn Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr
            100                 105                 110
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser
    130                 135                 140
Ser Gln Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
145                 150                 155                 160
Ser Gln Ser Leu Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp
                165                 170                 175
Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala
            180                 185                 190
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser
        195                 200                 205
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
    210                 215                 220
Ala Asp Tyr Tyr Cys Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly
225                 230                 235                 240
Ser Gly Thr Lys Leu Glu Ile Lys Leu Glu Pro Lys Ser Ser Asp Lys
                245                 250                 255
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
            260                 265                 270
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
```

290 295 300
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305 310 315 320
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
325 330 335
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala
340 345 350
Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
355 360 365
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
370 375 380
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385 390 395 400
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
405 410 415
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
420 425 430
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
435 440 445
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
450 455 460
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465 470 475 480

<210> 240
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding anti-mouse CD86 (GL1)
heavy chain

<400> 240
gaggtgcagc tggtggagtc tgctggaggt ttagtgcagc ctggaaggtc cctaaaactc 60
tcctgtgcag cctcaggatt cactttcagt gactattaca tggcctgggt ccgccaggct 120
ccaacgaagg ggctggagtg ggtcgcaacc attagtcatg acggtagtag tacttactat 180
cgagactccg tgaagggccg attcacaatc tccagagata atgcaaaaac catcctatac 240
ctgcaaatgg acagtctgag gtctgaggac acggccactt atttctgtgc aagacagaat 300
attatggatt attggggcca aggagtcatg gtcacagtct cctca 345

<210> 241
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) heavy chain

<400> 241
Glu Val Gln Leu Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr
65 70 75 80
Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95
Ala Arg Gln Asn Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr
100 105 110
Val Ser Ser
115

<210> 242
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding Anti-mouse CD86 (GL1)
light chain

<400> 242
gacattgtga tgacccagac tccatcctcc caggctgtgt cagcagggga gaaggtcact 60
atgagctgca agtccagtca gagtcttttg tacagtagag accagagtaa ctacttggcc 120
tggtaccagc agaaacctgg gcagtctcct aaactactta tctacttggc atccactagg 180
gaatcagggg tccctgatcg cttcataggc agtggctctg ggacagactt cactctgacc 240
atcagcagtg tgcaggctga agatctggca gattattact gtcagcagca ttacaactat 300
ccgctcacgt tcggttctgg gaccaagcta gaaatcaaa 339

<210> 243
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) light chain

<400> 243
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1 5 10 15
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30
Arg Asp Gln Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45
Ser Pro Lys Leu Leu Ile Tyr Leu Ala Ser Thr Arg Glu Ser Gly Val
50 55 60
Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Tyr Cys Gln Gln
85 90 95
His Tyr Asn Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
100 105 110
Lys

<210> 244
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) scFv linker

<400> 244
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15
Gly Gly Gly Ser
20

<210> 245
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) HCDR1

<400> 245
Asp Tyr Tyr Met Ala
 1   5

<210> 246
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) HCDR2

<400> 246
Thr Ile Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val Lys
 1   5   10   15
Gly

<210> 247
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) HCDR3

<400> 247
Gln Asn Ile Met Asp Tyr
 1   5

<210> 248
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) LCDR1

<400> 248
Lys Ser Ser Gln Ser Leu Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu
 1   5   10   15
Ala

<210> 249
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) LCDR2

<400> 249
Leu Ala Ser Thr Arg Glu Ser
 1   5

<210> 250
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-mouse CD86 (GL1) LCDR3

<400> 250
Gln Gln His Tyr Asn Tyr Pro Leu Thr
 1   5

<210> 251
<211> 1983
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding mouse anti-CD86::IL10
      fusion protein

<400> 251
gaggtgcagc tggtggagtc tgctggaggt ttagtgcagc ctggaaggtc cctaaaactc 60
tcctgtgcag cctcaggatt cactttcagt gactattaca tggcctgggt ccgccaggct 120
ccaacgaagg ggctggagtg ggtcgcaacc attagtcatg acggtagtag tacttactat 180
cgagactccg tgaagggccg attcacaatc tccagagata atgcaaaaac catcctatac 240
ctgcaaatgg acagtctgag gtctgaggac acggccactt atttctgtgc aagacagaat 300
attatggatt attggggcca aggagtcatg gtcacagtct cctcaggggg tggaggctct 360
ggtggcggtg gctctggcgg aggtggatcc ggtggcggcg gatctgacat tgtgatgacc 420
cagactccat cctcccaggc tgtgtcagca ggggagaagg tcactatgag ctgcaagtcc 480
agtcagagtc ttttgtacag tagagaccag agtaactact tggcctggta ccagcagaaa 540
cctgggcagt ctcctaaact acttatctac ttggcatcca ctagggaatc aggggtccct 600
gatcgcttca taggcagtgg ctctgggaca gacttcactc tgaccatcag cagtgtgcag 660
gctgaagatc tggcagatta ttactgtcag cagcattaca actatccgct cacgttcggt 720
tctgggacca agctagaaat caaactcgag cccaaatctt ctgacaaaac tcacacatgc 780
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt ccccccaaaa 840
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 900
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 960
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1020
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 1080
gccctcccag ccccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1140
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1200
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 1260
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tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1380
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ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 1860
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 1920
agtgagtttg acatcttcat caactacata gaagcctaca tgacaatgaa gatacgaaac 1980
taa   1983

<210> 252
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse anti-CD86::IL10 fusion protein

<400> 252
Glu Val Gln Leu Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg
 1   5   10   15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30
Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
        35   40   45
Ala Thr Ile Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
    50   55   60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr
65                  70                  75                  80
Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95
Ala Arg Gln Asn Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr
            100                 105                 110
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser
    130                 135                 140
Ser Gln Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
145                 150                 155                 160
Ser Gln Ser Leu Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp
                165                 170                 175
Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala
            180                 185                 190
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser
        195                 200                 205
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
    210                 215                 220
Ala Asp Tyr Tyr Cys Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly
225                 230                 235                 240
Ser Gly Thr Lys Leu Glu Ile Lys Leu Glu Pro Lys Ser Ser Asp Lys
                245                 250                 255
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
            260                 265                 270
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala
            340                 345                 350
Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480
Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
                485                 490                 495
Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys
            500                 505                 510
Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp
        515                 520                 525
Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp
    530                 535                 540
Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu
545                 550                 555                 560
Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val
                565                 570                 575
Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn
            580                 585                 590
Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys
        595                 600                 605
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His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val
    610                 615                 620
Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met
625                 630                 635                 640
Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met
                645                 650                 655
Lys Ile Arg Asn
            660
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<210> 253
<211> 2013
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10::humanized Fun1 M0115 fusion protein

<400> 253

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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
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gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
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gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
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gacgacacgg ccgtgtatta ctgtgcgaga tgggactata ggtacgacga cgggagggct 1560
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<210> 254
<211> 670
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10::humanized Fun1 M0115 fusion protein

<400> 254

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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
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Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
385                 390                 395                 400
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu
                405                 410                 415
Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
            420                 425                 430
Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met Asn Trp
        435                 440                 445
Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Asn Ile Asp
    450                 455                 460
Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Arg Val
465                 470                 475                 480
Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser
                485                 490                 495
Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Asp
            500                 505                 510
Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly
        515                 520                 525
Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    530                 535                 540
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
545                 550                 555                 560
Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala
                565                 570                 575
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Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln
580 585 590
Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys
595 600 605
Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
610 615 620
Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
625 630 635 640
Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr
645 650 655
Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
660 665 670

<210> 255
<211> 1983
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10::anti-mouse CD86
fusion protein

<400> 255
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
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gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
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cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
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cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
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tgtcagcagc attacaacta tccgctcacg ttcggttctg ggaccaagct agaaatcaaa 1980
taa 1983

<210> 256
<211> 660
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10::anti-mouse CD86 fusion protein

<400> 256

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            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val
385                 390                 395                 400
Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Glu Val Gln Leu
                405                 410                 415
Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu
            420                 425                 430
Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ala Trp
        435                 440                 445
Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val Ala Thr Ile Ser
    450                 455                 460
His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val Lys Gly Arg Phe
465                 470                 475                 480
Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr Leu Gln Met Asp
                485                 490                 495
Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gln Asn
            500                 505                 510
Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly
        515                 520                 525
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    530                 535                 540
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Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val
545                 550                 555                 560
Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu
                565                 570                 575
Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
            580                 585                 590
Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala Ser Thr Arg Glu
        595                 600                 605
Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe
    610                 615                 620
Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Tyr
625                 630                 635                 640
Cys Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys
                645                 650                 655
Leu Glu Ile Lys
            660
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<210> 257
<211> 2016
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::humanized
Fun1 M0115 fusion protein with H75 linker

<400> 257

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cagcagaaac caggacagcc tcctaagctg ctcatttact gggcatctac ccgggaatcc 1860
ggggtccctg accgattcag tggcagcggg tctgggacag atttcactct caccatcagc 1920
agcctgcagg ctgaagatgt ggcagtttat tactgtcatc aatacctcta ctcgtggacg 1980
tttggccagg ggaccaagct ggagatcaaa cggtaa                           2016
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<210> 258
<211> 671
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A::humanized Fun1 M0115 fusion protein
with H75 linker

<400> 258

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Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu
385                 390                 395                 400
Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser Gln Val Gln
                405                 410                 415
Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys
            420                 425                 430
Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met Asn
        435                 440                 445
Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Asn Ile
    450                 455                 460
Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Arg
465                 470                 475                 480
Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu
                485                 490                 495
Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp
```

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                500                 505                 510
Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp
        515                 520                 525
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    530                 535                 540
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
545                 550                 555                 560
Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg
                565                 570                 575
Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn
            580                 585                 590
Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        595                 600                 605
Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp
    610                 615                 620
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
625                 630                 635                 640
Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Leu
                645                 650                 655
Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            660                 665                 670
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<210> 259
<211> 1986
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::anti-mouse CD86 fusion protein with H75 linker

<400> 259

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agcccaggcc agggcaccca gtctgagaac agctgcaccc acttcccagg caacctgcct 60
aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggtcaga ggcacaacaa ttcttccctg 1200
aatacaggaa ctcagatggc aggtcattct ccgaattctg aggtgcagct ggtggagtct 1260
gctggaggtt tagtgcagcc tggaaggtcc ctaaaactct cctgtgcagc ctcaggattc 1320
actttcagtg actattacat ggcctgggtc cgccaggctc caacgaaggg gctggagtgg 1380
gtcgcaacca ttagtcatga cggtagtagt acttactatc gagactccgt gaagggccga 1440
ttcacaatct ccagagataa tgcaaaaacc atcctatacc tgcaaatgga cagtctgagg 1500
tctgaggaca cggccactta tttctgtgca agacagaata ttatggatta ttggggccaa 1560
ggagtcatgg tcacagtctc ctcaggggt ggaggctctg gtggcggtgg ctctggcgga 1620
ggtggatccg gtggcggcgg atctgacatt gtgatgaccc agactccatc ctcccaggct 1680
gtgtcagcag gggagaaggt cactatgagc tgcaagtcca gtcagagtct tttgtacagt 1740
agagaccaga gtaactactt ggcctggtac cagcagaaac ctgggcagtc tcctaaacta 1800
cttatctact tggcatccac tagggaatca ggggtccctg atcgcttcat aggcagtggc 1860
tctgggacag acttcactct gaccatcagc agtgtgcagg ctgaagatct ggcagattat 1920
tactgtcagc agcattacaa ctatccgctc acgttcggtt ctgggaccaa gctagaaatc 1980
aaataa                                                          1986
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<210> 260
<211> 661
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A::anti-mouse CD86 fusion protein with H75 linker

<400> 260

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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu
385                 390                 395                 400
Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser Glu Val Gln
                405                 410                 415
Leu Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys
            420                 425                 430
Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ala
        435                 440                 445
Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val Ala Thr Ile
    450                 455                 460
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Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val Lys Gly Arg
465 470 475 480
Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr Leu Gln Met
485 490 495
Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gln
500 505 510
Asn Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser
515 520 525
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
530 535 540
Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala
545 550 555 560
Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
565 570 575
Leu Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp Tyr Gln Gln
580 585 590
Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala Ser Thr Arg
595 600 605
Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp
610 615 620
Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr
625 630 635 640
Tyr Cys Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly Ser Gly Thr
645 650 655
Lys Leu Glu Ile Lys
660

<210> 261
<211> 1614
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::IL10 I87A
fusion protein with H75 linker

<400> 261
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tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacagg aactcagatg gcaggtcatt ctccgaattc tagcccaggc 1140
cagggcaccc agtctgagaa cagctgcacc cacttcccag gcaacctgcc taacatgctt 1200
cgagatctcc gagatgcctt cagcagagtg aagactttct ttcaaatgaa ggatcagctg 1260
gacaacttgt tgttaaagga gtccttgctg gaggacttta agggttacct gggttgccaa 1320
gccttgtctg agatgatcca gttttacctg gaggaggtga tgccccaagc tgagaaccaa 1380
gacccagacg ccaaggcgca tgtgaactcc ctgggggaga acctgaagac cctcaggctg 1440
aggctacggc gctgtcatcg atttcttccc tgtgaaaaca agagcaaggc cgtggagcag 1500
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1560
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1614

<210> 262
<211> 537

<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::IL10 I87A fusion protein with H75 linker

<400> 262
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225   230   235   240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245   250   255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260   265   270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290   295   300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305   310   315   320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325   330   335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340   345   350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr
        355   360   365
Gln Met Ala Gly His Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln
    370   375   380
Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu
385   390   395   400
Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met
                405   410   415
Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp
            420   425   430
Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe
        435   440   445
Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ala
    450   455   460
Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu
465   470   475   480
Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys

485 490 495
Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly
500 505 510
Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu
515 520 525
Ala Tyr Met Thr Met Lys Ile Arg Asn
530 535

<210> 263
<211> 1380
<212> DNA
<213> Artificial Sequence

<220>
<223> Lymphotoxin beta receptor (LTBetaR) - Ig
synthesized molecule

<400> 263
atgctcctgc cttgggccac ctctgccccc ggcctggcct gggggcctct ggtgctgggc 60
ctcttcgggc tcctggcagc atcgcagccc caggcggtgc ctccatatgc gtcggagaac 120
cagacctgca gggaccagga aaaggaatac tatgagcccc agcaccgcat ctgctgctcc 180
cgctgcccgc caggcaccta tgtctcagct aaatgtagcc gcatccggga cacagtttgt 240
gccacatgtg ccgagaactc ctacaacgag cactggaact acctgaccat ctgccagctg 300
tgccgccccc gtgacccagt gatgggccta gaggagattg ccccctgcac aagcaaacgg 360
aagacccagt gccgctgcca gccgggaatg ttctgtgctg cctgggccct agagtgcaca 420
cactgcgagc tactttctga ctgcccgcct ggcactgaag ccgagctcaa agatgaagtt 480
gggaagggta acaaccactg cgtcccctgc aaggcagggc acttccagaa tacctcctcc 540
cccagcgccc gctgccagcc ccacaccagg tgtgagaacc aaggtctggt ggaggcagct 600
ccaggcactg cccagtccga cacaacctgc aaaaatccat tagagccact gcccccagag 660
atgtcaggaa ccatgctgat gctcgagccc aaatcttctg acaaaactca cacatgccca 720
ccgtgcccag cacctgaagc cgcgggtgca ccgtcagtct tcctcttccc cccaaaaccc 780
aaggacaccc tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc 840
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 900
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 960
gtcctgcacc aggactggct gaatggcaag gcgtacgcgt gcgcggtctc caacaaagcc 1020
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1080
gtgtacaccc tgccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 1140
ctggtcaaag gcttctatcc aagcgacatc gccgtggagt gggagagcaa tgggcagccg 1200
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1260
agcaagctca ccgtggacaa gagccggtgg cagcagggga acgtcttctc atgctccgtg 1320
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggttaa 1380

<210> 264
<211> 459
<212> PRT
<213> Artificial Sequence

<220>
<223> Lymphotoxin beta receptor (LTBetaR) - Ig
synthesized molecule

<400> 264
Met Leu Leu Pro Trp Ala Thr Ser Ala Pro Gly Leu Ala Trp Gly Pro
1 5 10 15
Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
20 25 30
Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
35 40 45
Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
50 55 60
Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65 70 75 80
Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
85 90 95
Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
100 105 110

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Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
        115                 120                 125
Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
    130                 135                 140
Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145                 150                 155                 160
Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
                165                 170                 175
Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
            180                 185                 190
Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
        195                 200                 205
Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Thr
    210                 215                 220
Met Leu Met Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
225                 230                 235                 240
Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe
                245                 250                 255
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
            260                 265                 270
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
        275                 280                 285
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
    290                 295                 300
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
305                 310                 315                 320
Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val
                325                 330                 335
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
            340                 345                 350
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
        355                 360                 365
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
    370                 375                 380
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385                 390                 395                 400
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
                405                 410                 415
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
            420                 425                 430
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
        435                 440                 445
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
    450                 455
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<210> 265
<211> 2217
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding LTBetaR::M0115 fusion protein

<400> 265
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atgctcctgc cttgggccac ctctgccccc ggcctggcct gggggcctct ggtgctgggc 60
ctcttcgggc tcctggcagc atcgcagccc caggcggtgc ctccatatgc gtcggagaac 120
cagacctgca gggaccagga aaaggaatac tatgagcccc agcaccgcat ctgctgctcc 180
cgctgcccgc caggcaccta tgtctcagct aaatgtagcc gcatccggga cacagtttgt 240
gccacatgtg ccgagaactc ctacaacgag cactggaact acctgaccat ctgccagctg 300
tgccgccccc gtgacccagt gatgggccta gaggagattg ccccctgcac aagcaaacgg 360
aagacccagt gccgctgcca gccgggaatg ttctgtgctg cctgggcccc agagtgcaca 420
cactgcgagc tactttctga ctgcccgcct ggcactgaag ccgagctcaa agatgaagtt 480
gggaagggta acaaccactg cgtcccctgc aaggcagggc acttccagaa tacctcctcc 540
cccagcgccc gctgccagcc ccacaccagg tgtgagaacc aaggtctggt ggaggcagct 600
ccaggcactg cccagtccga cacaacctgc aaaaatccat tagagccact gccccagag 660
atgtcaggaa ccatgctgat gctcgagccc aaatcttctg acaaaactca cacatgccca 720
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ccgtgcccag cacctgaagc cgcgggtgca ccgtcagtct tcctcttccc cccaaaaccc 780
aaggacaccc tcatgatctc ccggaccccc gaggtcacat gcgtggtggt ggacgtgagc 840
cacgaagacc ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 900
aagacaaagc cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc 960
gtcctgcacc aggactggct gaatggcaag gcgtacgcgt gcgcggtctc caacaaagcc 1020
ctcccagccc ccatcgagaa aaccatctcc aaagccaaag ggcagccccg agaaccacag 1080
gtgtacaccc tgcccccatc ccgggatgag ctgaccaaga accaggtcag cctgacctgc 1140
ctggtcaaag gcttctatcc aagcgacatc gccgtggagt gggagagcaa tgggcagccg 1200
gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac 1260
agcaagctca ccgtggacaa gagcaggtgg cagcagggga acgtcttctc atgctccgtg 1320
atgcatgagg ctctgcacaa ccactacacg cagaagagcc tctccctgtc tccgggtcag 1380
aggcacaaca attcttccct gaatacagga actcagatgg caggtcattc tccgaattct 1440
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 1500
tcctgcaagg cttctggata caccttcacc gactacaaca tgaactgggt gcgacaggcc 1560
cctggacaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 1620
aatcagaagt tcaagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 1680
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagatgggac 1740
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 1800
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 1860
ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 1920
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 1980
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 2040
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 2100
gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 2160
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<210> 266
<211> 738
<212> PRT
<213> Artificial Sequence

<220>
<223> LTBetaR::M0115 fusion protein

<400> 266
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Leu Val Leu Gly Leu Phe Gly Leu Leu Ala Ala Ser Gln Pro Gln Ala
            20   25   30
Val Pro Pro Tyr Ala Ser Glu Asn Gln Thr Cys Arg Asp Gln Glu Lys
        35   40   45
Glu Tyr Tyr Glu Pro Gln His Arg Ile Cys Cys Ser Arg Cys Pro Pro
    50   55   60
Gly Thr Tyr Val Ser Ala Lys Cys Ser Arg Ile Arg Asp Thr Val Cys
65   70   75   80
Ala Thr Cys Ala Glu Asn Ser Tyr Asn Glu His Trp Asn Tyr Leu Thr
                85   90   95
Ile Cys Gln Leu Cys Arg Pro Cys Asp Pro Val Met Gly Leu Glu Glu
            100   105   110
Ile Ala Pro Cys Thr Ser Lys Arg Lys Thr Gln Cys Arg Cys Gln Pro
        115   120   125
Gly Met Phe Cys Ala Ala Trp Ala Leu Glu Cys Thr His Cys Glu Leu
    130   135   140
Leu Ser Asp Cys Pro Pro Gly Thr Glu Ala Glu Leu Lys Asp Glu Val
145   150   155   160
Gly Lys Gly Asn Asn His Cys Val Pro Cys Lys Ala Gly His Phe Gln
                165   170   175
Asn Thr Ser Ser Pro Ser Ala Arg Cys Gln Pro His Thr Arg Cys Glu
            180   185   190
Asn Gln Gly Leu Val Glu Ala Ala Pro Gly Thr Ala Gln Ser Asp Thr
        195   200   205
Thr Cys Lys Asn Pro Leu Glu Pro Leu Pro Pro Glu Met Ser Gly Thr
    210   215   220
Met Leu Met Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro
225   230   235   240
Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe
                245   250   255
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

260 265 270
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
275 280 285
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
290 295 300
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
305 310 315 320
Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val
325 330 335
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
340 345 350
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
355 360 365
Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
370 375 380
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
385 390 395 400
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
405 410 415
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
420 425 430
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
435 440 445
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn
450 455 460
Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser
465 470 475 480
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
485 490 495
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
500 505 510
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
515 520 525
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
530 535 540
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
545 550 555 560
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
565 570 575
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
580 585 590
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
595 600 605
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
610 615 620
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
625 630 635 640
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
645 650 655
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
660 665 670
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
675 680 685
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
690 695 700
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
705 710 715 720
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
725 730 735
Lys Arg

<210> 267
<211> 1359
<212> DNA
<213> Artificial Sequence

<220>
<223> PDL1 Ig synthesized molecule

<400> 267
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gaatgcaaat tcccagtaga aaaacaatta gacctggctg cactaattgt ctattgggaa 120
atggaggata agaacattat tcaatttgtg catggagagg aagacctgaa ggttcagcat 180
agtagctaca gacagagggc ccggctgttg aaggaccagc tctccctggg aaatgctgca 240
cttcagatca cagatgtgaa attgcaggat gcaggggtgt accgctgcat gatcagctat 300
ggtggtgccg actacaagcg aattactgtg aaagtcaatg ccccatacaa caaaatcaac 360
caaagaattt tggttgtgga tccagtcacc tctgaacatg aactgacatg tcaggctgag 420
ggctacccca aggccgaagt catctggaca agcagtgacc atcaagtcct gagtggtaag 480
accaccacca ccaattccaa gagagaggag aagcttttca atgtgaccag cacactgaga 540
atcaacacaa caactaatga gattttctac tgcactttta ggagattaga tcctgaggaa 600
aaccatacag ctgaattggt catcccagaa ctacctctgg cacatcctcc aaatgaaagg 660
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 720
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 780
cggaccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 840
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 900
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 960
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 1020
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 1080
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 1140
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1200
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1260
agccggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1320
cactacacgc agaagagcct ctccctgtct ccgggttaa 1359

<210> 268
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> PDL1 Ig synthesized molecule

<400> 268
Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr Gly Ser
 1   5   10   15
Asn Met Thr Ile Glu Cys Lys Phe Pro Val Glu Lys Gln Leu Asp Leu
            20   25   30
Ala Ala Leu Ile Val Tyr Trp Glu Met Glu Asp Lys Asn Ile Ile Gln
        35   40   45
Phe Val His Gly Glu Glu Asp Leu Lys Val Gln His Ser Ser Tyr Arg
    50   55   60
Gln Arg Ala Arg Leu Leu Lys Asp Gln Leu Ser Leu Gly Asn Ala Ala
65   70   75   80
Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr Arg Cys
                85   90   95
Met Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Val Lys Val
            100   105   110
Asn Ala Pro Tyr Asn Lys Ile Asn Gln Arg Ile Leu Val Val Asp Pro
        115   120   125
Val Thr Ser Glu His Glu Leu Thr Cys Gln Ala Glu Gly Tyr Pro Lys
    130   135   140
Ala Glu Val Ile Trp Thr Ser Ser Asp His Gln Val Leu Ser Gly Lys
145   150   155   160
Thr Thr Thr Thr Asn Ser Lys Arg Glu Glu Lys Leu Phe Asn Val Thr
                165   170   175
Ser Thr Leu Arg Ile Asn Thr Thr Thr Asn Glu Ile Phe Tyr Cys Thr
            180   185   190
Phe Arg Arg Leu Asp Pro Glu Glu Asn His Thr Ala Glu Leu Val Ile
        195   200   205
Pro Glu Leu Pro Leu Ala His Pro Pro Asn Glu Arg Leu Glu Pro Lys
    210   215   220
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
225   230   235   240
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr

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                245                 250                 255
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        355                 360                 365
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445
Leu Ser Pro Gly
    450
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<210> 269
<211> 1302
<212> DNA
<213> Artificial Sequence

<220>
<223> PDL2 Ig synthesized molecule

<400> 269
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caaaaggtgg aaaatgatac atccccacac cgtgaaagag ccactttgct ggaggagcag 180
ctgcccttag ggaaggcctc gttccacata cctcaagtcc aagtgaggga cgaaggacag 240
taccaatgca taatcatcta tggggtcgcc tgggactaca agtacctgac tctgaaagtc 300
aaagcttcct acaggaaaat aaacactcac atcctaaagg ttccagaaac agatgaggta 360
gagctcacct gccaggctac aggttatcct ctggcagaag tatcctggcc aaacgtcagc 420
gttcctgcca acaccagcca ctccaggacc cctgaaggcc tctaccaggt caccagtgtt 480
ctgcgcctaa agccaccccc tggcagaaac ttcagctgtg tgttctggaa tactcacgtg 540
agggaactta ctttggccag cattgacctt caaagtcaga tggaacccag gacccatcca 600
actctcgagc ccaaatcttc tgacaaaact cacacatgcc caccgtgccc agcacctgaa 660
gccgcgggtg caccgtcagt cttcctcttc cccccaaaac ccaaggacac cctcatgatc 720
tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 780
aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 840
gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg 900
ctgaatggca aggcgtacgc gtgcgcggtc tccaacaaag ccctcccagc ccccatcgag 960
aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca 1020
tcccgggatg agctgaccaa gaaccaggtc agcctgacct gcctggtcaa aggcttctat 1080
ccaagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc 1140
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac 1200
aagagccggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac 1260
aaccactaca cgcagaagag cctctccctg tctccgggtt aa                    1302
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<210> 270
<211> 433
<212> PRT
<213> Artificial Sequence

<220>
<223> PDL2 Ig synthesized molecule

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

<210> 271
<211> 534
<212> DNA
<213> Artificial Sequence

<220>
<223> (GITR-L)-AFH synthesized molecule

<400> 271
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tggcacgaag attacaagga tgacgacgat aaggattaca aggatgacga cgataaggat 120
tacaaggatg acgacgataa gctcgagcaa ttagagactg ctaaggagcc ctgtatggct 180
aagtttggac cattaccctc aaaatggcaa atggcatctt ctgaacctcc ttgcgtgaat 240
aaggtgtctg actggaagct ggagatactt cagaatggct tatatttaat ttatggccaa 300
gtggctccca atgcaaacta caatgatgta gctccttttg aggtgcggct gtataaaaac 360
aaagacatga tacaaactct aacaaacaaa tctaaaatcc aaaatgtagg agggacttat 420
gaattgcatg ttggggacac catagacttg atattcaact ctgagcatca ggttctaaaa 480
aataatacat actggggtat cattttacta gcaaatcccc aattcatctc ctaa 534

<210> 272
<211> 177
<212> PRT
<213> Artificial Sequence

<220>
<223> (GITR-L)-AFH synthesized molecule

<400> 272
Ser Gly Ser His His His His His His Leu Asn Asp Ile Phe Glu Ala
 1   5   10   15
Gln Lys Ile Glu Trp His Glu Asp Tyr Lys Asp Asp Asp Asp Lys Asp
            20   25   30
Tyr Lys Asp Asp Asp Asp Lys Asp Tyr Lys Asp Asp Asp Asp Lys Leu
        35   40   45
Glu Gln Leu Glu Thr Ala Lys Glu Pro Cys Met Ala Lys Phe Gly Pro
    50   55   60
Leu Pro Ser Lys Trp Gln Met Ala Ser Ser Glu Pro Pro Cys Val Asn
65   70   75   80
Lys Val Ser Asp Trp Lys Leu Glu Ile Leu Gln Asn Gly Leu Tyr Leu
                85   90   95
Ile Tyr Gly Gln Val Ala Pro Asn Ala Asn Tyr Asn Asp Val Ala Pro
            100   105   110
Phe Glu Val Arg Leu Tyr Lys Asn Lys Asp Met Ile Gln Thr Leu Thr
        115   120   125
Asn Lys Ser Lys Ile Gln Asn Val Gly Gly Thr Tyr Glu Leu His Val
    130   135   140
Gly Asp Thr Ile Asp Leu Ile Phe Asn Ser Glu His Gln Val Leu Lys
145   150   155   160
Asn Asn Thr Tyr Trp Gly Ile Ile Leu Leu Ala Asn Pro Gln Phe Ile
                165   170   175
Ser

<210> 273
<211> 1281
<212> DNA
<213> Artificial Sequence

<220>
<223> mIg LIGHT synthesized molecule

<400> 273
agctccccca gagtgcccat aacacagaac ccctgtcctc cactcaaaga gtgtccccca 60
tgcgcagctc cagacgcagc gggtgcgcca tccgtcttca tcttccctcc aaagatcaag 120
gatgtactca tgatctccct gagccccatg gtcacatgtg tggtggtgga tgtgagcgag 180
gatgacccag acgtccagat cagctggttt gtgaacaacg tggaagtaca cacagctcag 240
acacaaaccc atagagagga ttacaacagt actctccggg tggtcagtgc cctccccatc 300
cagcaccagg actggatgag tggcaaggcg ttcgcatgcg cggtcaacaa cagagccctc 360
ccatccccca tcgagaaaac catctcaaaa cccagagggc cagtaagagc tccacaggta 420
tatgtcttgc ctccaccagc agaagagatg actaagaaag agttcagtct gacctgcatg 480
atcacaggct tcttacctgc cgaaattgct gtggactgga ccagcaatgg gcgtacagag 540
caaaactaca agaacaccgc aacagtcctg gactctgatg gttcttactt catgtacagc 600
aagctcagag tacaaaagag cacttgggaa agaggaagtc ttttcgcctg ctcagtggtc 660
cacgagggtc tgcacaatca ccttacgact aagaccatct cccggtctct gggtaaaaac 720
tcattattca accaagaagt tcaaattccc ttgaccgaaa gttacagccc gaattctgac 780

ggacctgcag gctcctggga gcagctgata caagagcgaa ggtctcacga ggtcaaccca 840
gcagcgcatc tcacaggggc caactccagc ttgaccggca gcgggggcc gctgttatgg 900
gagactcagc tgggcctggc cttcctgagg ggcctcagct accacgatgg ggcccttgtg 960
gtcaccaaag ctggctacta ctacatctac tccaaggtgc agctgggcgg tgtgggctgc 1020
ccgctgggcc tggccagcac catcacccac ggcctctaca agcgcacacc ccgctacccc 1080
gaggagctgg agctgttggt cagccagcag tcaccctgcg gacgggccac cagcagctcc 1140
cgggtctggt gggacagcag cttcctgggt ggtgtggtac acctggaggc tggggagaag 1200
gtggtcgtcc gtgtgctgga tgaacgcctg gttcgactgc gtgatggtac ccggtcttac 1260
ttcggggctt tcatggtgta g 1281

<210> 274
<211> 426
<212> PRT
<213> Artificial Sequence

<220>
<223> mIg LIGHT synthesized molecule

<400> 274

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

385 390 395 400
Val Val Val Arg Val Leu Asp Glu Arg Leu Val Arg Leu Arg Asp Gly
405 410 415
Thr Arg Ser Tyr Phe Gly Ala Phe Met Val
420 425

<210> 275
<211> 2022
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding monoIL10-A2
hinge::M0115 fusion protein with H75 linker

<400> 275
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aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacgg tggtggatcc 360
ggcggtaaga gcaaggccgt ggagcaggtg aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaacct cgagccccca cctcccccat gcccaccgtg cccagcacct 540
gaagccgcgg gtgcaccgtc agtcttcctc ttcccccccaa aacccaagga caccctcatg 600
atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 660
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 720
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 780
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agcccccatc 840
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 900
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 960
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1020
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1080
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1140
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtcagaggca caacaattct 1200
tccctgaata caggaactca gatggcaggt cattctccga attctcaggt gcagctggtg 1260
cagtctgggg ctgaggtgaa gaagcctggg gcctcagtga aggtctcctg caaggcttct 1320
ggatacacct tcaccgacta caacatgaac tgggtgcgac aggcccctgg acaagggctt 1380
gagtggatgg gaaatattga tccttactat ggtggtacta gttacaatca gaagttcaag 1440
ggcagggtca ccatgaccag ggacacgtcc atcagcacag cctacatgga gctgagcagg 1500
ctgagatctg acgacacggc cgtgtattac tgtgcgagat gggactatag gtacgacgac 1560
gggagggctt actatgttat ggacttctgg ggccaaggga ccacggtcac cgtctcctca 1620
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gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 1740
atcaactgca agtccagcca gagtgtttta tacagctcca accagaagaa ctacttagct 1800
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctacccgg 1860
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 1920
atcagcagcc tgcaggctga agatgtggca gtttattact gtcatcaata cctctactcg 1980
tggacgtttg gccaggggac caagctggag atcaaacggt aa 2022

<210> 276
<211> 673
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10-A2 hinge::M0115 fusion protein with H75
linker

<400> 276
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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45

Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115 120 125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130 135 140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145 150 155 160
Thr Met Lys Ile Arg Asn Leu Glu Pro Pro Pro Pro Pro Cys Pro Pro
165 170 175
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
180 185 190
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
195 200 205
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
210 215 220
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
225 230 235 240
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
245 250 255
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
260 265 270
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
275 280 285
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
290 295 300
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
305 310 315 320
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
325 330 335
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
340 345 350
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
355 360 365
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
370 375 380
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn Ser
385 390 395 400
Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser Gln
405 410 415
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser
420 425 430
Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn
435 440 445
Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly
450 455 460
Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys
465 470 475 480
Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met
485 490 495
Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
500 505 510
Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp
515 520 525
Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
530 535 540
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
545 550 555 560
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
565 570 575
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
580 585 590

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Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        595                 600                 605
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    610                 615                 620
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
625                 630                 635                 640
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln
                645                 650                 655
Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            660                 665                 670
Arg
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<210> 277
<211> 1185
<212> DNA
<213> Artificial Sequence

<220>
<223> HVEM Ig synthesized molecule

<400> 277
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ccaggttatc gtgtgaagga ggcctgcggg gagctgacgg gcacagtgtg tgaaccctgc 120
cctccaggca cctacattgc ccacctcaat ggcctaagca agtgtctgca gtgccaaatg 180
tgtgacccag ccatgggcct gcgcgcgagc cggaactgct ccaggacaga gaacgccgtg 240
tgtggctgca gcccaggcca cttctgcatc gtccaggacg gggaccactg cgccgcgtgc 300
cgcgcttacg ccacctccag cccgggccag agggtgcaga agggaggcac cgagagtcag 360
gacaccctgt gtcagaactg ccccccgggg accttctctc ccaatgggac cctggaggaa 420
tgtcagcacc agaccaagtg cagctggctg gtgacgaagg ccggagctgg gaccagcagc 480
tcccacctcg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct 540
gaagccgcgg gtgcaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg 600
atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag 660
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg 720
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac 780
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agcccccatc 840
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc 900
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc 960
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag 1020
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg 1080
gacaagagcc ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg 1140
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gttaa   1185

<210> 278
<211> 394
<212> PRT
<213> Artificial Sequence

<220>
<223> HVEM Ig synthesized molecule

<400> 278
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Pro Lys Cys Ser Pro Gly Tyr Arg Val Lys Glu Ala Cys Gly Glu Leu
            20                  25                  30
Thr Gly Thr Val Cys Glu Pro Cys Pro Pro Gly Thr Tyr Ile Ala His
        35                  40                  45
Leu Asn Gly Leu Ser Lys Cys Leu Gln Cys Gln Met Cys Asp Pro Ala
    50                  55                  60
Met Gly Leu Arg Ala Ser Arg Asn Cys Ser Arg Thr Glu Asn Ala Val
65                  70                  75                  80
Cys Gly Cys Ser Pro Gly His Phe Cys Ile Val Gln Asp Gly Asp His
                85                  90                  95
Cys Ala Ala Cys Arg Ala Tyr Ala Thr Ser Ser Pro Gly Gln Arg Val
            100                 105                 110
Gln Lys Gly Gly Thr Glu Ser Gln Asp Thr Leu Cys Gln Asn Cys Pro
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        115                 120                 125
Pro Gly Thr Phe Ser Pro Asn Gly Thr Leu Glu Glu Cys Gln His Gln
    130                 135                 140
Thr Lys Cys Ser Trp Leu Val Thr Lys Ala Gly Ala Gly Thr Ser Ser
145                 150                 155                 160
Ser His Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
                165                 170                 175
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
            180                 185                 190
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        195                 200                 205
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    210                 215                 220
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
225                 230                 235                 240
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                245                 250                 255
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
            260                 265                 270
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        275                 280                 285
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
    290                 295                 300
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
305                 310                 315                 320
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                325                 330                 335
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            340                 345                 350
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        355                 360                 365
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    370                 375                 380
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
385                 390
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<210> 279
<211> 1179
<212> DNA
<213> Artificial Sequence

<220>
<223> IL10-Fc synthesized molecule

<400> 279

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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggaccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agccggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggttaa                          1179
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<210> 280

<211> 392
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10-Fc synthesized molecule

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

<210> 281
<211> 1179
<212> DNA
<213> Artificial Sequence

<220>
<223> IL10 I87A-Fc synthesized molecule

<400> 281
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aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agccggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggttaa 1179

<210> 282
<211> 392
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A-Fc synthesized molecule

<400> 282
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Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145 150 155 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
260 265 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu

290 295 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
370 375 380
Lys Ser Leu Ser Leu Ser Pro Gly
385 390

<210> 283
<211> 1197
<212> DNA
<213> Artificial Sequence

<220>
<223> monoIL10-Fc synthesized molecule

<400> 283
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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacat caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacgg tggtggatcc 360
ggcggtaaga gcaaggccgt ggagcaggtg aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatg 480
acaatgaaga tacgaaacct cgagcccaaa tcttctgaca aaactcacac atgcccaccg 540
tgcccagcac ctgaagccgc gggtgcaccg tcagtcttcc tcttcccccc aaaacccaag 600
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 660
gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 720
acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc 780
ctgcaccagg actggctgaa tggcaaggcg tacgcgtgcg cggtctccaa caaagccctc 840
ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg 900
tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg 960
gtcaaaggct tctatccaag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1020
aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1080
aagctcaccg tggacaagag ccggtggcag caggggaacg tcttctcatg ctccgtgatg 1140
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggttaa 1197

<210> 284
<211> 398
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10-Fc synthesized molecule

<400> 284
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110

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Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
        115                 120                 125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
    130                 135                 140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met
145                 150                 155                 160
Thr Met Lys Ile Arg Asn Leu Glu Pro Lys Ser Ser Asp Lys Thr His
                165                 170                 175
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
            180                 185                 190
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
        195                 200                 205
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    210                 215                 220
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225                 230                 235                 240
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                245                 250                 255
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
            260                 265                 270
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
        275                 280                 285
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    290                 295                 300
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
305                 310                 315                 320
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
                325                 330                 335
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
            340                 345                 350
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
        355                 360                 365
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
    370                 375                 380
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
385                 390                 395
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<210> 285
<211> 1197
<212> DNA
<213> Artificial Sequence

<220>
<223> monoIL10 I87A-Fc synthesized molecule

<400> 285

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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacgg tggtggatcc 360
ggcggtaaga gcaaggccgt ggagcaggtg aagaatgcct ttaataagct ccaagagaaa 420
ggcatctaca aagccatgag tgagtttgac atcttcatca actacataga agcctacatt 480
acaatgaaga tacgaaacct cgagcccaaa tcttctgaca aaactcacac atgcccaccg 540
tgcccagcac ctgaagccgc gggtgcaccg tcagtcttcc tcttcccccc aaaacccaag 600
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac 660
gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag 720
acaaagccgc gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc 780
ctgcaccagg actggctgaa tggcaaggcg tacgcgtgcg cggtctccaa caaagccctc 840
ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg 900
tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg 960
gtcaaaggct tctatccaag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1020
aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc 1080
aagctcaccg tggacaagag ccggtggcag caggggaacg tcttctcatg ctccgtgatg 1140
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<210> 286
<211> 398
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10 I87A-Fc synthesized molecule

<400> 286
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
115 120 125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
130 135 140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile
145 150 155 160
Thr Met Lys Ile Arg Asn Leu Glu Pro Lys Ser Ser Asp Lys Thr His
165 170 175
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val
180 185 190
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
195 200 205
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
210 215 220
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225 230 235 240
Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
245 250 255
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala
260 265 270
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
275 280 285
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
290 295 300
Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
305 310 315 320
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
325 330 335
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
340 345 350
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
355 360 365
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
370 375 380
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
385 390 395

<210> 287
<211> 1239
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc-IL10 synthesized molecule

<400> 287
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ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat 720
acaagaactc agaaagcacg tcattctccg aattctagcc caggccaggg cacccagtct 780
gagaacagct gcacccactt cccaggcaac ctgcctaaca tgcttcgaga tctccgagat 840
gccttcagca gagtgaagac tttctttcaa atgaaggatc agctggacaa cttgttgtta 900
aaggagtcct tgctggagga ctttaagggt tacctgggtt gccaagcctt gtctgagatg 960
atccagtttt acctggagga ggtgatgccc caagctgaga accaagaccc agacatcaag 1020
gcgcatgtga actccctggg ggagaacctg aagaccctca ggctgaggct acggcgctgt 1080
catcgatttc ttccctgtga aaacaagagc aaggccgtgg agcaggtgaa gaatgccttt 1140
aataagctcc aagagaaagg catctacaaa gccatgagtg agtttgacat cttcatcaac 1200
tacatagaag cctacatgac aatgaagata cgaaactaa 1239

<210> 288
<211> 412
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc-IL10 synthesized molecule

<400> 288
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1   5   10   15
Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20   25   30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35   40   45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50   55   60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65   70   75   80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85   90   95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
            100   105   110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115   120   125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130   135   140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145   150   155   160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165   170   175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180   185   190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195   200   205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210   215   220
Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn
225   230   235   240
Thr Arg Thr Gln Lys Ala Arg His Ser Pro Asn Ser Ser Pro Gly Gln
                245   250   255
Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro
            260   265   270
Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe

```
        275                 280                 285
Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu
    290                 295                 300
Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met
305                 310                 315                 320
Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp
                325                 330                 335
Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr
            340                 345                 350
Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn
        355                 360                 365
Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln
    370                 375                 380
Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn
385                 390                 395                 400
Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
                405                 410
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<210> 289
<211> 1236
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc-IL10 I87A synthesized molecule

<400> 289

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acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccgat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctagcccag gccagggcac ccagtctgag 780
aacagctgca cccacttccc aggcaacctg cctaacatgc ttcgagatct ccgagatgcc 840
ttcagcagag tgaagacttt ctttcaaatg aaggatcagc tggacaactt gttgttaaag 900
gagtccttgc tggaggactt taagggttac ctgggttgcc aagccttgtc tgagatgatc 960
cagttttacc tggaggaggt gatgccccaa gctgagaacc aagacccaga cgccaaggcg 1020
catgtgaact ccctggggga gaacctgaag accctcaggc tgaggctacg gcgctgtcat 1080
cgatttcttc cctgtgaaaa caagagcaag gccgtggagc aggtgaagaa tgcctttaat 1140
aagctccaag agaaaggcat ctacaaagcc atgagtgagt ttgacatctt catcaactac 1200
atagaagcct acatgacaat gaagatacga aactaa                          1236
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<210> 290
<211> 411
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc-IL10 I87A synthesized molecule

<400> 290

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

65 70 75 80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
100 105 110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225 230 235 240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly
245 250 255
Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn
260 265 270
Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe
275 280 285
Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu
290 295 300
Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile
305 310 315 320
Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro
325 330 335
Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu
340 345 350
Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys
355 360 365
Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu
370 375 380
Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr
385 390 395 400
Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
405 410

<210> 291
<211> 1254
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc-monoIL10 synthesized molecule

<400> 291
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acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctagcccag gccagggcac ccagtctgag 780
aacagctgca cccacttccc aggcaacctg cctaacatgc ttcgagatct ccgagatgcc 840

ttcagcagag tgaagacttt ctttcaaatg aaggatcagc tggacaactt gttgttaaag 900
gagtccttgc tggaggactt taagggttac ctgggttgcc aagccttgtc tgagatgatc 960
cagttttacc tggaggaggt gatgccccaa gctgagaacc aagacccaga catcaaggcg 1020
catgtgaact ccctggggga gaacctgaag accctcaggc tgaggctacg gcgctgtcat 1080
cgatttcttc cctgtgaaaa cggtggtgga tccggcggta agagcaaggc cgtggagcag 1140
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1200
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1254

<210> 292
<211> 417
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc-monoIL10 synthesized molecule

<400> 292

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1				5					10					15	
Pro	Glu	Ala	Ala	Gly	Ala	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
			20					25					30		
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
		35					40					45			
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val
	50					55					60				
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
65					70					75					80
Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
				85					90					95	
Asp	Trp	Leu	Asn	Gly	Lys	Ala	Tyr	Ala	Cys	Ala	Val	Ser	Asn	Lys	Ala
			100					105					110		
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro
		115					120					125			
Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr
	130					135					140				
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
145					150					155					160
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
				165					170					175	
Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
			180					185					190		
Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
		195					200					205			
Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
	210					215					220				
Ser	Leu	Ser	Leu	Ser	Pro	Gly	Asn	Ser	Leu	Phe	Asn	Gln	Glu	Val	Gln
225					230					235					240
Ile	Pro	Leu	Thr	Glu	Ser	Tyr	Ser	Pro	Asn	Ser	Ser	Pro	Gly	Gln	Gly
				245					250					255	
Thr	Gln	Ser	Glu	Asn	Ser	Cys	Thr	His	Phe	Pro	Gly	Asn	Leu	Pro	Asn
			260					265					270		
Met	Leu	Arg	Asp	Leu	Arg	Asp	Ala	Phe	Ser	Arg	Val	Lys	Thr	Phe	Phe
		275					280					285			
Gln	Met	Lys	Asp	Gln	Leu	Asp	Asn	Leu	Leu	Leu	Lys	Glu	Ser	Leu	Leu
	290					295					300				
Glu	Asp	Phe	Lys	Gly	Tyr	Leu	Gly	Cys	Gln	Ala	Leu	Ser	Glu	Met	Ile
305					310					315					320
Gln	Phe	Tyr	Leu	Glu	Glu	Val	Met	Pro	Gln	Ala	Glu	Asn	Gln	Asp	Pro
				325					330					335	
Asp	Ile	Lys	Ala	His	Val	Asn	Ser	Leu	Gly	Glu	Asn	Leu	Lys	Thr	Leu
			340					345					350		
Arg	Leu	Arg	Leu	Arg	Arg	Cys	His	Arg	Phe	Leu	Pro	Cys	Glu	Asn	Gly
		355					360					365			
Gly	Gly	Ser	Gly	Gly	Lys	Ser	Lys	Ala	Val	Glu	Gln	Val	Lys	Asn	Ala
	370					375					380				
Phe	Asn	Lys	Leu	Gln	Glu	Lys	Gly	Ile	Tyr	Lys	Ala	Met	Ser	Glu	Phe
385					390					395					400
Asp	Ile	Phe	Ile	Asn	Tyr	Ile	Glu	Ala	Tyr	Met	Thr	Met	Lys	Ile	Arg

405 410 415
Asn

<210> 293
<211> 1254
<212> DNA
<213> Artificial Sequence

<220>
<223> Fc-monoIL10 I87A synthesized molecule

<400> 293
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ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctagcccag gccagggcac ccagtctgag 780
aacagctgca cccacttccc aggcaacctg cctaacatgc ttcgagatct ccgagatgcc 840
ttcagcagag tgaagacttt ctttcaaatg aaggatcagc tggacaactt gttgttaaag 900
gagtccttgc tggaggactt taagggttac ctgggttgcc aagccttgtc tgagatgatc 960
cagttttacc tggaggaggt gatgccccaa gctgagaacc aagacccaga cgccaaggcg 1020
catgtgaact ccctgggggа gaacctgaag accctcaggc tgaggctacg gcgctgtcat 1080
cgatttcttc cctgtgaaaa cggtggtgga tccggcggta agagcaaggc cgtggagcag 1140
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1200
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1254

<210> 294
<211> 417
<212> PRT
<213> Artificial Sequence

<220>
<223> Fc-monoIL10 I87A synthesized molecule

<400> 294
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15
Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
100 105 110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr

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            180                 185                 190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225                 230                 235                 240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Ser Pro Gly Gln Gly
                245                 250                 255
Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn
            260                 265                 270
Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe
        275                 280                 285
Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu
    290                 295                 300
Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile
305                 310                 315                 320
Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro
                325                 330                 335
Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu
            340                 345                 350
Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Gly
        355                 360                 365
Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala
    370                 375                 380
Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe
385                 390                 395                 400
Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg
                405                 410                 415
Asn
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<210> 295
<211> 1200
<212> DNA
<213> Artificial Sequence

<220>
<223> mouse IL10-mouse null Fc synthesized molecule

<400> 295

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agcaggggcc agtacagccg ggaagacaat aactgcaccc acttcccagt cggccagagc 60
cacatgctcc tagagctgcg gactgccttc agccaggtga agactttctt tcaaacaaag 120
gaccagctgg acaacatact gctaaccgac tccttaatgc aggactttaa gggttacttg 180
ggttgccaag ccttatcgga aatgatccag ttttacctgg tagaagtgat gccccaggca 240
gagaagcatg gcccagaaat caaggagcat ttgaattccc tgggtgagaa gctgaagacc 300
ctcaggatgc ggctgaggcg ctgtcatcga tttctcccct gtgaaaataa gagcaaggca 360
gtggagcagg tgaagagtga ttttaataag ctccaagacc aaggtgtcta caaggccatg 420
aatgaatttg acatcttcat caactgcata gaagcataca tgatgatcaa aatgaaaagc 480
ctcgagccca gagtgcccat aacacagaac ccctgtcctc cactcaaaga gtgtccccca 540
tgcgcagctc cagacgcagc gggtgcgcca tccgtcttca tcttccctcc aaagatcaag 600
gatgtactca tgatctccct gagccccatg gtcacatgtg tggtggtgga tgtgagcgag 660
gatgacccag acgtccagat cagctggttt gtgaacaacg tggaagtaca cacagctcag 720
acacaaaccc atagagagga ttacaacagt actctccggg tggtcagtgc cctccccatc 780
cagcaccagg actggatgag tggcaaggcg ttcgcatgcg cggtcaacaa cagagccctc 840
ccatccccca tcgagaaaac catctcaaaa cccagagggc cagtaagagc tccacaggta 900
tatgtcttgc ctccaccagc agaagagatg actaagaaag agttcagtct gacctgcatg 960
atcgcaggct tcttacctgc cgaaattgct gtggactgga ccagcaatgg gcgtacagag 1020
caaaactaca agaacaccgc aacagtcctg gactctgatg gttcttactt catgtacagc 1080
aagctcagag tacaaaagag cacttgggaa agaggaagtc ttttcgcctg ctcagtggtc 1140
cacgagggtc tgcacaatca ccttacgact aagaccatct cccggtctct gggtaaataa 1200
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<210> 296
<211> 399
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse IL10-mouse null Fc synthesized molecule

<400> 296
Ser Arg Gly Gln Tyr Ser Arg Glu Asp Asn Asn Cys Thr His Phe Pro
1 5 10 15
Val Gly Gln Ser His Met Leu Leu Glu Leu Arg Thr Ala Phe Ser Gln
20 25 30
Val Lys Thr Phe Phe Gln Thr Lys Asp Gln Leu Asp Asn Ile Leu Leu
35 40 45
Thr Asp Ser Leu Met Gln Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Val Glu Val Met Pro Gln Ala
65 70 75 80
Glu Lys His Gly Pro Glu Ile Lys Glu His Leu Asn Ser Leu Gly Glu
85 90 95
Lys Leu Lys Thr Leu Arg Met Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Ser Asp Phe
115 120 125
Asn Lys Leu Gln Asp Gln Gly Val Tyr Lys Ala Met Asn Glu Phe Asp
130 135 140
Ile Phe Ile Asn Cys Ile Glu Ala Tyr Met Met Ile Lys Met Lys Ser
145 150 155 160
Leu Glu Pro Arg Val Pro Ile Thr Gln Asn Pro Cys Pro Pro Leu Lys
165 170 175
Glu Cys Pro Pro Cys Ala Ala Pro Asp Ala Ala Gly Ala Pro Ser Val
180 185 190
Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser
195 200 205
Pro Met Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp
210 215 220
Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln
225 230 235 240
Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser
245 250 255
Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe Ala
260 265 270
Cys Ala Val Asn Asn Arg Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile
275 280 285
Ser Lys Pro Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val Leu Pro
290 295 300
Pro Pro Ala Glu Glu Met Thr Lys Lys Glu Phe Ser Leu Thr Cys Met
305 310 315 320
Ile Ala Gly Phe Leu Pro Ala Glu Ile Ala Val Asp Trp Thr Ser Asn
325 330 335
Gly Arg Thr Glu Gln Asn Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser
340 345 350
Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr
355 360 365
Trp Glu Arg Gly Ser Leu Phe Ala Cys Ser Val Val His Glu Gly Leu
370 375 380
His Asn His Leu Thr Thr Lys Thr Ile Ser Arg Ser Leu Gly Lys
385 390 395

<210> 297
<211> 1095
<212> DNA
<213> Artificial Sequence

<220>
<223> mouse CTLA4-mouse null2 Fc synthesized molecule

<400> 297
gccatacagg tgacccaacc ttcagtggtg ttggctagca gccatggtgt cgccagcttt 60
ccatgtgaat attcaccatc acacaacact gatgaggtcc gggtgactgt gctgcggcag 120

acaaatgacc aaatgactga ggtctgtgcc acgacattca cagagaagaa tacagtgggc 180
ttcctagatt acccccttctg cagtggtacc tttaatgaaa gcagagtgaa cctcaccatc 240
caaggactga gagctgttga cacgggactg tacctctgca aggtggaact catgtaccca 300
ccgccatact ttgtgggcat gggcaacggg acgcagattt atgtcattga tccagaacca 360
tgcccggatt ctgacctcga gcccagagtg cccataacac agaacccctg tcctccactc 420
aaagagtgtc ccccatgcgc agctccagac gcagcgggtg cgccatccgt cttcatcttc 480
cctccaaaga tcaaggatgt actcatgatc tccctgagcc ccatggtcac atgtgtggtg 540
gtggatgtga gcgaggatga cccagacgtc cagatcagct ggtttgtgaa caacgtggaa 600
gtacacacag ctcagacaca aacccataga gaggattaca acagtactct ccgggtggtc 660
agtgccctcc ccatccagca ccaggactgg atgagtggca aggcgttcgc atgcgcggtc 720
aacaacagag ccctcccatc ccccatcgag aaaaccatct caaaacccag agggccagta 780
agagctccac aggtatatgt cttgcctcca ccagcagaag agatgactaa gaaagagttc 840
agtctgacct gcatgatcgc aggcttctta cctgccgaaa ttgctgtgga ctggaccagc 900
aatgggcgta cagagcaaaa ctacaagaac accgcaacag tcctggactc tgatggttct 960
tacttcatgt acagcaagct cagagtacaa aagagcactt gggaaagagg aagtcttttc 1020
gcctgctcag tggtccacga gggtctgcac aatcacctta cgactaagac catctcccgg 1080
tctctgggta aataa 1095

<210> 298
<211> 364
<212> PRT
<213> Artificial Sequence

<220>
<223> mouse CTLA4-mouse null2 Fc synthesized molecule

<400> 298
Ala Ile Gln Val Thr Gln Pro Ser Val Val Leu Ala Ser Ser His Gly
 1   5   10   15
Val Ala Ser Phe Pro Cys Glu Tyr Ser Pro Ser His Asn Thr Asp Glu
            20   25   30
Val Arg Val Thr Val Leu Arg Gln Thr Asn Asp Gln Met Thr Glu Val
        35   40   45
Cys Ala Thr Thr Phe Thr Glu Lys Asn Thr Val Gly Phe Leu Asp Tyr
    50   55   60
Pro Phe Cys Ser Gly Thr Phe Asn Glu Ser Arg Val Asn Leu Thr Ile
65   70   75   80
Gln Gly Leu Arg Ala Val Asp Thr Gly Leu Tyr Leu Cys Lys Val Glu
                85   90   95
Leu Met Tyr Pro Pro Pro Tyr Phe Val Gly Met Gly Asn Gly Thr Gln
            100   105   110
Ile Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro
        115   120   125
Arg Val Pro Ile Thr Gln Asn Pro Cys Pro Pro Leu Lys Glu Cys Pro
    130   135   140
Pro Cys Ala Ala Pro Asp Ala Ala Gly Ala Pro Ser Val Phe Ile Phe
145   150   155   160
Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val
                165   170   175
Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile
            180   185   190
Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr
        195   200   205
His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro
    210   215   220
Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val
225   230   235   240
Asn Asn Arg Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro
                245   250   255
Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala
            260   265   270
Glu Glu Met Thr Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Ala Gly
        275   280   285
Phe Leu Pro Ala Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr
    290   295   300
Glu Gln Asn Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser
305   310   315   320
Tyr Phe Met Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg

325 330 335
Gly Ser Leu Phe Ala Cys Ser Val Val His Glu Gly Leu His Asn His
340 345 350
Leu Thr Thr Lys Thr Ile Ser Arg Ser Leu Gly Lys
355 360

<210> 299
<211> 858
<212> DNA
<213> Artificial Sequence

<220>
<223> NHP CD86-AFH synthesized molecule

<400> 299
atgggactga gtaacattct ctttgtgatg gccttcctgc tctctggtgc tgctcccctg 60
aagattcagg cttatttcaa tgagactgca gacctgccat gccagtttgc aaactctcaa 120
aaccgaagcc tgagtgagct agtagtattt tggcagaacc aggaaaactt ggttctgaat 180
gaggtatact taggcaaaga gaaatttgac agcgttcatt ccaagtatat gggccgcaca 240
agttttgatc cggagagttg gaccctgagg cttcacaacc ttcagatcaa ggacaagggc 300
ttgtatcaat gtatcatcca ccacaaaagg cccacaggaa tgatccgcat ccaccagatg 360
aactctgaac tgtcagtgct tgctaacttc agtcaacctg aaatagtccc aatttctaat 420
ataacagaaa atatgtacat aaatttgacc tgctcatcta tacacggtta cccagaacct 480
gagaagatga gtgttttgct aagaaccaag aactcaacta tcgagtatga tggtgttatg 540
cagaaatctc aagataatgt cacagaactg tacgacgttt ccatcagctt gtctgtttca 600
ttccctgatg ttacgagcaa catgaccatc ttctgtgttc tggaaactga caagacacag 660
cttttatcct caccttttctc tatagagctt gaggaccctc agcctccccc agactcctcg 720
agcctgaacg acatcttcga ggctcagaaa atcgaatggc acgaagatta caaggatgac 780
gacgataagg attacaagga tgacgacgat aaggattaca aggatgacga cgataagcat 840
catcatcatc atcactga 858

<210> 300
<211> 285
<212> PRT
<213> Artificial Sequence

<220>
<223> NHP CD86-AFH synthesized molecule

<400> 300
Asn Gly Leu Ser Asn Ile Leu Phe Val Met Ala Phe Leu Leu Ser Gly
1 5 10 15
Ala Ala Pro Leu Lys Ile Gln Ala Tyr Phe Asn Glu Thr Ala Asp Leu
20 25 30
Pro Cys Gln Phe Ala Asn Ser Gln Asn Arg Ser Leu Ser Glu Leu Val
35 40 45
Val Phe Trp Gln Asn Gln Glu Asn Leu Val Leu Asn Glu Val Tyr Leu
50 55 60
Gly Lys Glu Lys Phe Asp Ser Val His Ser Lys Tyr Met Gly Arg Thr
65 70 75 80
Ser Phe Asp Pro Glu Ser Trp Thr Leu Arg Leu His Asn Leu Gln Ile
85 90 95
Lys Asp Lys Gly Leu Tyr Gln Cys Ile Ile His His Lys Arg Pro Thr
100 105 110
Gly Met Ile Arg Ile His Gln Met Asn Ser Glu Leu Ser Val Leu Ala
115 120 125
Asn Phe Ser Gln Pro Glu Ile Val Pro Ile Ser Asn Ile Thr Glu Asn
130 135 140
Met Tyr Ile Asn Leu Thr Cys Ser Ser Ile His Gly Tyr Pro Glu Pro
145 150 155 160
Glu Lys Met Ser Val Leu Leu Arg Thr Lys Asn Ser Thr Ile Glu Tyr
165 170 175
Asp Gly Val Met Gln Lys Ser Gln Asp Asn Val Thr Glu Leu Tyr Asp
180 185 190
Val Ser Ile Ser Leu Ser Val Ser Phe Pro Asp Val Thr Ser Asn Met
195 200 205
Thr Ile Phe Cys Val Leu Glu Thr Asp Lys Thr Gln Leu Leu Ser Ser

210 215 220
Pro Phe Ser Ile Glu Leu Glu Asp Pro Gln Pro Pro Pro Asp Ser Ser
225 230 235 240
Ser Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu Asp
245 250 255
Tyr Lys Asp Asp Asp Asp Lys Asp Tyr Lys Asp Asp Asp Asp Lys Asp
260 265 270
Tyr Lys Asp Asp Asp Asp Lys His His His His His His
275 280 285

<210> 301
<211> 1629
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::IL10 fusion protein with H69 linker

<400> 301
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtga gcagaagctg 1080
agcaacatgg agaacagact gaagcccttc ttcacaagcg gctcagcaga cacctccccg 1140
aattctagcc caggccaggg cacccagtct gagaacagct gcacccactt cccaggcaac 1200
ctgcctaaca tgcttcgaga tctccgagat gccttcagca gagtgaagac tttctttcaa 1260
atgaaggatc agctggacaa cttgttgtta aaggagtcct tgctggagga ctttaagggt 1320
tacctgggtt gccaagcctt gtctgagatg atccagtttt acctggagga ggtgatgccc 1380
caagctgaga accaagaccc agacatcaag gcgcatgtga actccctggg ggagaacctg 1440
aagaccctca ggctgaggct acggcgctgt catcgatttc ttccctgtga aaacaagagc 1500
aaggccgtgg agcaggtgaa gaatgccttt aataagctcc aagagaaagg catctacaaa 1560
gccatgagtg agtttgacat cttcatcaac tacatagaag cctacatgac aatgaagata 1620
cgaaactaa 1629

<210> 302
<211> 542
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::IL10 fusion protein with H69 linker

<400> 302
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln

65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Glu Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys
355 360 365
Pro Phe Phe Thr Ser Gly Ser Ala Asp Thr Ser Pro Asn Ser Ser Pro
370 375 380
Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn
385 390 395 400
Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys
405 410 415
Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu
420 425 430
Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser
435 440 445
Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn
450 455 460
Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu
465 470 475 480
Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys
485 490 495
Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys
500 505 510
Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe
515 520 525
Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
530 535 540

<210> 303
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<223> FUN1 SMIP synthesized molecule

<400> 303
gaggtccaac tgcagcagtc tggacctgag ctggagaagc ctggcgcttc agtgaagata 60
tcctgcaagg cttctggtta ctcattcact gactacaaca tgaactgggt gaagcagagc 120
aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240
atgcagctca acagcctgac atctgaagac tctgcagtct atttctgtgc aagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggtca aggaacctca 360
gtcaccgtct cctcaggggg tggaggctct ggtggcggtg gctctggcgg aggtggatcc 420
ggtggcggcg gatctgagct ccagatgacc cagtctccat catctctggc tgcgtctgca 480
ggagaaaagg tcactatgag ctgtaagtcc agtcaaagtg ttttatacag ttcaaatcag 540
aagaactact tggcctggta ccagcagaaa ccagggcagt ctcctaaact gctgatctac 600
tgggcatcca ctagggaatc tggtgtccct gatcgcttca caggcagtgg atctgggaca 660
cattttactc tgaccgtcag cagtgtgcaa gctgaagacc tggcagttta ttactgtcat 720
caatacctct actcgtggac gttcggtgga ggcaccaacc tggaaatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagccgg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt taa 1473

<210> 304
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 SMIP synthesized molecule

<400> 304
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
 1   5   10   15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
            20   25   30
Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile
        35   40   45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50   55   60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85   90   95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100   105   110
Asp Phe Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly
        115   120   125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130   135   140
Ser Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ala Ala Ser Ala
145   150   155   160
Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165   170   175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180   185   190
Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195   200   205
Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr His Phe Thr Leu
    210   215   220
Thr Val Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His
225   230   235   240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile

```
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490


<210> 305
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 heavy chain

<400> 305
Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
 1                5                  10                  15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Asp Tyr
            20                  25                  30
Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100                 105                 110
Asp Phe Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120                 125


<210> 306
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 light chain
```

<400> 306
Glu Leu Gln Met Thr Gln Ser Pro Ser Ser Leu Ala Ala Ser Ala Gly
 1   5   10   15
Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
            20   25   30
Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35   40   45
Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60
Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr
65   70   75   80
Val Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His Gln
                85   90   95
Tyr Leu Tyr Ser Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys
            100   105   110
Arg

<210> 307
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 scFV linker

<400> 307
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 1   5   10   15
Gly Gly Gly Ser
            20

<210> 308
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 HCDR1

<400> 308
Asp Tyr Asn Met Asn
 1   5

<210> 309
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 HCDR2

<400> 309
Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly
 1   5   10   15

<210> 310
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 HCDR3

<400> 310
Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe
 1   5   10   15

<210> 311
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 LCDR1

<400> 311
Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
 1   5   10   15
Ala

<210> 312
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 LCDR2

<400> 312
Trp Ala Ser Thr Arg Glu Ser
 1   5

<210> 313
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 LCDR3

<400> 313
His Gln Tyr Leu Tyr Ser Trp Thr
 1   5

<210> 314
<211> 1530
<212> DNA
<213> Artificial Sequence

<220>
<223> FUN1 PIMS synthesized molecule

<400> 314
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 60
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctgaggtcc aactgcagca gtctggacct 780

gagctggaga agcctggcgc ttcagtgaag atatcctgca aggcttctgg ttactcattc 840
actgactaca acatgaactg ggtgaagcag agcaatggaa agagccttga gtggattgga 900
aatattgatc cttactatgg tggtactagt tacaatcaga agttcaaggg caaggccaca 960
ttgactgtag acaaatcctc cagcacagcc tacatgcagc tcaacagcct gacatctgaa 1020
gactctgcag tctatttctg tgcaagatgg gactataggt acgacgacgg gagggcttac 1080
tatgttatgg acttctgggg tcaaggaacc tcagtcaccg tctcctcagg gggtggaggc 1140
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctga gctccagatg 1200
acccagtctc catcatctct ggctgcgtct gcaggagaaa aggtcactat gagctgtaag 1260
tccagtcaaa gtgttttata cagttcaaat cagaagaact acttggcctg gtaccagcag 1320
aaaccagggc agtctcctaa actgctgatc tactgggcat ccactaggga atctggtgtc 1380
cctgatcgct tcacaggcag tggatctggg acacatttta ctctgaccgt cagcagtgtg 1440
caagctgaag acctggcagt ttattactgt catcaatacc tctactcgtg gacgttcggt 1500
ggaggcacca acctggaaat caaacggtaa 1530

<210> 315
<211> 509
<212> PRT
<213> Artificial Sequence

<220>
<223> FUN1 PIMS synthesized molecule

<400> 315

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

```
        355                 360                 365
Gly Thr Ser Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met
385                 390                 395                 400
Thr Gln Ser Pro Ser Ser Leu Ala Ala Ser Ala Gly Glu Lys Val Thr
                405                 410                 415
Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys
            420                 425                 430
Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu
        435                 440                 445
Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
    450                 455                 460
Thr Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr Val Ser Ser Val
465                 470                 475                 480
Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr Ser
                485                 490                 495
Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg
            500                 505
```

<210> 316
<211> 1443
<212> DNA
<213> Artificial Sequence

<220>
<223> 3D1 SMIP synthesized molecule

<400> 316

```
caggtccagc tgcagcagtc tgggcctgag ctggtgaggc ctggggaatc agtgaagatt 60
tcctgcaagg gttccggcta cacattcact gattatgcta tacagtgggt gaagcagagt 120
catgcaaaga gtctagagtg gattggagtt attaatattt actatgataa tacaaactac 180
aaccagaagt ttaagggcaa ggccacaatg actgtagaca aatcctccag cacagcctat 240
atggaacttg ccagattgac atctgaggat tctgccatct attactgtgc aagagcggcc 300
tggtatatgg actactgggg tcaaggaacc tcagtcaccg tctcctcagg gggtggaggc 360
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctga cattgtgctg 420
tcacagtctc catcctccct ggctgtgtca gcaggagaga aggtcactat gagctgcaaa 480
tccagtcaga gtctgctcaa cagtagaacc cgagagaact acttggcttg gtaccagcag 540
aaaccagggc agtctcctaa actgctgatc tactgggcat ccactaggga atctggggtc 600
cctgatcgct tcacaggcag tggatctggg acagatttca ctctcaccat cagcagtgtg 660
caggctgaag acctggcagt ttattactgc acgcaatctt ataatcttta cacgttcgga 720
gggggacca agctggaaat aaaactcgag cccaaatctt ctgacaaaac tcacacatgc 780
ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt ccccccaaaa 840
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 900
agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 960
gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1020
accgtcctgc accaggactg gctgaatggc aaggcgtacg cgtgcgcggt ctccaacaaa 1080
gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1140
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1200
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 1260
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1320
tacagcaagc tcaccgtgga caagagccgg tggcagcagg ggaacgtctt ctcatgctcc 1380
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1440
taa                                                                 1443
```

<210> 317
<211> 480
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 SMIP synthesized molecule

<400> 317

```
Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu
 1               5                  10                  15
Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
```

```
            20                  25                  30
Ala Ile Gln Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile
        35                  40                  45
Gly Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ala Arg Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys
                85                  90                  95
Ala Arg Ala Ala Trp Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
            100                 105                 110
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125
Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro
    130                 135                 140
Ser Ser Leu Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys
145                 150                 155                 160
Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala
                165                 170                 175
Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp
            180                 185                 190
Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly
        195                 200                 205
Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp
    210                 215                 220
Leu Ala Val Tyr Tyr Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly
225                 230                 235                 240
Gly Gly Thr Lys Leu Glu Ile Lys Leu Glu Pro Lys Ser Ser Asp Lys
                245                 250                 255
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
            260                 265                 270
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
        275                 280                 285
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    290                 295                 300
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305                 310                 315                 320
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                325                 330                 335
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala
            340                 345                 350
Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
        355                 360                 365
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
    370                 375                 380
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385                 390                 395                 400
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                405                 410                 415
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
            420                 425                 430
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        435                 440                 445
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480
```

<210> 318
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 heavy chain

<400> 318

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

<210> 319
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 light chain

<400> 319

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

<210> 320
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1scFv linker

<400> 320

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 1               5                  10                  15
Gly Gly Gly Ser
            20
```

<210> 321
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 HCDR1

<400> 321

```
Asp Tyr Ala Ile Gln
```

1 5

<210> 322
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 HCDR2

<400> 322
Val Ile Asn Ile Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe Lys
1 5 10 15
Gly

<210> 323
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 HCDR3

<400> 323
Ala Ala Trp Tyr Met Asp Tyr
1 5

<210> 324
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 LCDR1

<400> 324
Lys Ser Ser Gln Ser Leu Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu
1 5 10 15
Ala

<210> 325
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 LCDR2

<400> 325
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 326
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 LCDR3

<400> 326

Thr Gln Ser Tyr Asn Leu Tyr Thr
1 5

<210> 327
<211> 1500
<212> DNA
<213> Artificial Sequence

<220>
<223> 3D1 PIMS synthesized molecule

<400> 327
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 60
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctcaggtcc agctgcagca gtctgggcct 780
gagctggtga ggcctgggga atcagtgaag atttcctgca agggttccgg ctacacattc 840
actgattatg ctatacagtg ggtgaagcag agtcatgcaa agagtctaga gtggattgga 900
gttattaata tttactatga taatacaaac tacaaccaga agtttaaggg caaggccaca 960
atgactgtag acaaatcctc cagcacagcc tatatggaac ttgccagatt gacatctgag 1020
gattctgcca tctattactg tgcaagagcg gcctggtata tggactactg gggtcaagga 1080
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tcagcaggag agaaggtcac tatgagctgc aaatccagtc agagtctgct caacagtaga 1260
acccgagaga actacttggc ttggtaccag cagaaaccag ggcagtctcc taaactgctg 1320
atctactggg catccactag ggaatctggg gtccctgatc gcttcacagg cagtggatct 1380
gggacagatt tcactctcac catcagcagt gtgcaggctg aagacctggc agtttattac 1440
tgcacgcaat cttataatct ttacacgttc ggaggggggga ccaagctgga aataaaataa 1500

<210> 328
<211> 499
<212> PRT
<213> Artificial Sequence

<220>
<223> 3D1 PIMS synthesized molecule

<400> 328
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15
Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
100 105 110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser

145 150 155 160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225 230 235 240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Gln
245 250 255
Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Glu Ser Val Lys Ile Ser
260 265 270
Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr Ala Ile Gln Trp Val
275 280 285
Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile Gly Val Ile Asn Ile
290 295 300
Tyr Tyr Asp Asn Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr
305 310 315 320
Met Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Ala Arg
325 330 335
Leu Thr Ser Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Ala Ala Trp
340 345 350
Tyr Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly
355 360 365
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380
Gly Gly Ser Asp Ile Val Leu Ser Gln Ser Pro Ser Ser Leu Ala Val
385 390 395 400
Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu
405 410 415
Leu Asn Ser Arg Thr Arg Glu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
420 425 430
Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
435 440 445
Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe
450 455 460
Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr
465 470 475 480
Cys Thr Gln Ser Tyr Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Leu
485 490 495
Glu Ile Lys

<210> 329
<211> 2016
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding M0115::IL10 I87A
fusion protein with H75 linker

<400> 329
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cctggacaag ggcttgagtg gatgggaaat attgatcctt actatggtgg tactagttac 180
aatcagaagt tcaagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggagctga gcaggctgag atctgacgac acggccgtgt attactgtgc gagatgggac 300
tataggtacg acgacgggag ggcttactat gttatggact tctggggcca agggaccacg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gatccggcgg tggcggatcg 420
ggtggcggcg gatctgacat cgtgatgacc cagtctccag actccctggc tgtgtctctg 480
ggcgagaggg ccaccatcaa ctgcaagtcc agccagagtg ttttatacag ctccaaccag 540
aagaactact tagcttggta ccagcagaaa ccaggacagc ctcctaagct gctcatttac 600
tgggcatcta cccgggaatc cggggtccct gaccgattca gtggcagcgg gtctgggaca 660

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gatttcactc tcaccatcag cagcctgcag gctgaagatg tggcagttta ttactgtcat 720
caatacctct actcgtggac gtttggccag gggaccaagc tggagatcaa acggctcgag 780
cccaaatctt ctgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggt 840
gcaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 900
cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 960
tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 1020
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 1080
aaggcgtacg cgtgcgcggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1140
tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggat 1200
gagctgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta tccaagcgac 1260
atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1320
gtgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1380
tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1440
acgcagaaga gcctctccct gtctccgggt cagaggcaca acaattcttc cctgaataca 1500
ggaactcaga tggcaggtca ttctccgaat tctagcccag gccagggcac ccagtctgag 1560
aacagctgca cccacttccc aggcaacctg cctaacatgc ttcgagatct ccgagatgcc 1620
ttcagcagag tgaagacttt ctttcaaatg aaggatcagc tggacaactt gttgttaaag 1680
gagtccttgc tggaggactt taagggttac ctgggttgcc aagccttgtc tgagatgatc 1740
cagttttacc tggaggaggt gatgccccaa gctgagaacc aagacccaga cgccaaggcg 1800
catgtgaact ccctgggggа gaacctgaag accctcaggc tgaggctacg gcgctgtcat 1860
cgatttcttc cctgtgaaaa caagagcaag gccgtggagc aggtgaagaa tgcctttaat 1920
aagctccaag agaaaggcat ctacaaagcc atgagtgagt ttgacatctt catcaactac 1980
atagaagcct acatgacaat gaagatacga aactaa                           2016

<210> 330
<211> 671
<212> PRT
<213> Artificial Sequence

<220>
<223> M0115::IL10 I87A fusion protein with H75 linker

<400> 330
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60
Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met
            100                 105                 110
Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140
Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu
145                 150                 155                 160
Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr
                165                 170                 175
Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
            180                 185                 190
Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly
        195                 200                 205
Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    210                 215                 220
Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His
225                 230                 235                 240
Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
                245                 250                 255
Lys Arg Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro
            260                 265                 270
Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
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        275                 280                 285
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    290                 295                 300
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305                 310                 315                 320
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
                325                 330                 335
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
            340                 345                 350
Leu His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser
        355                 360                 365
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    370                 375                 380
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
385                 390                 395                 400
Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                405                 410                 415
Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            420                 425                 430
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        435                 440                 445
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    450                 455                 460
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465                 470                 475                 480
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gln Arg His Asn Asn Ser
                485                 490                 495
Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser Ser
            500                 505                 510
Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro Gly
        515                 520                 525
Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg Val
    530                 535                 540
Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys
545                 550                 555                 560
Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu
                565                 570                 575
Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala Glu
            580                 585                 590
Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu Asn
        595                 600                 605
Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu Pro
    610                 615                 620
Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe Asn
625                 630                 635                 640
Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile
                645                 650                 655
Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
            660                 665                 670
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<210> 331
<211> 1500
<212> DNA
<213> Artificial Sequence

<220>
<223> GL1 PIMS synthesized molecule

<400> 331
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ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctgaggtgc agctggtgga gtctgctgga 780
ggtttagtgc agcctggaag gtccctaaaa ctctcctgtg cagcctcagg attcactttc 840
agtgactatt acatggcctg ggtccgccag gctccaacga aggggctgga gtgggtcgca 900
accattagtc atgacggtag tagtacttac tatcgagact ccgtgaaggg ccgattcaca 960
atctccagag ataatgcaaa aaccatccta tacctgcaaa tggacagtct gaggtctgag 1020
gacacggcca cttatttctg tgcaagacag aatattatgg attattgggg ccaaggagtc 1080
atggtcacag tctcctcagg gggtggaggc tctggtggcg gtggctctgg cggaggtgga 1140
tccggtggcg gcggatctga cattgtgatg acccagactc catcctccca ggctgtgtca 1200
gcaggggaga aggtcactat gagctgcaag tccagtcaga gtcttttgta cagtagagac 1260
cagagtaact acttggcctg gtaccagcag aaacctgggc agtctcctaa actacttatc 1320
tacttggcat ccactaggga atcaggggtc cctgatcgct tcataggcag tggctctggg 1380
acagacttca ctctgaccat cagcagtgtg caggctgaag atctggcaga ttattactgt 1440
cagcagcatt acaactatcc gctcacgttc ggttctggga ccaagctaga aatcaaataa 1500

<210> 332
<211> 499
<212> PRT
<213> Artificial Sequence

<220>
<223> GL1 PIMS synthesized molecule

<400> 332
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
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Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20   25   30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35   40   45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50   55   60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65   70   75   80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85   90   95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
            100   105   110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115   120   125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130   135   140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145   150   155   160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165   170   175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180   185   190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195   200   205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210   215   220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225   230   235   240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Glu Val Gln Leu Val
                245   250   255
Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu Ser
            260   265   270
Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ala Trp Val
        275   280   285
Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val Ala Thr Ile Ser His
    290   295   300
Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val Lys Gly Arg Phe Thr
305   310   315   320

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Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr Leu Gln Met Asp Ser
                325                 330                 335
Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gln Asn Ile
            340                 345                 350
Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly
        355                 360                 365
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380
Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser
385                 390                 395                 400
Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu
                405                 410                 415
Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
            420                 425                 430
Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala Ser Thr Arg Glu Ser
        435                 440                 445
Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr
    450                 455                 460
Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Tyr Cys
465                 470                 475                 480
Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu
                485                 490                 495
Glu Ile Lys
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<210> 333
<211> 1986
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding GL1::IL10 I87A fusion
protein with H75 linker

<400> 333

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ccaacgaagg ggctggagtg ggtcgcaacc attagtcatg acggtagtag tacttactat 180
cgagactccg tgaagggccg attcacaatc tccagagata atgcaaaaac catcctatac 240
ctgcaaatgg acagtctgag gtctgaggac acggccactt atttctgtgc aagacagaat 300
attatggatt attggggcca aggagtcatg gtcacagtct cctcaggggg tggaggctct 360
ggtggcggtg gctctggcgg aggtggatcc ggtggcggcg gatctgacat tgtgatgacc 420
cagactccat cctcccaggc tgtgtcagca ggggagaagg tcactatgag ctgcaagtcc 480
agtcagagtc ttttgtacag tagagaccag agtaactact tggcctggta ccagcagaaa 540
cctgggcagt ctcctaaact acttatctac ttggcatcca ctagggaatc aggggtccct 600
gatcgcttca taggcagtgg ctctgggaca gacttcactc tgaccatcag cagtgtgcag 660
gctgaagatc tggcagatta ttactgtcag cagcattaca actatccgct cacgttcggt 720
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ccaccgtgcc cagcacctga agccgcgggt gcaccgtcag tcttcctctt cccccaaaa 840
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt ggtggacgtg 900
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gccctcccag ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1140
caggtgtaca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1200
tgcctggtca aaggcttcta tccaagcgac atcgccgtgg agtgggagag caatgggcag 1260
ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggctc cttcttcctc 1320
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctcc 1380
gtgatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1440
cagaggcaca acaattcttc cctgaataca ggaactcaga tggcaggtca ttctccgaat 1500
tctagcccag gccagggcac ccagtctgag aacagctgca cccacttccc aggcaacctg 1560
cctaacatgc ttcgagatct ccgagatgcc ttcagcagag tgaagacttt ctttcaaatg 1620
aaggatcagc tggacaactt gttgttaaag gagtccttgc tggaggactt taagggttac 1680
ctgggttgcc aagccttgtc tgagatgatc cagttttacc tggaggaggt gatgccccaa 1740
gctgagaacc aagacccaga cgccaaggcg catgtgaact ccctggggga gaacctgaag 1800
accctcaggc tgaggctacg gcgctgtcat cgatttcttc cctgtgaaaa caagagcaag 1860
gccgtggagc aggtgaagaa tgcctttaat aagctccaag agaaaggcat ctacaaagcc 1920
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atgagtgagt ttgacatctt catcaactac atagaagcct acatgacaat gaagatacga 1980
aactaa 1986

<210> 334
<211> 661
<212> PRT
<213> Artificial Sequence

<220>
<223> GL1::IL10 I87A fusion protein with H75 linker

<400> 334
Glu Val Gln Leu Val Glu Ser Ala Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
35 40 45
Ala Thr Ile Ser His Asp Gly Ser Ser Thr Tyr Tyr Arg Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Ile Leu Tyr
65 70 75 80
Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95
Ala Arg Gln Asn Ile Met Asp Tyr Trp Gly Gln Gly Val Met Val Thr
100 105 110
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125
Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser
130 135 140
Ser Gln Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
145 150 155 160
Ser Gln Ser Leu Leu Tyr Ser Arg Asp Gln Ser Asn Tyr Leu Ala Trp
165 170 175
Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Leu Ala
180 185 190
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser
195 200 205
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
210 215 220
Ala Asp Tyr Tyr Cys Gln Gln His Tyr Asn Tyr Pro Leu Thr Phe Gly
225 230 235 240
Ser Gly Thr Lys Leu Glu Ile Lys Leu Glu Pro Lys Ser Ser Asp Lys
245 250 255
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
260 265 270
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
275 280 285
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
290 295 300
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
305 310 315 320
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
325 330 335
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Ala
340 345 350
Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
355 360 365
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
370 375 380
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
385 390 395 400
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
405 410 415
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
420 425 430
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
435 440 445

```
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    450                 455                 460
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
465                 470                 475                 480
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
                485                 490                 495
His Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser
            500                 505                 510
Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg
        515                 520                 525
Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu
    530                 535                 540
Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr
545                 550                 555                 560
Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu
                565                 570                 575
Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val
            580                 585                 590
Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg
        595                 600                 605
Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln
    610                 615                 620
Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala
625                 630                 635                 640
Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr
                645                 650                 655
Met Lys Ile Arg Asn
            660
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<210> 335
<211> 1737
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::PDL2 fusion
protein with H65 linker

<400> 335
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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccgat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacaag aactcagaaa gcacgtcatt ctccgaattc tttattcaca 1140
gtgacagtcc ctaaggaact gtacataata gagcatggca gcaatgtgac cctggaatgc 1200
aactttgaca ctggaagtca tgtgaacctt ggagcaataa cagccagttt gcaaaaggtg 1260
gaaaatgata catccccaca ccgtgaaaga gccactttgc tggaggagca gctgccccta 1320
gggaaggcct cgttccacat acctcaagtc caagtgaggg acgaaggaca gtaccaatgc 1380
ataatcatct atggggtcgc ctgggactac aagtacctga ccctgaaagt caaagcttcc 1440
tacaggaaaa taaacactca catcctaaag gttccagaaa cagatgaggt agagctcacc 1500
tgccaggcta caggttatcc tctggcagaa gtatcctggc caaacgtcag cgttcctgcc 1560
aacaccagcc actccaggac ccctgaaggc ctctaccagg tcaccagtgt tctgcgccta 1620
aagccacccc ctggcagaaa cttcagctgt gtgttctgga atactcacgt gagggaactt 1680
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actttggcca gcattgacct tcaaagtcag atggaaccca ggacccatcc aacttaa 1737

<210> 336
<211> 578
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::PDL2 fusion protein with H65 linker

<400> 336
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
355 360 365
Gln Lys Ala Arg His Ser Pro Asn Ser Leu Phe Thr Val Thr Val Pro
370 375 380
Lys Glu Leu Tyr Ile Ile Glu His Gly Ser Asn Val Thr Leu Glu Cys
385 390 395 400
Asn Phe Asp Thr Gly Ser His Val Asn Leu Gly Ala Ile Thr Ala Ser
405 410 415
Leu Gln Lys Val Glu Asn Asp Thr Ser Pro His Arg Glu Arg Ala Thr
420 425 430
Leu Leu Glu Glu Gln Leu Pro Leu Gly Lys Ala Ser Phe His Ile Pro
435 440 445
Gln Val Gln Val Arg Asp Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr

```
    450                 455                 460
Gly Val Ala Trp Asp Tyr Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser
465                 470                 475                 480
Tyr Arg Lys Ile Asn Thr His Ile Leu Lys Val Pro Glu Thr Asp Glu
                485                 490                 495
Val Glu Leu Thr Cys Gln Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser
            500                 505                 510
Trp Pro Asn Val Ser Val Pro Ala Asn Thr Ser His Ser Arg Thr Pro
        515                 520                 525
Glu Gly Leu Tyr Gln Val Thr Ser Val Leu Arg Leu Lys Pro Pro Pro
    530                 535                 540
Gly Arg Asn Phe Ser Cys Val Phe Trp Asn Thr His Val Arg Glu Leu
545                 550                 555                 560
Thr Leu Ala Ser Ile Asp Leu Gln Ser Gln Met Glu Pro Arg Thr His
                565                 570                 575
Pro Thr
```

<210> 337
<211> 1551
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::GITR fusion protein with H65 linker

<400> 337

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atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacaag aactcagaaa gcacgtcatt ctccgaattc tcagcgcccc 1140
accgggggtc ccgggtgcgg ccctgggcgc ctcctgcttg ggacgggaac ggacgcgcgc 1200
tgctgccggg ttcacacgac gcgctgctgc cgcgattacc cgggcgagga gtgctgttcc 1260
gagtgggact gcatgtgtgt ccagcctgaa ttccactgcg gagacccttg ctgcacgacc 1320
tgccggcacc acccttgtcc cccaggccag ggggtacagt cccaggggaa attcagtttt 1380
ggcttccagt gtatcgactg tgcctcgggg accttctccg ggggccacga aggccactgc 1440
aaaccttgga cagactgcac ccagttcggg tttctcactg tgttccctgg gaacaagacc 1500
cacaacgctg tgtgcgtccc agggtccccc ccggcagagc cgcttgggta a           1551
```

<210> 338
<211> 516
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::GITR fusion protein with H65 linker

<400> 338

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Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1               5                  10                  15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
```

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                20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
            35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115                 120                 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130                 135                 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145                 150                 155                 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165                 170                 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180                 185                 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195                 200                 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210                 215                 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225                 230                 235                 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245                 250                 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260                 265                 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275                 280                 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
        355                 360                 365
Gln Lys Ala Arg His Ser Pro Asn Ser Gln Arg Pro Thr Gly Gly Pro
    370                 375                 380
Gly Cys Gly Pro Gly Arg Leu Leu Leu Gly Thr Gly Thr Asp Ala Arg
385                 390                 395                 400
Cys Cys Arg Val His Thr Thr Arg Cys Cys Arg Asp Tyr Pro Gly Glu
                405                 410                 415
Glu Cys Cys Ser Glu Trp Asp Cys Met Cys Val Gln Pro Glu Phe His
            420                 425                 430
Cys Gly Asp Pro Cys Cys Thr Thr Cys Arg His His Pro Cys Pro Pro
        435                 440                 445
Gly Gln Gly Val Gln Ser Gln Gly Lys Phe Ser Phe Gly Phe Gln Cys
    450                 455                 460
Ile Asp Cys Ala Ser Gly Thr Phe Ser Gly Gly His Glu Gly His Cys
465                 470                 475                 480
Lys Pro Trp Thr Asp Cys Thr Gln Phe Gly Phe Leu Thr Val Phe Pro
                485                 490                 495
Gly Asn Lys Thr His Asn Ala Val Cys Val Pro Gly Ser Pro Pro Ala
            500                 505                 510
Glu Pro Leu Gly
        515
```

<210> 339
<211> 1437
<212> DNA

<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4::TGFBetaR1
fusion protein with H65 linker

<400> 339
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300
ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtca gaggcacaac 1080
aattcttccc tgaatacaag aactcagaaa gcacgtcatt ctccgaattc tgcggcgctg 1140
ctcccggggg cgacggcgtt acagtgtttc tgccacctct gtacaaaaga caatttact 1200
tgtgtgacag atgggctctg ctttgtctct gtcacagaga ccacagacaa agttatacac 1260
aacagcatgt gtatagctga aattgactta attcctcgag ataggccgtt tgtatgtgca 1320
ccctcttcaa aaactgggtc tgtgactaca acatattgct gcaatcagga ccattgcaat 1380
aaaatagaac ttccaactac tgtaaagtca tcacctggcc ttggtcctgt ggaataa 1437

<210> 340
<211> 478
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4::TGFBetaR1 fusion protein with H65 linker

<400> 340
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
1 5 10 15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
20 25 30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
35 40 45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
50 55 60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65 70 75 80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
85 90 95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
100 105 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
115 120 125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
130 135 140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145 150 155 160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
165 170 175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
180 185 190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
195 200 205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu

210 215 220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225 230 235 240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
245 250 255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
260 265 270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
275 280 285
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
290 295 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305 310 315 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
325 330 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
340 345 350
Leu Ser Pro Gly Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr
355 360 365
Gln Lys Ala Arg His Ser Pro Asn Ser Ala Ala Leu Leu Pro Gly Ala
370 375 380
Thr Ala Leu Gln Cys Phe Cys His Leu Cys Thr Lys Asp Asn Phe Thr
385 390 395 400
Cys Val Thr Asp Gly Leu Cys Phe Val Ser Val Thr Glu Thr Thr Asp
405 410 415
Lys Val Ile His Asn Ser Met Cys Ile Ala Glu Ile Asp Leu Ile Pro
420 425 430
Arg Asp Arg Pro Phe Val Cys Ala Pro Ser Ser Lys Thr Gly Ser Val
435 440 445
Thr Thr Thr Tyr Cys Cys Asn Gln Asp His Cys Asn Lys Ile Glu Leu
450 455 460
Pro Thr Thr Val Lys Ser Ser Pro Gly Leu Gly Pro Val Glu
465 470 475

<210> 341
<211> 798
<212> DNA
<213> Artificial Sequence

<220>
<223> Human CD86-AFH synthesized molecule

<400> 341
ctgaagattc aagcttattt caataagact gcagacctgc catgccaatt tgcaaactct 60
caaaaccaaa gcctgagtga gctagtagta ttttggcagg accaggaaaa cttggttctg 120
aatgaggtat acttaggcaa agagaaattt gacagcgttc attccaagta tatgggccgc 180
acaagttttg attcagacag ttggaccctg agacttcaca atcttcagat caaggacaag 240
ggcttgtatc aatgtatcat ccatcacaaa aagcccacag gaatgattcg catccaccag 300
atgaattctg aactgtcagt gcttgctaac ttcagtcaac ctgaaatagt accaatttct 360
aatataacag aaaatgtgta cataaatttg acctgctcat ctatacacgg ttacccagaa 420
cctaagaaga tgagtgtttt gctaagaacc aagaattcaa ctatcgagta tgatggtatt 480
atgcagaaat ctcaagataa tgtcacagaa ctgtacgacg tttccatcag cttgtctgtt 540
tcattccctg atgttacgag caatatgacc atcttctgta ttctggaaac tgacaagacg 600
cggcttttat cttcaccttt ctctatagag cttgaggacc ctcagcctcc cccagactct 660
agactgaacg acatcttcga ggctcagaaa atcgaatggc acgaagatta caaggatgac 720
gacgataagg attacaagga tgacgacgat aaggattaca aggatgacga cgataagcat 780
catcatcatc atcactga 798

<210> 342
<211> 265
<212> PRT
<213> Artificial Sequence

<220>
<223> Human CD86-AFH synthesized molecule

<400> 342

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

<210> 343
<211> 801
<212> DNA
<213> Artificial Sequence

<220>
<223> Mouse CD86-AFH synthesized molecule

<400> 343

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gtggagacgc aagcttattt caatgggact gcatatctgc cgtgcccatt tacaaaggct 60
caaaacataa gcctgagtga gctggtagta ttttggcagg accagcaaaa gttggttctg 120
tacgagcact atttgggcac agagaaactt gatagtgtga atgccaagta cctgggccgc 180
acgagctttg acaggaacaa ctggactcta cgacttcaca atgttcagat caaggacatg 240
ggctcgtatg attgttttat acaaaaaaag ccacccacag gatcaattat cctccaacag 300
acattaacag aactgtcagt gatcgccaac ttcagtgaac ctgaaataaa actggctcag 360
aatgtaacag gaaattctgg cataaatttg acctgcacgt ctaagcaagg tcacccgaaa 420
cctaagaaga tgtattttct gataactaat tcaactaatg agtatggtga taacatgcag 480
atatcacaag ataatgtcac agaactgttc agtatctcca acagcctctc tctttcattc 540
ccggatggtg tgtggcatat gaccgttgtg tgtgttctgg aaacggagtc aatgaagatt 600
tcctccaaac ctctcaattt cactcaagag tttccatctc ctcaaacgta ttggaaggag 660
tctagactga acgacatctt cgaggctcag aaaatcgaat ggcacgaaga ttacaaggat 720
gacgacgata aggattacaa ggatgacgac gataaggatt acaaggatga cgacgataag 780
catcatcatc atcatcactg a                                           801
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<210> 344
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<223> Mouse CD86-AFH synthesized molecule

<400> 344
Val Glu Thr Gln Ala Tyr Phe Asn Gly Thr Ala Tyr Leu Pro Cys Pro
 1   5   10   15
Phe Thr Lys Ala Gln Asn Ile Ser Leu Ser Glu Leu Val Val Phe Trp
            20   25   30
Gln Asp Gln Gln Lys Leu Val Leu Tyr Glu His Tyr Leu Gly Thr Glu
        35   40   45
Lys Leu Asp Ser Val Asn Ala Lys Tyr Leu Gly Arg Thr Ser Phe Asp
    50   55   60
Arg Asn Asn Trp Thr Leu Arg Leu His Asn Val Gln Ile Lys Asp Met
65   70   75   80
Gly Ser Tyr Asp Cys Phe Ile Gln Lys Lys Pro Pro Thr Gly Ser Ile
                85   90   95
Ile Leu Gln Gln Thr Leu Thr Glu Leu Ser Val Ile Ala Asn Phe Ser
            100   105   110
Glu Pro Glu Ile Lys Leu Ala Gln Asn Val Thr Gly Asn Ser Gly Ile
        115   120   125
Asn Leu Thr Cys Thr Ser Lys Gln Gly His Pro Lys Pro Lys Lys Met
    130   135   140
Tyr Phe Leu Ile Thr Asn Ser Thr Asn Glu Tyr Gly Asp Asn Met Gln
145   150   155   160
Ile Ser Gln Asp Asn Val Thr Glu Leu Phe Ser Ile Ser Asn Ser Leu
                165   170   175
Ser Leu Ser Phe Pro Asp Gly Val Trp His Met Thr Val Val Cys Val
            180   185   190
Leu Glu Thr Glu Ser Met Lys Ile Ser Ser Lys Pro Leu Asn Phe Thr
        195   200   205
Gln Glu Phe Pro Ser Pro Gln Thr Tyr Trp Lys Glu Ser Arg Leu Asn
    210   215   220
Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu Asp Tyr Lys Asp
225   230   235   240
Asp Asp Asp Lys Asp Tyr Lys Asp Asp Asp Asp Lys Asp Tyr Lys Asp
                245   250   255
Asp Asp Asp Lys His His His His His His
            260   265

<210> 345
<211> 1116
<212> DNA
<213> Artificial Sequence

<220>
<223> GITR Ig synthesized molecule

<400> 345
cagcgcccca ccgggggtcc cgggtgcggc cctgggcgcc tcctgcttgg gacgggaacg 60
gacgcgcgct gctgccgggt tcacacgacg cgctgctgcc gcgattaccc gggcgaggag 120
tgctgttccg agtgggactg catgtgtgtc cagcctgaat tccactgcgg agacccttgc 180
tgcacgacct gccggcacca cccttgtccc ccaggccagg gggtacagtc ccaggggaaa 240
ttcagttttg gcttccagtg tatcgactgt gcctcgggga ccttctccgg gggccacgaa 300
ggccactgca aaccttggac agactgcacc cagttcgggt ttctcactgt gttccctggg 360
aacaagaccc acaacgctgt gtgcgtccca gggtccccgc cggcagagcc gcttgggctc 420
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 480
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 540
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 600
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 660
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 720
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 780
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 840
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 900
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 960
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 1020
cggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 1080
tacacgcaga agagcctctc cctgtctccg ggttaa 1116

<210> 346
<211> 371

<212> PRT
<213> Artificial Sequence

<220>
<223> GITR Ig synthesized molecule

<400> 346
Gln Arg Pro Thr Gly Gly Pro Gly Cys Gly Pro Gly Arg Leu Leu Leu
 1   5   10   15
Gly Thr Gly Thr Asp Ala Arg Cys Cys Arg Val His Thr Thr Arg Cys
            20   25   30
Cys Arg Asp Tyr Pro Gly Glu Glu Cys Cys Ser Glu Trp Asp Cys Met
        35   40   45
Cys Val Gln Pro Glu Phe His Cys Gly Asp Pro Cys Cys Thr Thr Cys
    50   55   60
Arg His His Pro Cys Pro Pro Gly Gln Gly Val Gln Ser Gln Gly Lys
65   70   75   80
Phe Ser Phe Gly Phe Gln Cys Ile Asp Cys Ala Ser Gly Thr Phe Ser
                85   90   95
Gly Gly His Glu Gly His Cys Lys Pro Trp Thr Asp Cys Thr Gln Phe
            100   105   110
Gly Phe Leu Thr Val Phe Pro Gly Asn Lys Thr His Asn Ala Val Cys
        115   120   125
Val Pro Gly Ser Pro Pro Ala Glu Pro Leu Gly Leu Glu Pro Lys Ser
    130   135   140
Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
145   150   155   160
Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                165   170   175
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            180   185   190
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        195   200   205
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    210   215   220
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
225   230   235   240
Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
                245   250   255
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            260   265   270
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
        275   280   285
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    290   295   300
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
305   310   315   320
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                325   330   335
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            340   345   350
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        355   360   365
Ser Pro Gly
    370

<210> 347
<211> 1137
<212> DNA
<213> Artificial Sequence

<220>
<223> PD1 Ig synthesized molecule

<400> 347
ttagactccc cagacaggcc ctggaacccc cccaccttct ccccagccct gctcgtggtg 60
accgaagggg acaacgccac cttcacctgc agcttctcca acacatcgga gagcttcgtg 120

ctaaactggt accgcatgag ccccagcaac cagacggaca agctggccgc cttccccgag 180
gaccgcagcc agcccggcca ggactgccgc ttccgtgtca cacaactgcc caacgggcgt 240
gacttccaca tgagcgtggt cagggcccgg cgcaatgaca gcggcaccta cctctgtggg 300
gccatctccc tggcccccaa ggcgcagatc aaagagagcc tgcgggcaga gctcagggtg 360
acagagagaa gggcagaagt gcccacagcc caccccagcc cctcacccag gccagccggc 420
cagttccaac tcgagcagcc cagagggccc acaatcaagc cctgtcctcc atgcaaatgc 480
ccggctccaa atcttcttgg tggttcatcc gtcttcatct tccctccaaa gatcaaggat 540
gtactcatga tctccctgag ccccatagtc acatgtgtgg tggtggatgt gagcgaggac 600
gacccagatg tccagatcag ctggtttgtg aacaacgtgg aagtacacac agctcagaca 660
caaacccata gagaggatta caacagtact ctccgggtgg tcagtgccct ccccatccag 720
caccaggact ggatgagtgg caaggagttc aaatgcaagg tcaacaacaa agacctccca 780
gcgcccatcg agagaaccat ctcaaaaccc aaagggtcag taagagctcc acaggtatat 840
gtcttgcctc caccagaaga agagatgact aagaaacagg tcactctgac ctgcatggtc 900
acagacttca tgcctgaaga catttacgtg gagtggacta acaacgggaa aacagagcta 960
aactacaaga acactgaacc agtcctggac tctgatggtt cttacttcat gtacagcaag 1020
ctgagagtgg aaaagaagaa ctgggtggaa agaaatagct actcctgttc agtggtccac 1080
gagggtctgc acaatcacca cacgactaag agcttctccc ggactccggg taaataa 1137

<210> 348
<211> 378
<212> PRT
<213> Artificial Sequence

<220>
<223> PD1 Ig synthesized molecule

<400> 348
Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala
 1   5   10   15
Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser Phe
            20   25   30
Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro
        35   40   45
Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln
    50   55   60
Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg
65   70   75   80
Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr
                85   90   95
Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu
            100   105   110
Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro
        115   120   125
Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln Leu
    130   135   140
Glu Gln Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys
145   150   155   160
Pro Ala Pro Asn Leu Leu Gly Gly Ser Ser Val Phe Ile Phe Pro Pro
                165   170   175
Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys
            180   185   190
Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp
        195   200   205
Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg
    210   215   220
Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln
225   230   235   240
His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn
                245   250   255
Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly
            260   265   270
Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu
        275   280   285
Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met
    290   295   300
Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu
305   310   315   320
Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe

325 330 335
Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn
340 345 350
Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr
355 360 365
Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
370 375

<210> 349
<211> 1995
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::M0115
fusion protein with H81 linker

<400> 349
agcccaggcc agggcaccca gtctgagaac agctgcaccc acttcccagg caacctgcct 60
aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggtgaag ttcaaattcc cttgaccgaa 1200
agttacagcc cgaattctca ggtgcagctg gtgcagtctg gggctgaggt gaagaagcct 1260
ggggcctcag tgaaggtctc ctgcaaggct tctggataca ccttcaccga ctacaacatg 1320
aactgggtgc gacaggcccc tggacaaggg cttgagtgga tgggaaatat tgatccttac 1380
tatggtggta ctagttacaa tcagaagttc aagggcaggg tcaccatgac cagggacacg 1440
tccatcagca cagcctacat ggagctgagc aggctgagat ctgacgacac ggccgtgtat 1500
tactgtgcga gatgggacta taggtacgac gacgggaggg cttactatgt tatggacttc 1560
tggggccaag ggaccacggt caccgtctcc tcaggtggag gcggttcagg cggaggtgga 1620
tccggcggtg gcggatcggg tggcggcgga tctgacatcg tgatgaccca gtctccagac 1680
tccctggctg tgtctctggg cgagagggcc accatcaact gcaagtccag ccagagtgtt 1740
ttatacagct ccaaccagaa gaactactta gcttggtacc agcagaaacc aggacagcct 1800
cctaagctgc tcatttactg ggcatctacc cgggaatccg gggtccctga ccgattcagt 1860
ggcagcgggt ctgggacaga tttcactctc accatcagca gcctgcaggc tgaagatgtg 1920
gcagtttatt actgtcatca atacctctac tcgtggacgt ttggccaggg gaccaagctg 1980
gagatcaaac ggtaa 1995

<210> 350
<211> 664
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A::M0115 fusion protein with H81 linker

<400> 350
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu

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        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly Glu Val Gln Ile Pro Leu Thr Glu
385                 390                 395                 400
Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu
                405                 410                 415
Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
            420                 425                 430
Tyr Thr Phe Thr Asp Tyr Asn Met Asn Trp Val Arg Gln Ala Pro Gly
        435                 440                 445
Gln Gly Leu Glu Trp Met Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr
    450                 455                 460
Ser Tyr Asn Gln Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr
465                 470                 475                 480
Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp
                485                 490                 495
Thr Ala Val Tyr Tyr Cys Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly
            500                 505                 510
Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly Gln Gly Thr Thr Val Thr
        515                 520                 525
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    530                 535                 540
Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp
545                 550                 555                 560
Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser
                565                 570                 575
Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp
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580 585 590
Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala
595 600 605
Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
610 615 620
Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val
625 630 635 640
Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln
645 650 655
Gly Thr Lys Leu Glu Ile Lys Arg
660

<210> 351
<211> 1986
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::M0115
fusion protein with H82 linker

<400> 351
agcccaggcc agggcaccca gtctgagaac agctgcaccc acttcccagg caacctgcct 60
aacatgcttc gagatctccg agatgccttc agcagagtga agactttctt tcaaatgaag 120
gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
cactacacgc agaagagcct ctccctgtct ccgggtcacg acggctcttc cctgaataca 1200
ccgaattctc aggtgcagct ggtgcagtct ggggctgagg tgaagaagcc tggggcctca 1260
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cgacaggccc ctggacaagg gcttgagtgg atgggaaata ttgatcctta ctatggtggt 1380
actagttaca atcagaagtt caagggcagg gtcaccatga ccagggacac gtccatcagc 1440
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agatgggact ataggtacga cgacgggagg gcttactatg ttatggactt ctggggccaa 1560
gggaccacgg tcaccgtctc ctcaggtgga ggcggttcag gcggaggtgg atccggcggt 1620
ggcggatcgg gtggcggcgg atctgacatc gtgatgaccc agtctccaga ctccctggct 1680
gtgtctctgg gcgagagggc caccatcaac tgcaagtcca gccagagtgt tttatacagc 1740
tccaaccaga agaactactt agcttggtac cagcagaaac caggacagcc tcctaagctg 1800
ctcatttact gggcatctac ccgggaatcc ggggtccctg accgattcag tggcagcggg 1860
tctgggacag atttcactct caccatcagc agcctgcagg ctgaagatgt ggcagtttat 1920
tactgtcatc aatacctcta ctcgtggacg tttggccagg ggaccaagct ggagatcaaa 1980
cggtaa 1986

<210> 352
<211> 661
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A::M0115 fusion protein with H82 linker

<400> 352
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro

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 1               5                  10                  15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20                  25                  30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35                  40                  45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50                  55                  60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65                  70                  75                  80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
                85                  90                  95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100                 105                 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
        115                 120                 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
    130                 135                 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145                 150                 155                 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                165                 170                 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
            180                 185                 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        195                 200                 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    210                 215                 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225                 230                 235                 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                245                 250                 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
            260                 265                 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        275                 280                 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    290                 295                 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305                 310                 315                 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                325                 330                 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            340                 345                 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        355                 360                 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    370                 375                 380
Lys Ser Leu Ser Leu Ser Pro Gly His Asp Gly Ser Ser Leu Asn Thr
385                 390                 395                 400
Pro Asn Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
                405                 410                 415
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
            420                 425                 430
Thr Asp Tyr Asn Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
        435                 440                 445
Glu Trp Met Gly Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn
    450                 455                 460
Gln Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
465                 470                 475                 480
Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
                485                 490                 495
Tyr Tyr Cys Ala Arg Trp Asp Tyr Arg Tyr Asp Asp Gly Arg Ala Tyr
            500                 505                 510
Tyr Val Met Asp Phe Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        515                 520                 525
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    530                 535                 540
Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
```

```
545                 550                 555                 560
Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
                565                 570                 575
Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
            580                 585                 590
Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
        595                 600                 605
Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    610                 615                 620
Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
625                 630                 635                 640
Tyr Cys His Gln Tyr Leu Tyr Ser Trp Thr Phe Gly Gln Gly Thr Lys
                645                 650                 655
Leu Glu Ile Lys Arg
            660
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<210> 353
<211> 2001
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding IL10 I87A::MO115
fusion protein with H83 linker

<400> 353

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gatcagctgg acaacttgtt gttaaaggag tccttgctgg aggactttaa gggttacctg 180
ggttgccaag ccttgtctga gatgatccag ttttacctgg aggaggtgat gccccaagct 240
gagaaccaag acccagacgc caaggcgcat gtgaactccc tgggggagaa cctgaagacc 300
ctcaggctga ggctacggcg ctgtcatcga tttcttccct gtgaaaacaa gagcaaggcc 360
gtggagcagg tgaagaatgc ctttaataag ctccaagaga aaggcatcta caaagccatg 420
agtgagtttg acatcttcat caactacata gaagcctaca ttacaatgaa gatacgaaac 480
ctcgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
gcgggtgcac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 600
cggaccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 660
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 720
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
aatggcaagg cgtacgcgtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 840
accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 900
cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatcca 960
agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 1080
agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140
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aagcctgggg cctcagtgaa ggtctcctgc aaggcttctg gatacacctt caccgactac 1320
aacatgaact gggtgcgaca ggcccctgga caagggcttg agtggatggg aaatattgat 1380
ccttactatg gtggtactag ttacaatcag aagttcaagg gcagggtcac catgaccagg 1440
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ccagactccc tggctgtgtc tctgggcgag agggccacca tcaactgcaa gtccagccag 1740
agtgttttat acagctccaa ccagaagaac tacttagctt ggtaccagca gaaaccagga 1800
cagcctccta agctgctcat ttactgggca tctacccggg aatccggggt ccctgaccga 1860
ttcagtggca gcgggtctgg gacagatttc actctcacca tcagcagcct gcaggctgaa 1920
gatgtggcag tttattactg tcatcaatac ctctactcgt ggacgtttgg ccaggggacc 1980
aagctggaga tcaaacggta a                                          2001
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<210> 354
<211> 666
<212> PRT
<213> Artificial Sequence

<220>

<223> IL10 I87A::M0115 fusion protein with H83 linker

<400> 354
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Ile Thr Met Lys Ile Arg Asn
145 150 155 160
Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
260 265 270
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
290 295 300
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
370 375 380
Lys Ser Leu Ser Leu Ser Pro Gly Ser Ser Leu Asn Thr Gly Thr Gln
385 390 395 400
Met Ala Gly His Ser Pro Asn Ser Gln Val Gln Leu Val Gln Ser Gly
405 410 415
Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
420 425 430
Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met Asn Trp Val Arg Gln Ala
435 440 445
Pro Gly Gln Gly Leu Glu Trp Met Gly Asn Ile Asp Pro Tyr Tyr Gly
450 455 460
Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Arg Val Thr Met Thr Arg
465 470 475 480
Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser
485 490 495
Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Asp Tyr Arg Tyr Asp
500 505 510
Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly Gln Gly Thr Thr

515 520 525
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
530 535 540
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
545 550 555 560
Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
565 570 575
Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu
580 585 590
Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
595 600 605
Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
610 615 620
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
625 630 635 640
Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr Ser Trp Thr Phe
645 650 655
Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
660 665

<210> 355
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> H68 Linker

<400> 355
Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 356
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> H69 Linker

<400> 356
Glu Gln Lys Leu Ser Asn Met Glu Asn Arg Leu Lys Pro Phe Phe Thr
1 5 10 15
Ser Gly Ser Ala Asp Thr Ser Pro Asn Ser
20 25

<210> 357
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> H77 Linker

<400> 357
Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Pro Asn
1 5 10 15
Ser

<210> 358
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<223> H78 Linker

<400> 358
Asn Ser Leu Phe Asn Gln Glu Val Gln Ile Pro Pro Asn Ser
 1   5   10

<210> 359
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> H79 Linker

<400> 359
Asn Ser Leu Phe Asn Gln Glu Val Pro Asn Ser
 1   5   10

<210> 360
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> H80 Linker

<400> 360
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Pro Asn Ser
 1   5   10

<210> 361
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> H81 Linker

<400> 361
Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
 1   5   10

<210> 362
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> H82 Linker

<400> 362
His Asp Gly Ser Ser Leu Asn Thr Pro Asn Ser
 1   5   10

<210> 363
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> H83 Linker

<400> 363
Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser Pro Asn Ser
 1   5   10   15

<210> 364
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> A2 Hinge

<400> 364
Pro Pro Pro Pro Pro Cys Pro Pro Cys
 1   5

<210> 365
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75 Linker

<400> 365
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 366
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75aLinker

<400> 366
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr Gln Lys Ala Arg
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 367
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75b Linker

<400> 367
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Arg
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 368
<211> 21

<212> PRT
<213> Artificial Sequence

<220>
<223> H75c Linker

<400> 368
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Lys Ala Gly
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 369
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75d Linker

<400> 369
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Met Ala Gly
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 370
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75e Linker

<400> 370
Gln Arg His Asn Asn Ser Ser Leu Asn Thr Arg Thr Gln Met Ala Arg
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 371
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75f Linker

<400> 371
Gln Arg His Ala Asn Ser Ala Leu Asn Thr Gly Thr Gln Met Ala Gly
 1   5   10   15
His Ser Pro Asn Ser
            20

<210> 372
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75g Linker

<400> 372
Gln Arg His Asn Ala Ala Ser Leu Asn Thr Gly Thr Gln Met Ala Gly

1 5 10 15
His Ser Pro Asn Ser
20

<210> 373
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75h Linker

<400> 373
Gln Arg His Ala Ala Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
1 5 10 15
His Ser Pro Asn Ser
20

<210> 374
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> H68a Linker

<400> 374
Asn Ser Leu Ala Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 375
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> H68b Linker

<400> 375
Asn Ser Gly Phe Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 376
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> H68c Linker

<400> 376
Asn Ser Gly Ala Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr
1 5 10 15
Ser Pro Asn Ser
20

<210> 377
<211> 16
<212> PRT

<213> Artificial Sequence

<220>
<223> H68s Linker

<400> 377
Asn Gln Glu Val Gln Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser
 1   5   10   15

<210> 378
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Variable Region Linker Subunit

<400> 378
Gly Gly Gly Gly Ser
 1   5

<210> 379
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10 Linker

<400> 379
Gly Gly Gly Ser Gly Gly
 1   5

<210> 380
<211> 166
<212> PRT
<213> Artificial Sequence

<220>
<223> monoIL10 synthesized molecule

<400> 380
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
 1   5   10   15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
            20   25   30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
        35   40   45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
    50   55   60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65   70   75   80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
                85   90   95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
            100   105   110
Pro Cys Glu Asn Gly Gly Gly Ser Gly Gly Lys Ser Lys Ala Val Glu
        115   120   125
Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys
    130   135   140
Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met
145   150   155   160
Thr Met Lys Ile Arg Asn
                165

<210> 381
<211> 160
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87A synthesized molecule

<400> 381
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ala Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 382
<211> 160
<212> PRT
<213> Artificial Sequence

<220>
<223> IL10 I87S synthesized molecule

<400> 382
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ser Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95
Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 383
<211> 10
<212> PRT
<213> Homo sapiens

<400> 383
Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 1   5   10

<210> 384
<211> 7
<212> PRT
<213> Homo sapiens

<400> 384
Glu Arg Lys Cys Cys Val Glu
 1   5

<210> 385
<211> 12
<212> PRT
<213> Homo sapiens

<400> 385
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr
 1   5   10

<210> 386
<211> 10
<212> PRT
<213> Homo sapiens

<400> 386
Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro
 1   5   10

<210> 387
<211> 7
<212> PRT
<213> Homo sapiens

<400> 387
Glu Ser Lys Tyr Gly Pro Pro
 1   5

<210> 388
<211> 5
<212> PRT
<213> Homo sapiens

<400> 388
Cys Pro Arg Cys Pro
 1   5

<210> 389
<211> 5
<212> PRT
<213> Homo sapiens

<400> 389
Cys Pro Ser Cys Pro
 1   5

<210> 390
<211> 17
<212> PRT

<213> Homo sapiens

<400> 390
Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro Arg Cys
 1   5   10   15
Pro

<210> 391
<211> 15
<212> PRT
<213> Homo sapiens

<400> 391
Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 1   5   10   15

<210> 392
<211> 34
<212> PRT
<213> Homo sapiens

<400> 392
Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala Gln Pro Gln
 1   5   10   15
Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala Thr Thr Arg
            20   25   30
Asn Thr

<210> 393
<211> 24
<212> PRT
<213> Homo sapiens

<400> 393
Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys Glu Lys Glu Glu Gln
 1   5   10   15
Glu Glu Arg Glu Thr Lys Thr Pro
            20

<210> 394
<211> 19
<212> PRT
<213> Homo sapiens

<400> 394
Val Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro Pro Thr Pro
 1   5   10   15
Ser Pro Ser

<210> 395
<211> 6
<212> PRT
<213> Homo sapiens

<400> 395
Val Pro Pro Pro Pro Pro
 1   5

<210> 396

<211> 107
<212> PRT
<213> Homo sapiens

<400> 396
Val Cys Ser Arg Asp Phe Thr Pro Pro Thr Val Lys Ile Leu Gln Ser
 1   5   10   15
Ser Ser Asp Gly Gly Gly His Phe Pro Pro Thr Ile Gln Leu Leu Cys
            20   25   30
Leu Val Ser Gly Tyr Thr Pro Gly Thr Ile Asn Ile Thr Trp Leu Glu
        35   40   45
Asp Gly Gln Val Met Asp Val Asp Leu Ser Thr Ala Ser Thr Thr Gln
    50   55   60
Glu Gly Glu Leu Ala Ser Thr Gln Ser Glu Leu Thr Leu Ser Gln Lys
65   70   75   80
His Trp Leu Ser Asp Arg Thr Tyr Thr Cys Gln Val Thr Tyr Gln Gly
                85   90   95
His Thr Phe Glu Asp Ser Thr Lys Lys Cys Ala
            100   105

<210> 397
<211> 112
<212> PRT
<213> Homo sapiens

<400> 397
Val Ile Ala Glu Leu Pro Pro Lys Val Ser Val Phe Val Pro Pro Arg
 1   5   10   15
Asp Gly Phe Phe Gly Asn Pro Arg Lys Ser Lys Leu Ile Cys Gln Ala
            20   25   30
Thr Gly Phe Ser Pro Arg Gln Ile Gln Val Ser Trp Leu Arg Glu Gly
        35   40   45
Lys Gln Val Gly Ser Gly Val Thr Thr Asp Gln Val Gln Ala Glu Ala
    50   55   60
Lys Glu Ser Gly Pro Thr Thr Tyr Lys Val Thr Ser Thr Leu Thr Ile
65   70   75   80
Lys Glu Ser Asp Trp Leu Gly Gln Ser Met Phe Thr Cys Arg Val Asp
                85   90   95
His Arg Gly Leu Thr Phe Gln Gln Asn Ala Ser Ser Met Cys Val Pro
            100   105   110

<210> 398
<211> 5
<212> PRT
<213> Homo sapiens

<400> 398
Cys Pro Pro Cys Pro
 1   5

<210> 399
<211> 1614
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding CTLA4 x IL10 IgA
      fusion protein

<400> 399
atgcacgtgg cccagcctgc tgtggtactg gccagcagcc gaggcatcgc cagctttgtg 60
tgtgagtatg catctccagg caaagccact gaggtccggg tgacagtgct tcggcaggct 120
gacagccagg tgactgaagt ctgtgcggca acctacatga tggggaatga gttgaccttc 180
ctagatgatt ccatctgcac gggcacctcc agtggaaatc aagtgaacct cactatccaa 240
ggactgaggg ccatggacac gggactctac atctgcaagg tggagctcat gtacccaccg 300

ccatactacc tgggcatagg caacggaacc cagatttatg taattgatcc agaaccgtgc 360
ccagattctg acctcgagcc caaatcttct gacaaaactc acacatgccc accgtgccca 420
gcacctgaag ccgcgggtgc accgtcagtc ttcctcttcc ccccaaaacc caaggacacc 480
ctcatgatct cccggacccc tgaggtcaca tgcgtggtgg tggacgtgag ccacgaagac 540
cctgaggtca agttcaactg gtacgtggac ggcgtggagg tgcataatgc caagacaaag 600
ccgcgggagg agcagtacaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac 660
caggactggc tgaatggcaa ggcgtacgcg tgcgcggtct ccaacaaagc cctcccagcc 720
cccatcgaga aaaccatctc caaagccaaa gggcagcccc gagaaccaca ggtgtacacc 780
ctgccccccat cccgggatga gctgaccaag aaccaggtca gcctgacctg cctggtcaaa 840
ggcttctatc caagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 900
tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaagctc 960
accgtggaca agagcaggtg gcagcagggg aacgtcttct catgctccgt gatgcatgag 1020
gctctgcaca accactacac gcagaagagc ctctccctgt ctccgggtcc ctcaactcca 1080
cctaccccat ctccctcaac tccacctacc ccatctccct caccgaattc tagcccaggc 1140
cagggcaccc agtctgagaa cagctgcacc cacttcccag gcaacctgcc taacatgctt 1200
cgagatctcc gagatgcctt cagcagagtg aagactttct ttcaaatgaa ggatcagctg 1260
gacaacttgt tgttaaagga gtccttgctg gaggacttta agggttacct gggttgccaa 1320
gccttgtctg agatgatcca gttttacctg gaggaggtga tgccccaagc tgagaaccaa 1380
gacccagaca tcaaggcgca tgtgaactcc ctgggggaga acctgaagac cctcaggctg 1440
aggctacggc gctgtcatcg atttcttccc tgtgaaaaca agagcaaggc cgtggagcag 1500
gtgaagaatg cctttaataa gctccaagag aaaggcatct acaaagccat gagtgagttt 1560
gacatcttca tcaactacat agaagcctac atgacaatga agatacgaaa ctaa 1614

<210> 400
<211> 537
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4 x IL10 IgA fusion protein

<400> 400
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1   5   10   15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20   25   30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35   40   45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50   55   60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65   70   75   80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85   90   95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100   105   110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp Leu Glu Pro Lys
        115   120   125
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
    130   135   140
Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
145   150   155   160
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                165   170   175
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            180   185   190
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        195   200   205
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    210   215   220
Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala Leu Pro Ala
225   230   235   240
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                245   250   255
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
            260   265   270
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
        275   280   285

```
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
    290                 295                 300
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
305                 310                 315                 320
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
                325                 330                 335
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
            340                 345                 350
Leu Ser Pro Gly Pro Ser Thr Pro Pro Thr Pro Ser Pro Ser Thr Pro
        355                 360                 365
Pro Thr Pro Ser Pro Ser Pro Asn Ser Ser Pro Gly Gln Gly Thr Gln
    370                 375                 380
Ser Glu Asn Ser Cys Thr His Phe Pro Gly Asn Leu Pro Asn Met Leu
385                 390                 395                 400
Arg Asp Leu Arg Asp Ala Phe Ser Arg Val Lys Thr Phe Phe Gln Met
                405                 410                 415
Lys Asp Gln Leu Asp Asn Leu Leu Leu Lys Glu Ser Leu Leu Glu Asp
            420                 425                 430
Phe Lys Gly Tyr Leu Gly Cys Gln Ala Leu Ser Glu Met Ile Gln Phe
        435                 440                 445
Tyr Leu Glu Glu Val Met Pro Gln Ala Glu Asn Gln Asp Pro Asp Ile
    450                 455                 460
Lys Ala His Val Asn Ser Leu Gly Glu Asn Leu Lys Thr Leu Arg Leu
465                 470                 475                 480
Arg Leu Arg Arg Cys His Arg Phe Leu Pro Cys Glu Asn Lys Ser Lys
                485                 490                 495
Ala Val Glu Gln Val Lys Asn Ala Phe Asn Lys Leu Gln Glu Lys Gly
            500                 505                 510
Ile Tyr Lys Ala Met Ser Glu Phe Asp Ile Phe Ile Asn Tyr Ile Glu
        515                 520                 525
Ala Tyr Met Thr Met Lys Ile Arg Asn
    530                 535
```

<210> 401
<211> 1530
<212> DNA
<213> Artificial Sequence

<220>
<223> M0115 PIMS synthesized molecule

<400> 401

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gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 60
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctcaggtgc agctggtgca gtctggggct 780
gaggtgaaga agcctggggc ctcagtgaag gtctcctgca aggcttctgg atacaccttc 840
accgactaca acatgaactg ggtgcgacag gcccctggac aagggcttga gtggatggga 900
aatattgatc cttactatgg tggtactagt tacaatcaga agttcaaggg cagggtcacc 960
atgaccaggg acacgtccat cagcacagcc tacatggagc tgagcaggct gagatctgac 1020
gacacggccg tgtattactg tgcgagatgg gactataggt acgacgacgg gagggcttac 1080
tatgttatgg acttctgggg ccaagggacc acggtcaccg tctcctcagg tggaggcggt 1140
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catcgtgatg 1200
acccagtctc cagactccct ggctgtgtct ctgggcgaga gggccaccat caactgcaag 1260
tccagccaga gtgttttata cagctccaac cagaagaact acttagcttg gtaccagcag 1320
aaaccaggac agcctcctaa gctgctcatt tactgggcat ctacccggga atccggggtc 1380
cctgaccgat tcagtggcag cgggtctggg acagatttca ctctcaccat cagcagcctg 1440
caggctgaag atgtggcagt ttattactgt catcaatacc tctactcgtg gacgtttggc 1500
```

caggggacca agctggagat caaacggtaa 1530

<210> 402
<211> 509
<212> PRT
<213> Artificial Sequence

<220>
<223> M0115 PIMS synthesized molecule

<400> 402
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15
Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
100 105 110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130 135 140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225 230 235 240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Val
245 250 255
Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser
260 265 270
Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met Asn Trp Val
275 280 285
Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Asn Ile Asp Pro
290 295 300
Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Arg Val Thr
305 310 315 320
Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg
325 330 335
Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Asp Tyr
340 345 350
Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly Gln
355 360 365
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
370 375 380
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
385 390 395 400
Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
405 410 415
Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys
420 425 430
Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
435 440 445
Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe

```
    450                 455                 460
Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
465                 470                 475                 480
Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr Ser
                485                 490                 495
Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            500                 505
```

<210> 403
<211> 1095
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding murine CTLA4 fusion
to human Fc domains

<400> 403

```
gccatacagg tgacccaacc ttcagtggtg ttggctagca gccatggtgt cgccagcttt 60
ccatgtgaat attcaccatc acacaacact gatgaggtcc gggtgactgt gctgcggcag 120
acaaatgacc aaatgactga ggtctgtgcc acgacattca cagagaagaa tacagtgggc 180
ttcctagatt acccccttctg cagtggtacc tttaatgaaa gcagagtgaa cctcaccatc 240
caaggactga gagctgttga cacgggactg tacctctgca aggtggaact catgtaccca 300
ccgccatact ttgtgggcat gggcaacggg acgcagattt atgtcattga tccagaacca 360
tgcccggatt ctgacctcga gcccagagtg cccataacac agaaccctg tcctccactc 420
aaagagtgtc ccccatgcgc agctccagac gcagcgggtg cgccatccgt cttcatcttc 480
cctccaaaga tcaaggatgt actcatgatc tccctgagcc ccatggtcac atgtgtggtg 540
gtggatgtga gcgaggatga cccagacgtc cagatcagct ggtttgtgaa caacgtggaa 600
gtacacacag ctcagacaca aacccataga gaggattaca acagtactct ccgggtggtc 660
agtgccctcc ccatccagca ccaggactgg atgagtggca aggcgttcgc atgcgcggtc 720
aacaacagag ccctcccatc ccccatcgag aaaaccatct caaaacccag agggccagta 780
agagctccac aggtatatgt cttgcctcca ccagcagaag agatgactaa gaaagagttc 840
agtctgacct gcatgatcgc aggcttctta cctgccgaaa ttgctgtgga ctggaccagc 900
aatgggcgta cagagcaaaa ctacaagaac accgcaacag tcctggactc tgatggttct 960
tacttcatgt acagcaagct cagagtacaa aagagcactt gggaaagagg aagtcttttc 1020
gcctgctcag tggtccacga gggtctgcac aatcacctta cgactaagac catctcccgg 1080
tctctgggta aataa                                                  1095
```

<210> 404
<211> 364
<212> PRT
<213> Artificial Sequence

<220>
<223> Murine CTLA4 fusion to human Fc domains

<400> 404

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

```
Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val
                165                 170                 175
Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile
            180                 185                 190
Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr
        195                 200                 205
His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro
    210                 215                 220
Ile Gln His Gln Asp Trp Met Ser Gly Lys Ala Phe Ala Cys Ala Val
225                 230                 235                 240
Asn Asn Arg Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro
                245                 250                 255
Arg Gly Pro Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala
            260                 265                 270
Glu Glu Met Thr Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Ala Gly
        275                 280                 285
Phe Leu Pro Ala Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr
    290                 295                 300
Glu Gln Asn Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser
305                 310                 315                 320
Tyr Phe Met Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg
                325                 330                 335
Gly Ser Leu Phe Ala Cys Ser Val Val His Glu Gly Leu His Asn His
            340                 345                 350
Leu Thr Thr Lys Thr Ile Ser Arg Ser Leu Gly Lys
        355                 360
```

<210> 405
<211> 570
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence encoding PD1 ectodomain fused to a C-terminal AviTag

<400> 405
ttagactccc cagacaggcc ctggaacccc cccaccttct ccccagccct gctcgtggtg 60
accgaagggg acaacgccac cttcacctgc agcttctcca acacatcgga gagcttcgtg 120
ctaaactggt accgcatgag ccccagcaac cagacggaca agctggccgc cttccccgag 180
gaccgcagcc agcccggcca ggactgccgc ttccgtgtca cacaactgcc caacgggcgt 240
gacttccaca tgagcgtggt cagggcccgg cgcaatgaca gcggcaccta cctctgtggg 300
gccatctccc tggcccccaa ggcgcagatc aaagagagcc tgcgggcaga gctcagggtg 360
acagagagaa gggcagaagt gcccacagcc caccccagcc cctcacccag gccagccggc 420
cagttccaat ctagactgaa cgacatcttc gaggctcaga aaatcgaatg gcacgaagat 480
tacaaggatg acgacgataa ggattacaag gatgacgacg ataaggatta caaggatgac 540
gacgataagc atcatcatca tcatcactga   570

<210> 406
<211> 189
<212> PRT
<213> Artificial Sequence

<220>
<223> PD1 ectodomain fused to a C-terminal AviTag

<400> 406
```
Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr Phe Ser Pro Ala
 1                5                  10                  15
Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe Thr Cys Ser Phe
            20                  25                  30
Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr Arg Met Ser Pro
        35                  40                  45
Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln
    50                  55                  60
Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu Pro Asn Gly Arg
65                  70                  75                  80
```

Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn Asp Ser Gly Thr
85 90 95
Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu
100 105 110
Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg Ala Glu Val Pro
115 120 125
Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly Gln Phe Gln Ser
130 135 140
Arg Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu Asp
145 150 155 160
Tyr Lys Asp Asp Asp Asp Lys Asp Tyr Lys Asp Asp Asp Asp Lys Asp
165 170 175
Tyr Lys Asp Asp Asp Asp Lys His His His His His His
180 185

<210> 407
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> H75i Linker

<400> 407
Gln Arg His Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly His Ser
1 5 10 15
Pro Asn Ser

<210> 408
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> H75j Linker

<400> 408
Gln Arg His Gly Gly Ser Ser Leu Asn Thr Gly Thr Gln Met Ala Gly
1 5 10 15
His Ser Pro Asn Ser
20

<210> 409
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> human IgG1 CH2 and CH3 regions

<400> 409
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

```
            100                 105                 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        115                 120                 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205
Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215


<210> 410
<211> 124
<212> PRT
<213> Homo sapiens

<400> 410
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1               5                  10                  15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Ala Thr Glu Val
            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Leu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp
        115                 120


<210> 411
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> CTLA4 with  A29Y L104E mutatations

<400> 411
Met His Val Ala Gln Pro Ala Val Val Leu Ala Ser Ser Arg Gly Ile
 1               5                  10                  15
Ala Ser Phe Val Cys Glu Tyr Ala Ser Pro Gly Lys Tyr Thr Glu Val
            20                  25                  30
Arg Val Thr Val Leu Arg Gln Ala Asp Ser Gln Val Thr Glu Val Cys
        35                  40                  45
Ala Ala Thr Tyr Met Met Gly Asn Glu Leu Thr Phe Leu Asp Asp Ser
    50                  55                  60
Ile Cys Thr Gly Thr Ser Ser Gly Asn Gln Val Asn Leu Thr Ile Gln
65                  70                  75                  80
Gly Leu Arg Ala Met Asp Thr Gly Leu Tyr Ile Cys Lys Val Glu Leu
                85                  90                  95
Met Tyr Pro Pro Pro Tyr Tyr Glu Gly Ile Gly Asn Gly Thr Gln Ile
            100                 105                 110
Tyr Val Ile Asp Pro Glu Pro Cys Pro Asp Ser Asp
        115                 120
```

<210> 412
<211> 134
<212> PRT
<213> Homo sapiens

<400> 412

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

<210> 413
<211> 1530
<212> DNA
<213> Artificial Sequence

<220>
<223> FUN1 PIMS M0115 synthesized molecule

<400> 413

```
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 60
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 120
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 180
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 240
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 300
ggcaaggcgt acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 360
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 420
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 480
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 540
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 600
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 660
tacacgcaga agagcctctc cctgtctccg ggtaactcat tattcaacca agaagttcaa 720
attcccttga ccgaaagtta cagcccgaat tctcaggtgc agctggtgca gtctggggct 780
gaggtgaaga agcctggggc ctcagtgaag gtctcctgca aggcttctgg atacaccttc 840
accgactaca acatgaactg ggtgcgacag gcccctggac aagggcttga gtggatggga 900
aatattgatc cttactatgg tggtactagt tacaatcaga agttcaaggg cagggtcacc 960
atgaccaggg acacgtccat cagcacagcc tacatggagc tgagcaggct gagatctgac 1020
gacacggccg tgtattactg tgcgagatgg gactataggt acgacgacgg gagggcttac 1080
tatgttatgg acttctgggg ccaagggacc acggtcaccg tctcctcagg tggaggcggt 1140
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catcgtgatg 1200
acccagtctc cagactccct ggctgtgtct ctgggcgaga gggccaccat caactgcaag 1260
tccagccaga gtgttttata cagctccaac cagaagaact acttagcttg gtaccagcag 1320
aaaccaggac agcctcctaa gctgctcatt tactgggcat ctacccggga atccggggtc 1380
cctgaccgat tcagtggcag cgggtctggg acagatttca ctctcaccat cagcagcctg 1440
caggctgaag atgtggcagt ttattactgt catcaatacc tctactcgtg gacgtttggc 1500
caggggacca agctggagat caaacggtaa                                  1530
```

<210> 414
<211> 509
<212> PRT
<213> Artificial Sequence

<220>

<223> FUN1 PIMS M0115 synthesized molecule

<400> 414

```
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1               5                  10                  15
Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95
Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys Ala
            100                 105                 110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
    130                 135                 140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220
Ser Leu Ser Leu Ser Pro Gly Asn Ser Leu Phe Asn Gln Glu Val Gln
225                 230                 235                 240
Ile Pro Leu Thr Glu Ser Tyr Ser Pro Asn Ser Gln Val Gln Leu Val
                245                 250                 255
Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser
            260                 265                 270
Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met Asn Trp Val
        275                 280                 285
Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Asn Ile Asp Pro
    290                 295                 300
Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Arg Val Thr
305                 310                 315                 320
Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg
                325                 330                 335
Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Asp Tyr
            340                 345                 350
Arg Tyr Asp Asp Gly Arg Ala Tyr Tyr Val Met Asp Phe Trp Gly Gln
        355                 360                 365
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met
385                 390                 395                 400
Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                405                 410                 415
Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Gln Lys
            420                 425                 430
Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
        435                 440                 445
Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
    450                 455                 460
Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
465                 470                 475                 480
Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln Tyr Leu Tyr Ser
                485                 490                 495
Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            500                 505
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<210> 415
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Human IgG1 CH2CH3 desLys

<400> 415
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
115 120 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205
Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 416
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> Human IgG1 CH2CH3 Null2

<400> 416
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
85 90 95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
115 120 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

145 150 155 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205
Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215

<210> 417
<211> 216
<212> PRT
<213> Human IgG1 CH2CH3 Null2 desLysArtificial Sequence

<220>
<223> Human IgG1 CH2CH3 Null2 desLys

<400> 417
Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80
Gln Asp Trp Leu Asn Gly Lys Ala Tyr Ala Cys Ala Val Ser Asn Lys
85 90 95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
100 105 110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
115 120 125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
130 135 140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145 150 155 160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
165 170 175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
180 185 190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205
Lys Ser Leu Ser Leu Ser Pro Gly
210 215

<210> 418
<211> 160
<212> PRT
<213> Homo sapiens

<400> 418
Ser Pro Gly Gln Gly Thr Gln Ser Glu Asn Ser Cys Thr His Phe Pro
1 5 10 15
Gly Asn Leu Pro Asn Met Leu Arg Asp Leu Arg Asp Ala Phe Ser Arg
20 25 30
Val Lys Thr Phe Phe Gln Met Lys Asp Gln Leu Asp Asn Leu Leu Leu
35 40 45
Lys Glu Ser Leu Leu Glu Asp Phe Lys Gly Tyr Leu Gly Cys Gln Ala
50 55 60
Leu Ser Glu Met Ile Gln Phe Tyr Leu Glu Glu Val Met Pro Gln Ala
65 70 75 80
Glu Asn Gln Asp Pro Asp Ile Lys Ala His Val Asn Ser Leu Gly Glu
85 90 95

Asn Leu Lys Thr Leu Arg Leu Arg Leu Arg Arg Cys His Arg Phe Leu
100 105 110
Pro Cys Glu Asn Lys Ser Lys Ala Val Glu Gln Val Lys Asn Ala Phe
115 120 125
Asn Lys Leu Gln Glu Lys Gly Ile Tyr Lys Ala Met Ser Glu Phe Asp
130 135 140
Ile Phe Ile Asn Tyr Ile Glu Ala Tyr Met Thr Met Lys Ile Arg Asn
145 150 155 160

<210> 419
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterologous leader sequence

<220>
<221> VARIANT
<222> 23
<223> Xaa = Any Amino Acid

<400> 419
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15
Val Ile Met Ser Arg Gly Xaa
20

<210> 420
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterologous leader sequence

<220>
<221> VARIANT
<222> 23, 24
<223> Xaa = Any Amino Acid

<400> 420
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15
Val Ile Met Ser Arg Gly Xaa Xaa
20

<210> 421
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterologous leader sequence

<220>
<221> VARIANT
<222> 23, 24, 25
<223> Xaa = Any Amino Acid

<400> 421
Met Asp Phe Gln Val Gln Ile Phe Ser Phe Leu Leu Ile Ser Ala Ser
1 5 10 15
Val Ile Met Ser Arg Gly Xaa Xaa Xaa
20 25

<210> 422
<211> 4
<212> PRT
<213> Unknown

<220>
<223> A naturally occurring or added motif that confers the capacity to form a disulfide bond

<400> 422
Cys Pro Pro Cys
 1