NOVEL RECEPTOR THAT BINDS CTLA-8

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ABSTRACT
Isolated receptors for CTLA-8, DNAs encoding such receptors, and pharmaceutical compositions made therefrom, are disclosed. The isolated receptors can be used to inhibit an immune response.
NOVEL RECEPTOR THAT BINDS CTLA-8
CROSS-REFERENCE TO RELATED APPLICATION


TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of cytokine receptors, and more specifically to cytokine receptor proteins having immunoregulatory activity.

BACKGROUND OF THE INVENTION

[0003] Cytokines are hormone-like molecules that regulate various aspects of an immune or inflammatory response. Cytokines exert their effects by specifically binding receptors present on cells, and transducing a signal to the cells. Rouvier et al. (J. Immunol. 150:5445; 1993) reported a novel cDNA which they termed CTLA-8. The putative CTLA-8 protein is 57% homologous to the predicted amino acid sequence of an open reading frame (ORF) present in Herpesvirus saimiri (HSV) referred to as HSV13 (Nicholas et al., Virology 179:189; 1990; Albrecht et al., J. Virol. 66:5047; 1992). However, the function, if any of either CTLA-8 or HSV13 was not known, nor was a receptor or binding protein for CTLA-8 or HSV13 known. Thus, prior to the present invention, there was a need in the art to determine the function of CTLA-8 and HSV13, and to identify receptor molecules or binding proteins that play a role in the function of these proteins.

SUMMARY OF THE INVENTION

[0004] The present invention identifies a novel receptor that binds CTLA-8 and HSV13, a viral homolog of CTLA-8; DNAs encoding the novel receptor and novel receptor proteins are provided. The receptor is a Type I transmembrane protein with 864 amino acid residues. Soluble forms of the receptor can be prepared and used to regulate immune responses in a therapeutic setting; accordingly, pharmaceutical compositions comprising soluble forms of the novel receptor are also disclosed. Deleted forms and fusion proteins comprising the novel receptor, and homologs thereof are also disclosed. Also provided are methods of regulating an immune response. These and other aspects of the present invention will become evident upon reference to the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0005] A soluble CTLA-8 protein and an ORF present in Herpesvirus saimiri (HSV13) expressed as a fusion protein comprising an immunoglobulin Fc region, and used to screen cells for expression of a receptor for CTLA-8. T cell thymoma EL4 cells were found to bind the HSV13/Fc as well as mCTLA/Fc fusion protein. A cDNA library from EL4 cells was prepared and screened for expression of the receptor. The receptor is a Type I transmembrane protein with 864 amino acid residues, which is referred to as CTLA-8R. Various forms of CTLA-8R were prepared, including CTLA-8R/Fc protein, a soluble CTLA8R which contains the signal peptide and extracellular domain of CTLA-8R, and a soluble CTLA8/Flag® construct.

CTLA-8, HSV13 and Homologous Proteins

[0006] CTLA-8 refers to a cDNA cloned from an activated T cell hybridoma clone (Rouvier et al., J. Immunol. 150:5445; 1993). Northern blot analysis indicated that CTLA-8 transcription was very tissue specific. The CTLA-8 gene was found to map at chromosomal site 1a in mice, and at 2q31 in humans. Although a protein encoded by the CTLA-8 gene was never identified by Rouvier et al, the predicted amino acid sequence of CTLA-8 was found to be 57% homologous to the predicted amino acid sequence of an ORF present in HSV, HSV13.

[0007] The complete nucleotide sequence of the genome of HSV has been reported (Albrecht et al., J. Virol. 66:5047; 1992). Additional studies on one of the HSV open reading frames (ORFs), HSV13, are described in Nicholas et al., Virology 179:189; 1990. HSV13 is a late gene which is present in the Hind III-G fragment of HSV. Antisera developed against peptides derived from HSV13 are believed to react with a late protein (Nicholas et al., supra).

[0008] As described U.S. Ser. No. 08/410,535, filed Mar. 23, 1995, full length murine CTLA-8 protein and a CTLA-8/ Fc fusion protein were expressed, tested, and found to act as a costimulant for the proliferation of T cells. Human CTLA-8 was identified by probing a human T cell library using a DNA fragment derived from degenerate PCR; homologs of CTLA-8 are expected to exist in other species as well. A full length HSV13 protein, as well as an HSV13/Fc fusion protein, were also expressed, and found to act in a similar manner to CTLA-8 protein. Moreover, other species of herpesviruses are also likely to encode proteins homologous to that encoded by HSV 13.

Proteins and Analogs

[0009] The present invention provides isolated CTLA-8R and homologs thereof having immunoregulatory activity. Such proteins are substantially free of contaminating endogenous materials and, optionally, without associated native- pattern glycosylation. Derivatives of CTLA-8R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionizable amino and carboxyl groups, for example, a CTLA-8R protein may be in the form of acidic or basic salts, or may be in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

[0010] The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. Covalent derivatives are prepared by linking particular functional groups to amino acid side chains or at the N- or C-termini.
Soluble forms of CTLA-8R are also within the scope of the invention. The nucleotide and predicted amino acid sequence is shown in SEQ ID NO:1 and 2. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 31 and 32. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. Soluble CTLA-8R comprises the signal peptide and the extracellular domain (residues 1 to 522 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for residues 1 through 31 of SEQ ID NO:1.

Other derivatives of the CTLA-8R protein and homologs thereof within the scope of this invention include covalent or aggregative conjugates of the protein or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, the conjugated peptide may be a signal (or leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the yeast α-factor leader).

Protein fusions may comprise peptides added to facilitate purification or identification of CTLA-8R proteins and homologs (e.g., poly-His). The amino acid sequence of the inventive proteins can also be linked to an identification peptide such as that described by Hopp et al., BioTechnology 6:1204 (1988). Such a highly antigenic peptide provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. The sequence of Hopp et al. is also specifically cleaved by bovine mucosal enterokinase, allowing removal of the peptide from the purified protein. Fusion proteins caged with such peptides may also be resistant to intracellular degradation in E. coli.

Fusion proteins further comprise the amino acid sequence of a CTLA-8R linked to an immunoglobulin Fc region. An exemplary Fc region is a human IgG1 having a nucleotide and amino acid sequence set forth in SEQ ID NO:4. Fragments of an Fc region may also be used, as can Fc mutemers such as those described in U.S. Ser. No. 08/145,830, filed Oct. 29, 1993. Depending on the portion of the Fc region used, a fusion protein may be expressed as a dimer, through formation of interchain disulfide bonds. If the fusion proteins are made with both heavy and light chains of an antibody, it is possible to form a protein oligomer with as many as four CTLA-8R regions.

In another embodiment, CTLA-8R and homologs thereof further comprise an oligomerizing zipper domain. Zipper domains are described in U.S. Ser. No. 08/107,353, filed Aug. 13, 1993, the relevant disclosure of which is incorporated by reference herein. Examples of leucine zipper domains are those found in the yeast transcription factor GCN4 and a heat-stable DNA-binding protein found in rat liver (C/EBP; Landschulz et al., Science 243:1681, 1989), the nuclear transforming proteins, fos and jun, which preferentially form a heterodimer (O’Shea et al., Science 245:646, 1989; Turner and Tjian, Science 243:1689, 1989), and the gene product of the murine proto-oncogene, c-myc (Landschulz et al., Science 240:1759, 1988). The fusogenic proteins of several different viruses, including paramyxovirus, coronaviruses, measles virus and many retroviruses, also possess leucine zipper domains (Buckland and Wild, Nature 338:547, 1989; Britton, Nature 353:394, 1991; Delwart and Mosialos, AIDS Research and Human Retroviruses 6:703, 1990).

Derivatives of CTLA-8R may also be used as immunogens, reagents in in vitro assays, or as binding agents for affinity purification procedures. Such derivatives may also be obtained by cross-linking agents, such as maleimidobenzoyl succinimide ester and N-hydroxysuccinimide, cytostatic and lysine residues. The inventive proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carboxydimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking). Once bound to a substrate, proteins may be used to selectively bind (for purposes of assay or purification) antibodies raised against the CTLA-8R or against other proteins which are similar to the CTLA-8R, as well as other proteins that bind CTLA-8R or its homologous proteins.

The present invention also includes CTLA-8R with or without associated native-pattern glycosylation. Proteins expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or slightly different in molecular weight and glycosylation pattern than the native molecules, depending on the expression system. Expression of DNAs encoding the inventive proteins in bacteria such as E. coli provides non-glycosylated molecules. Functional mutant analogs of CTLA-8R protein or homologs thereof having inactivated N-glycosylation sites can be produced by oligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogeneous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterized by the amino acid triplet Asn-X-Ser or Thr. In this sequence, asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A and Z, or an amino acid other than Asn between Asn and A.

CTLA-8R protein derivatives may also be obtained by mutations of the native CTLA-8R or its subunits. A CTLA-8R mutated protein, as referred to herein, is a polypeptide homologous to a CTLA-8R but which has an amino acid sequence different from the native CTLA-8R because of one or a plurality of deletions, insertions or substitutions. The effect of any mutation made in a DNA encoding a CTLA-8R peptide may be easily determined by analyzing the ability of the mutated CTLA-8R peptide to inhibit costimulation of T or B cells by CTLA-8 or homologous proteins, to bind proteins that specifically bind CTLA-8R (for example, antibodies or proteins encoded by the CTLA-8 cDNA or the hV813 ORF). Moreover, activity of CTLA-8R analogs, mutemers or derivatives can be determined by any of the assays methods described herein. Similar mutations may be made in homologs of CTLA-8R, and tested in a similar manner.

Bioequivalent analogs of the inventive proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent dibasic
amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present.

Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those having physicochemical characteristics resembling those of the residue to be replaced. Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered. Subunits of viral proteins may be constructed by deleting terminal or internal residues or sequences. Additional guidance as to the types of mutations that can be made is provided by a comparison of the sequence of CTLA-8R to proteins that have similar structures, as well as by performing structural analysis of the inventive proteins.

Mutations in nucleotide sequences constructed for expression of analog CTLA-8R must, of course, preserve the reading frame phase of the coding sequences and preferably will not create complementary regions that could hybridize to produce secondary mRNA structures such as loops or hairpins which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation per se be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted at the target codon and the expressed mutated viral proteins screened for the desired activity.

Not all mutations in the nucleotide sequence which encodes a CTLA-8R protein or homolog thereof will be expressed in the final product, for example, nucleotide substitutions may be made to enhance expression, primarily to avoid secondary structure loops in the transcribed mRNA (see EPA 75,444 A, incorporated herein by reference), or to provide codons that are more readily translated by the selected host, e.g., the well-known E. coli preference codons for E. coli expression.

Mutations can be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes an analog having the desired amino acid insertion, substitution, or deletion.

Alternatively, oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Exemplary methods of making the alterations set forth above are disclosed by Walder et al. (Gene 42:133, 1986); Rauer et al. (Gene 37:73, 1985); Craik (BioTechniques, January 1985, 12-19); Smith et al. (Genetic Engineering: Principles and Methods, Plenum Press, 1981); and U.S. Pat. Nos. 4,518,584 and 4,737,462 disclose suitable techniques, and are incorporated by reference herein.

Due to code degeneracy, there can be considerable variation in nucleotide sequences encoding the same amino acid sequence. Other embodiments include sequences capable of hybridizing under moderately stringent conditions (preshaving solution of 5xSSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of 50° C, 5xSSC, overnight) to the DNA sequences encoding CTLA-8R, and other sequences which are degenerate to those which encode the CTLA-8R. In a preferred embodiment, CTLA-8R analogs are at least about 70% identical in amino acid sequence to the amino acid sequence of CTLA-8R proteins as set forth in SEQ ID NO:1. Similarly, analogs of CTLA-8R homologs are at least about 70% identical in amino acid sequence to the amino acid sequence of the native, homologous proteins. In a most preferred embodiment, analogs of CTLA-8R or homologs thereof are at least about 80% identical in amino acid sequence to the native form of the inventive proteins.

Percent identity may be determined using a computer program, for example, the GAP computer program described by Deveraux et al. (Nucl. Acids Res. 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWgCG). For fragments derived from the CTLA-8R protein, the identity is calculated based on that portion of the CTLA-8R protein that is present in the fragment. Similar methods can be used to analyze homologs of CTLA-8R.

The ability of CTLA-8R analogs to bind CTLA-8 can be determined by testing the ability of the analogs to inhibit CTLA-8R-induced T cell proliferation. Alternatively, suitable assays, for example, an enzyme immunoassay or a dot blot, employing CTLA-8 or HSV13 (or a homolog thereof which binds native CTLA-8R) can be used to assess the ability of CTLA-8R analogs to bind CTLA-8. Such methods are well known in the art.

Expression of Recombinant Receptors for CTLA-8

The proteins of the present invention are preferably produced by recombinant DNA methods by inserting a DNA sequence encoding CTLA-8R protein or a homolog thereof into a recombinant expression vector and expressing the DNA sequence in a recombinant microbial expression system under conditions promoting expression. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being inserted in a recombinant expression vector and expressed in a recombinant transcriptional unit.

Recombinant expression vectors include synthetic or cDNA-derived DNA fragments encoding CTLA-8R, homologs, or bioequivalent analogs, operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, microbial, viral or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation, as described in detail below. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated.

DNA regions are operably linked when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation. Generally, operably linked means contiguous and, in the case of secretory leaders, contiguous and in reading frame. DNA sequences encoding CTLA-8R or homologs which are to be expressed in a microorganism will preferably contain no introns that could prematurely terminate transcription of DNA into mRNA.
Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well-known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEMI (Promega Biotec, Madison, Wis., USA). These pBR322 “backbone” sections are combined with an appropriate promoter and the structural sequence to be expressed. E. coli is typically transformed using derivatives of pBR322, a plasmid derived from an E. coli species (Bolivar et al., Gene 2:95, 1977). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells.

Promoters commonly used in recombinant microbial expression vectors include the β-lactamase (penicillinase) and lactose promoter system (Chang et al., Nature 275:615, 1978; and Goeddel et al., Nature 281:544, 1979), the tryptophan (trp) promoter system (Goeddel et al., Nucl. Acids Res. 8:4057, 1980; and EPA 36,776) and tac promoter (Maniatis, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, p. 412, 1982). A particularly useful bacterial expression system employs the phase I promoter and cI857 is thermostable repressor. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the I promoter include plasmid pBluescript II, resident in E. coli strain JM109 (ATCC 37092) and pBluescript II, resident in E. coli R11 (ATCC 53082).

Suitable promoter sequences in yeast vectors include the promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., J. Biol. Chem. 255:2073, 1980) and other glycolytic enzymes (Hess et al., J. Adv. Enzyme Reg. 7:149, 1968; and Holland et al., Biochem. 17:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucone isomerase, and glucokinase. Suitable vectors and promoters for use in yeast expression are further described in R. Hitzeman et al., EPA 73,657.

Preferred yeast vectors can be assembled using DNA sequences from pBR322 for selection and replication in E. coli (Amp gene and origin of replication) and yeast DNA sequences including a glucose-repressible ADH2 promoter and α-factor secretion leader. The ADH2 promoter has been described by Russell et al. (J. Biol. Chem. 258:2674, 1983) and Beier et al. (Nature 300:724, 1982). The yeast α-factor leader, which directs secretion of heterologous proteins, can be inserted between the promoter and the structural gene to be expressed. See, e.g., Kurjan et al., Cell 30:933, 1982; and Bitter et al., Proc. Natl. Acad. Sci. USA 81:5330, 1984. The leader sequence may be modified to contain, near its 3’ end, one or more useful restriction sites to facilitate fusion of the leader sequence to foreign genes.

The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. For example, commonly used promoters and enhancers are derived from Polyoma, Adenovirus 2, Simian Virus 40 (SV-40), and human cytomegalovirus. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide the other genetic elements required for expression of a heterologous DNA sequence. The early and late promoters are particularly useful because both are obtained easily from the virus as a fragment which also contains the SV40 viral origin of replication (Fiers et al., Nature 273:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 by sequence extending from the Hind III site toward the Bgl II site located in the viral origin of replication is included. Further, viral genomic promoter, control and/or signal sequences may be utilized, provided such control sequences are compatible with the host cell chosen. Exemplary vectors can be constructed as disclosed by Okayama and Berg (Mol. Cell. Biol. 3:280, 1983).

A useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by Cosman et al. (Mol. Immunol. 23:935, 1986). A preferred eukaryotic vector for expression of CTLA-4R DNA is referred to as pDC406 (McMahan et al., EMBO J. 10:2821, 1991), and includes regulatory sequences derived from SV40, human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV). Other preferred vectors include pDC409 and pDC410, which are derived from pDC406. pDC410 was derived from pDC406 by substituting the EBV origin of replication with sequences encoding the SV40 large T antigen. pDC409 differs from pDC406 in that a Bgl II restriction site outside of the multiple cloning site has been deleted, making the Bgl II site within the multiple cloning site unique.

A useful cell line that allows for episomal replication of expression vectors, such as pDC406 and pDC409, which contain the EBV origin of replication, is CV-1/EBNA (ATCC CRL 10478). The CV-1/EBNA cell line was derived by transfection of the CV-1 cell line with a gene encoding Epstein-Barr virus nuclear antigen-1 (EBNA-1) and constitutively express EBNA-1 driven from human CMV immediate-early enhancer/promoter.

Host Cells

Transformed host cells are cells which have been transformed or transfected with expression vectors constructed using recombinant DNA techniques and which contain sequences encoding the proteins of the present invention. Transformed host cells may express the desired protein (CTLA-4R or homologs thereof), but host cells transformed for purposes of cloning or amplifying the inventive DNA not need to express the protein. Expressed proteins will preferentially be secreted into the culture supernatant, depending on the DNA selected, but may be deposited in the cell membrane.

Suitable host cells for expression of viral proteins include prokaryotes, yeast or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram negative or gram positive organisms, for example E. coli or Bacillus spp. Higher eukaryotic cells include established cell lines of mammalian origin as described below. Cell-free translation systems could also be employed to produce viral proteins using RNAs derived from the DNA constructs disclosed herein. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., 1985), the relevant disclosure of which is hereby incorporated by reference.

Prokaryotic expression hosts may be used for expression of CTLA-4R or homologs that do not require extensive proteolytic and disulfide processing. Prokaryotic expression vectors generally comprise one or more pheno-
typic selectable markers, for example a gene encoding pro-
tein conferring antibiotic resistance or supplying an
autotrophic requirement, and an origin of replication recog-
nized by the host to ensure amplification within the host.
Suitable prokaryotic hosts for transformation include E. coli,
Bacillus subtilis, Salmonella typhimurium, and various spe-
cies within the genera Pseudomonas, Streptomyces, and Staph-
ylococcus, although others may also be employed as a
matter of choice.

Recombinant CTLA-8R may also be expressed in
yeast hosts, preferably from the Saccharomyces species, such as S. cerevisiae. Yeast of other genera, such as Pichia or
Kluyveromyces may also be employed. Yeast vectors will
generally contain an origin of replication from the 2μ yeast
plasmid or an autonomously replicating sequence (ARS),
promoter, DNA encoding the viral protein, sequences for
polyadenylation and transcription termination and a selection
gene. Preferably, yeast vectors will include an origin of replication
and selectable marker permitting transformation of
both yeast and E. coli, e.g., the ampicillin resistance gene of
E. coli and S. cerevisiae trp1 gene, which provides a selection
marker for a mutant strain of yeast lacking the ability to grow in
tryptophan, and a promoter derived from a highly expressed
gene to induce transcription of a structural sequence downstream. The presence of the trp1 lesion in the
yeast host genome then provides an effective environ-
ment for detecting transformation by growth in the absence of
tryptophan.

Suitable yeast transformation protocols are known to
those of skill in the art; an exemplary technique is
selecting for Trp" transformants in a selective medium con-
sisting of 0.67% yeast nitrogen base, 0.5% casamino acids,
2% glucose, 10 μg/ml adenine and 20 μg/ml uracil. Host
strains transformed by vectors comprising the ADH2 pro-
motor may be grown for expression in a rich medium consist-
ing of 1% yeast extract, 2% peptone, and 1% glucose supple-
mented with 80 μg/ml adenine and 80 μg/ml uracil. Derepression of the ADH2 promoter occurs upon exhaustion
of medium glucose. Crude yeast supernatants are harvested
by filtration and held at 4° C. prior to further purification.

Various mammalian or insect cell culture systems
may be employed to express recombinant protein. Baculovirus
systems for production of heterologous proteins in insect
cells are reviewed by Luckow and Summers, BioTechnology
6:47 (1988). Examples of suitable mammalian host cell lines
are the COS-7 lines of monkey kidney cells, described by
Gluzman (Cell 23:175, 1981), and other cell lines capable of
expressing an appropriate vector including, for example,
CV-1/EHBNA (ATCC CRL 10478), L cells, C127, 3T3, Chi-
nese hamster ovary (CHO), HeLa and BHK cell lines. Mamm-
alian expression vectors may comprise nontranscribed ele-
ments such as an origin of replication, a suitable promoter and
enhancer linked to the gene to be expressed, and other 5’ or 3’
flanking nontranscribed sequences, and 5’ or 3’ nontranslated
sequences, such as necessary ribosome binding sites, a poly-
adenylation site, splice donor and acceptor sites, and tran-
scriptional termination sequences.

Purification of Receptors for CTLA-8

Recruited CTLA-8R, homologs, or analogs are prepared
by culturing suitable host/vector systems to express the recom-
bintant translation products of the DNAs of the present
invention, which are then purified from culture media or cell
extracts. For example, supernatants from systems which
secrete recombinant protein into culture media can be first
concentrated using a commercially available protein concen-
tration filter, for example, an Amicon or Millipore Pellicon
ultrafiltration unit.

Following the concentration step, the concentrate
may be applied to a suitable purification matrix. For example,
a suitable affinity matrix may comprise a counter structure
protein or lectin or antibody molecule bound to a suitable
support. Alternatively, an anion exchange resin can be
employed, for example, a matrix or substrate having pendant
diethylaminoethyl (DEAE) groups. The matrices can be acryl-
late, agarose, dextran, cellulose or other types commonly
employed in protein purification. Alternatively, a cation
exchange step can be employed. Suitable cation exchangers
include various insoluble matrices comprising sulfopropyl or
carboxymethyl groups. Sulfopropyl groups are preferred. Gel
filtration chromatography also provides a means of purifying
the inventive proteins.

Affinity chromatography is a particularly preferred
method of purifying CTLA-8R and homologs thereof. For
example, a CTLA-8R expressed as a fusion protein compris-
ing an immunoglobulin Fe region can be purified using Pro-
tein A or Protein G affinity chromatography. Moreover, a
CTLA-8R protein comprising an oligomerizing zipper
domain may be purified on a resin comprising an antibody
specific to the oligomerizing zipper domain. Monoclonal
antibodies against the CTLA-8R protein may also be useful in
affinity chromatography purification, by utilizing methods
that are well-known in the art.

Finally, one or more reversed-phase high perfor-
mance liquid chromatography (RP-HPLC) steps employing
hydrophilic RP-HPLC media, e.g., silica gel having pendant
methyl or other aliphatic groups, can be employed to further
purify a CTLA-8R composition. Some or all of the foregoing
purification steps, in various combinations, can also be
employed to provide a homogenous recombinant protein.

Recombinant protein produced in bacterial culture
is usually isolated by initial extraction from cell pellets,
followed by one or more concentration, salting-out, aqueous ion
exchange or size exclusion chromatography steps. Finally,
high performance liquid chromatography (HPLC) can be
employed for final purification steps. Microbial cells
employed in expression of recombinant viral protein can be
disrupted by any convenient method, including freeze-thaw
freezing, sonication, mechanical disruption, or use of cell lysing
agents.

Fermentation of yeast which express the inventive
protein as a secreted protein greatly simplifies purification.
Secreted recombinant protein resulting from a large-scale
fermentation can be purified by methods analogous to those
disclosed by Urdal et al. (J. Chromatogr. 296:171, 1984). This
reference describes two sequential, reversed-phase HPLC
steps for purification of recombinant human GM-CSF on a
preparative HPLC column.

Protein synthesized in recombinant culture is char-
acterized by the presence of cell components, including pro-
teins, in amounts and of a character which depend upon the
purification steps taken to recover the inventive protein from
the culture. These components ordinarily will be of yeast,
prokaryotic or non-human higher eukaryotic origin and prefer-
ably are present in innocuous contaminant quantities, on the
order of less than about 1 percent by weight. Further, recom-
bintant cell culture enables the production of the inventive

proteins free of other proteins which may be normally associated with the proteins as they are found in nature in the species of origin.

Administration of CTLA-8R Compositions

[0051] The present invention provides methods of using therapeutic compositions comprising an effective amount of a protein and a suitable diluent and carrier, and methods for regulating an immune response. The use of CTLA-8R or homologs in conjunction with soluble cytokine receptors or cytokines, or other immunoregulatory molecules is also contemplated.

[0052] For therapeutic use, purified protein is administered to a patient, preferably a human, for treatment in a manner appropriate to the indication. Thus, for example, CTLA-8R protein compositions administered to regulate immune function can be given by bolus injection, continuous infusion, sustained release from implants, or other suitable technique. Typically, a therapeutic agent will be administered in the form of a composition comprising purified CTLA-8R, in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed.

[0053] Ordinarily, the preparation of such protein compositions entails combining the inventive protein with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilize using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

[0054] Receptors for CTLA-8 can be administered for the purpose of inhibiting T cell proliferation, or for inhibiting T cell activation. Soluble CTLA-8Rs are thus likely to be useful in preventing or treating organ or graft rejection, autoimmune disease, allergy or asthma. The inhibitory receptor proteins will also be useful for prevention or treatment of inflammatory disease in which activated T cells play a role. Similarly, HVS13 and homologs thereof stimulate B cell proliferation and immunoglobulin secretion; thus, receptors that bind HVS13 or CTLA-8 will be useful in vivo to inhibit B cell proliferation or immunoglobulin secretion. Receptors for CTLA-8 will also be useful to inhibit the binding of HVS13 to CTLA-8.

[0055] The following examples are offered by way of illustration, and not by way of limitation. Those skilled in the art will recognize that variations of the invention embodied in the examples can be made, especially in light of the teachings of the various references cited herein, the disclosures of which are incorporated by reference.

Example 1

[0056] This example describes identification of cells that express a receptor (or counterstructure) for HVS13/mCTLA8. A chimeric protein (HVS13 type II Fc) consisting of an Fc region of a human immunoglobulin (SEQ ID NO:4) followed by the amino acid 19 to 151 of HVS13 (SEQ ID NO:8) was prepared. A murine CTLA8/Fc (mCTLA8/Fc) was constructed by fusing amino acid 22 to 150 of mCTLA8 (SEQ ID NO:6) to the Fc region of human IgG1. A control Fc protein was constructed by a similar method. The HVS13/Fc and mCTLA-8 proteins were expressed and used to identify cell sources by flow cytometry.

[0057] Cells (1x10⁶) were preincubated on ice for 30 minutes in 100 µl of FACS buffer (PBS, 1% FCS and 0.1% NaN₃) containing 2% normal goat serum and 2% normal rabbit serum to block nonspecific binding. 100 µl of HVS 13/Fc, mCTLA-8/Fc or control/Fc protein was added at 5 µg/ml and incubated on ice for 30 min. After washing, the cells were stained with biotin labeled anti-human IgG (Fc specific) followed by PE-conjugated streptavidin (Becton Dickson & Co, Mountain View, Calif.) in 100 µl of FACS buffer. Cells were then washed and analyzed using a FACSscan (Becton Dickson). A minimum of 5,000 cells were analyzed for each sample. More than a dozen cell lines were screened and it was found that both HVS13/Fc and mCTLA8/Fc fusion proteins bound specifically to the murine thymoma cell line EL4. These cells did not bind to the control/Fc fusion protein.

Example 2

[0058] This example describes cloning of the gene that encodes CTLA-8R. After identification of a source for HVS13 counterstructure, an EL4 mammalian expression library was screened by a slide-binding autoradiographic method (Gearing et al., "EMBO. 8:3667, 1989). CV1/EBNA cells were maintained in Dulbecco's modified Eagle's medium (DMEM) containing 10% (v/v) fetal calf serum (FCS) at 37°C. In a humidified atmosphere containing 10% CO₂ and passaged twice weekly. Subconfluent CV1/EBNA cell monolayers on fibronectin-treated chamber slides (Labtek) were transfected by a chloroquine-mediated DEAE-dextran procedure with plasmid DNAs derived from pooled transformants (2,000 transformants per pool) of murine EL4 cDNA library.

[0059] The CV1/EBNA cells transfected with the murine EL4 cDNA pools were assayed for HVS13/Fc binding two days after transfection using [¹²⁵I]-labeled goat anti-human IgG binding and slide autoradiography. Transfected cell monolayers were washed with binding medium (RPMI 1640 containing 1% bovine serum albumin and 50 µg/ml non-fat dry milk), then incubated with 1 µg/ml of HVS13/Fc for one hour at room temperature. Cells were washed, incubated with [¹²⁵I]-labeled goat anti-human IgG (New England nuclear, Cambridge, Mass.). Cells were washed twice with binding medium, three times with PBS, and fixed in PBS containing 2.5% gluteraldehyde for 30 minutes, washed twice more with PBS and air dried. The chamber slides were then dipped in Kodak GNB-2 photographic emulsion and exposed for 3 days at 4°C before developing.

[0060] Forty pools of approximately 2,000 cDNA each were transfected into CV1/EBNA cells. Two pools of cDNA were found to confer binding to HVS13/Fc protein. These pools were broken down to pools of 100 cDNAs, and subsequently to individual clones. Two single cDNA clones were isolated. These clones were transfected into CV1/EBNA to determine whether the protein encoded thereby conferred binding to both HVS13/Fc and mCTLA8/Fc. Both HVS/Fc and mCTLA8/Fc bound to CV1/EBNA cells transfected with the cloned cDNA, but not to cells transfected with empty vector. Control/Fc did not bind to either of them.
Sequencing of these clones found that they contained a 3.2 kb and 1.7 kb insert derived from same mRNA. The 3.2 kb clone contained an open reading frame of 2595 by surrounded by 120 by at the 5' noncoding sequence and 573 by of 3' noncoding sequence. There were no in-frame stop codons upstream of the predicted initiator methionine, which is preceded by a purine residue (guanine) at -3 position, the most important indicator of a good translation initiation site (Kozak, Mol. Cell. Biol. 9:5134, 1989). It also has a guanine at +4 position, making it optimal for translation initiation. The open reading frame is predicted to encode a type I transmembrane protein of 864 amino acids. The nucleotide and predicted amino acid sequence is shown in SEQ ID NO:1 and 2.

Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 51 and 52. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. There are eight potential N-linked glycosylation sites in the extracellular domain of the protein. The predicted molecular weight for this protein is 97.8 kilodaltons with an estimated isoelectric point of 4.85. Comparison of both nucleotide and amino acid sequences with the GenBank or EMBL databases found no significant homology with known nucleotide and protein sequences.

Example 3

This example describes construction of a construct to express a soluble CTLA-8R/Flag® protein referred to as CTLA-8R/Flag. CTLA-8R/Flag® contains a leader sequence, and the region of CTLA-8R from amino acid 1 to amino acid 322 (SEQ ID NO:1), and the octapeptide referred to as Flag® (SEQ ID NO:3). The construct is prepared essentially as described for other soluble constructs, by ligating a DNA fragment encoding amino acids 1 through 322 of SEQ ID NO:1 (prepared as described in Example 4) into an appropriate expression vector which contains a suitable leader sequence. The resultant DNA construct is transfected into a suitable cell line such as the monkey kidney cell line CV-1 EBNA (ATCC CRL 10478). CTLA-8R/Flag® may be purified using a Flag® antibody affinity column, and analyzed for biological activity using any of the methods described herein.

Example 4

This example describes construction of a CTLA-8R DNA construct to express a CTLA-8R/Fc fusion protein. A soluble form of CTLA-8R fused to the Fc region of human IgG1 was constructed in the mammalian expression vector pDC409 in the following way: A pair of oligonucleotide primers containing a sense sequence and an antisense sequence of CTLA-8R were synthesized. The sense primer contained a Sal I site at the 5' end of the cDNA and antisense primer contained a Bgl II site and contained the CTLA-8R truncated just before the transmembrane region and a stop codon. A 980 by DNA fragment was amplified from CTLA-8R cDNA. The PCR product was cut with Sal I and Bgl II and used in a three way ligation with a fragment carrying the human IgG1 region cut with Bgl II and Not I into a plasmid (pDC409; see U.S. Ser. No. 08/235,397) previously cut with Sal I and Not I. The encoded insert contained the nucleotides encoding the amino acid sequence of residues 1 to 322 of CTLA-8R (SEQ ID NO:1). The sequence was confirmed by sequencing the whole region.

The CTLA-8R/Fc expression plasmids were transfected into CV-1/EBNA cells, and supernatants were collected for 1 week. The CTLA-8R/Fc fusion proteins were purified on a protein A sepharose column (Pharmacia, Uppsala, Sweden) as described below. Protein concentration was determined by an enzyme-linked immunosorbent assay specific for the constant domain of human IgG1 and by BCA analysis (Pharmacia), and purity was confirmed by SDS-polyacrylamide gel electrophoresis analysis followed by silver stain of the gel.

Example 5

This example describes purification of CTLA-8R fusion proteins. CTLA-8R/Fc fusion protein is purified by conventional methods using Protein A or Protein G chromatography. Approximately one liter of culture supernatant containing CTLA-8R/Fc fusion protein is purified by filtering mammalian cell supernatant (e.g., in a 0.45 m filter) and applying filtrate to a protein A/G antibody affinity column (Schleicher and Schuell, Keene, N.H.) at 4°C at a flow rate of 80 ml/hr for a 1.5 cm x 12.0 cm column. The column is washed with 0.5 M NaCl in PBS until free protein is not detected in the wash buffer. Finally, the column is washed with PBS. Bound fusion protein is eluted from the column with 25 mM citrate buffer, pH 2.8, and brought to pH 7 with 500 mM Hepes buffer, pH 9.1.

A CTLA-8R fusion protein comprising Flag® may also be detected and/or purified using an antibody that binds Flag®, substantially as described in Hopp et al., Bio/Technology 6:1204 (1988). Biological activity is measured by inhibition of CTLA-8 activity in any biological assay which quantifies the co-stimulatory effect of CTLA-8, for example, as described in the Examples herein.

Example 6

This example illustrates the preparation of monoclonal antibodies against CTLA-8R. Preparations of purified recombinant CTLA-8R, for example, or transfected cells expressing high levels of CTLA-8R, are employed to generate monoclonal antibodies against CTLA-8R using conventional techniques, such as those disclosed in U.S. Pat. No. 4,411,993. Such antibodies are likely to be useful in interfering with CTLA-8R binding to CTLA-8, as components of diagnostic or research assays for CTLA-8R, or in affinity purification of CTLA-8R.

To immunize rodents, CTLA-8R immunogen is emulsified in an adjuvant (such as complete or incomplete Freund's adjuvant, alum, or another adjuvant, such as Ribi adjuvant R700 (Ribi, Hamilton, Mont.), and injected in amounts ranging from 10-100 μg subcutaneously into a selected rodent, for example, BALB/c mice or Lewis rats. Ten days to three weeks later, the immunized animals are boosted with additional immunogen and periodically boosted thereafter on a weekly, biweekly or every third week immunization schedule. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay (antibody sandwich), ELISA (enzyme-linked immunosorbent assay), immunoprecipitation, or other suitable assays, including FACS analysis. Following detection of
an appropriate antibody titer, positive animals are given an
intravenous injection of antigen in saline. Three to four days
later, the animals are sacrificed, splenocytes harvested, and
fused to a murine myeloma cell line (e.g., NS1 or preferably
Ag 8.653 [ATCC CRL 1580]). Hybridoma cell lines gener-
ated by this procedure are plated in multiple microtiter plates
in a selective medium (for example, one containing hypox-
anthine, aminopterin, and thymidine, or HAT) to inhibit pro-
liferation of non-fused cells, myeloma-myeloma hybrids, and
splenocyte-splenocyte hybrids.

[0070] Hybridoma clones thus generated can be screened
by ELISA for reactivity with CTLA-8R, for example, by
adaptations of the techniques disclosed by Engvall et al.,
*Immunochim. 8*871 (1971) and in U.S. Pat. No. 4,703,004. A
preferred screening technique is the antibody capture tech-
nique described by Beckman et al., *J. Immunol.* 144:212
(1990). Positive clones are then injected into the peritoneal
cavities of syngeneic rodents to produce ascites containing
high concentrations (>1 mg/ml) of anti-CTLA-8R mono-
clonal antibody. The resulting monoclonal antibody can be
purified by ammonium sulfate precipitation followed by gel
exclusion chromatography. Alternatively, affinity chroma-
tography based upon binding of antibody to protein A or protein
G can also be used, as can affinity chromatography based
upon binding to CTLA-8R protein.

Example 6

[0071] This example illustrates the ability of CTLA-8R to
inhibit the proliferative response of T cells to mitogens. Lym-
phoid organs were harvested aseptically and cell suspension
was created. Splenic and lymph node T cells were isolated
from the cell suspension. The purity of the resulting splenic T
cell preparations was routinely >95% CD3* and <1% sIgM*.
Purified murine splenic T cells (2x10^6/well) were cultured
with either 1% PHA or 1 μg/ml Con A, and a soluble CTLA-
8R was filtered into the assay. Proliferation was determined
after 3 days with the addition of 1 μCi [3H]thymidine. Soluble
CTLA-8R/Fc inhibited the mitogen-induced proliferation of
purified murine splenic T cells in a dose dependent manner,
while a control Fc had no effect on the murine T cell prolif-
eration.

Example 7

[0072] This example presents the isolation of a DNA
coding human CTLA-8R by cross species hybridization. A
human peripheral blood lymphocyte library was prepared and
screened substantially as described in U.S. Ser. No. 08/249,
189, using murine CTLA-8R DNA under moderately high
stringency conditions. Several clones of varying length were
obtained. Initial sequencing data indicated that the human
CTLA-8R was approximately 76% identical to murine
CTLA-8R at the nucleotide level.

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SEQUENCE LISTING

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(iii) NUMBER OF SEQUENCES: 10

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   (B) STRAIN: HVS13 receptor

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210 215 220
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755 760 765
Pro Arg Pro Glu Val Val Leu Glu Gly Cys Thr Pro Ser Glu Glu Glu
770 775
Gln Arg Gln Ser Val Gln Ser Asp Gin Gin Tyr Ile Ser Arg Ser Ser
780 785 790 795
Pro Gin Pro Pro Gin Trp Leu Thr Glu Glu Glu Leu Glu Leu Gly
800 805 810 815
Glu Pro Val Glu Ser Leu Ser Pro Glu Leu Arg Ser Leu Arg Lys
820 825 830
Leu Gln Arg Gin Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp
835 840 845
Asp Ser Leu Glu Pro Arg Pro Pro Glu Glu Gin Asn Pro Ser
850 855 860

(2) INFORMATION FOR SEQ ID NO: 3:
  (i) SEQUENCE CHARACTERISTICS:
     (A) LENGTH: 8 amino acids
     (B) TYPE: amino acid
     (C) STRANDEDNESS: Not Relevant
     (D) TOPOLOGY: linear

  (ii) MOLECULE TYPE: peptide
  (vii) IMMEDIATE SOURCE:
     (B) CLONE: FLAG peptide
  (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Asp Tyr Lys Asp Asp Asp Lys

1  5

(2) INFORMATION FOR SEQ ID NO: 4:
  (i) SEQUENCE CHARACTERISTICS:
     (A) LENGTH: 212 amino acids
     (B) TYPE: amino acid
     (C) STRANDEDNESS: Not Relevant
     (D) TOPOLOGY: linear

  (ii) MOLECULE TYPE: protein
  (vi) ORIGINANL SOURCE:
     (A) ORGANISM: Human
  (vii) IMMEDIATE SOURCE:
     (B) CLONE: IgG1 Fc
  (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

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

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRAND: Not Relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(vi) IMMEDIATE SOURCE:
(B) CLONE: Polylinker

(x) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 498 base pairs
(B) TYPE: nucleic acid
(C) STRAND: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(v) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Murine CTLA-8

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 14..490

(ix) FEATURE:
(A) NAME/KEY: sig.peptide
GTCGACCCCC ACC ATG TTC CAT GTT TCT CCT Pro Pro Leu Ile Leu Val Leu Leu Pro Val Thr Ser Ser Ala Val Leu
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97
CTC CCA CTG ATC CTT GTT CTG CCT GTC ACT AGT TCT GCG GTA CTC
Pro Pro Glu Ser Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu
5 10 15
145
GAG AGT GAG GCC AAA ACT GAC GCC ACC GCA AAA
Gln Gln Val Lys Val Gln Ser Ser Leu Leu Gly Ala Lys
20 25 30 35
193
CTC AGC ACC AAA CTG ATT GTC TCC CCA GGC TCC ACC TCA CCC
Val Ser Ser Arg Arg Pro Ser Thr Leu Arg Arg Ser Thr Ser Pro
40 45 50
241
CTC ACT CTC CAC GCC AAT GAA GCT CAG GCC TGT GTC AAC CTC AAA GTC TTT AAC
Trp Thr Leu His Arg Asn Glu Asp Pro Asp Tyr Pro Ser Val Ile
55 60 65
289
CTC GAA CCT CAG TGC CAC CAC GCC TGT GTC AAC GCG GAG GCA AAG
Trp Glu Ala Gln Arg Arg Glu Asp Pro Ser GLy Ala Lys
70 75 80
337
CTC GAC CAC CAT GAT TCT CTC ACT CAG CAA GAG ATG GTC TCT
Leu Asp His His Met Asp Ser Val Leu Ile Gln Gln Ile Leu Val
85 90 95
385
CTC AAG AGG GAG CAC CAC GCC TGC CTC ACT TCC AGG GTC GAG GAG
Leu Lys Arg Glu Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu Lys
100 105 110 115
433
AGC CGT GGT GTC GCG GCC GGC GTG ACC TGC TCG ATT GTC CCC CAT
Met Leu Val Gly Val Gly Thr Cys Thr Val Ala Ser Ile Val Arg His
120 125 130
481
GCG TCC TAA GCGGCCGC
Ala Ser *
498

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 158 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO: 7:
Met Phe His Val Ser Phe Arg Tyr Ile Phe Gly Ile Pro Pro Leu Ile
-25 -20 -15
-10
Leu Val Leu Leu Pro Val Thr Ser Ser Ala Val Leu Leu Pro Glu Ser
-5 1 5
Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu Gln Asn Val Lys
10 15 20
Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala Lys Val Ser Ser Arg
25 30 35
Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser Pro Trp Thr Leu His
40  
Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val Ile Trp Glu Ala Gln  
60  
Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly Leu Asp His His  
75  
Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu Val Leu Lys Arg Glu  
90  
Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu Lys Met Leu Val Gly  
105  
Val Gly Cys Thr Cys Val Ala Ser Ile Val Arg His Ala Ser  
120  
125  
130

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 amino acids
(B) TYPE: amino acid
(C) STRANDNESS: Not Relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(v) ORIGINAL SOURCE:
(A) ORGANISM: Herpesvirus Saimiri
(B) STRAIN: ORF13
(x) SEQUENCE DESCRIPTION: SEQ ID NO: 8:
Met Thr Phe Arg Met Thr Ser Leu Val Leu Val Leu Leu Leu Leu Ser Ile  
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Asp Cys Ile Val Lys Ser Glu Ile Thr Ser Ala Gln Thr Pro Arg Cys  
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25  
30  
Leu Ala Ala Asn Asn Ser Phe Pro Arg Ser Val Met Val Thr Leu Ser  
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40  
45

(Ile Arg Asn Trp Asn Thr Ser Ser Lys Arg Ala Ser Asp Tyr Tyr Asn  
50  
55  
60
Arg Ser Thr Ser Pro Thr Thr Leu His Arg Asn Gln Glu Asp Arg  
65  
70  
75  
80
Tyr Pro Ser Val Ile Trp Glu Ala Lys Cys Arg Tyr Leu Gly Cys Val  
85  
90  
95
Asn Ala Asp Gly Asn Val Asp Tyr His Met Asn Ser Val Pro Ile Gln  
90  
105  
110
Gln Glu Ile Leu Val Val Lys Gly His Gln Pro Cys Pro Asn Ser  
115  
120  
125
Phe Arg Leu Glu Lys Met Leu Val Thr Val Gly Cys Thr Cys Thr  
130  
135  
140
Pro Ile Val His Asn Val Asp  
145  
150

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3223 base pairs
(B) TYPE: nucleic acid
(C) STRANDNESS: single
(D) TOPOLOGY: linear
MOLECULE TYPE: cDNA to mRNA

HYPOTHETICAL: NO

ANTI-SENSE: NO

ORIGINAL SOURCE:
(A) ORGANISM: Human
(B) STRAIN: IL-17 R (hCTLA8 receptor)

FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 93..2693

SEQUENCE DESCRIPTION: SEQ ID NO: 9:

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GGGAGACCGG AATTCCGGGA AAAGAAAGCC TCAGAACGTT GGGGCCGAGC CCTCCGCGAC GCCACCCGGG CC

Pro Ser Ala Val Pro Gly Pro Leu Leu Leu Leu Leu

10  15  20

GGC GTCG GCC GCG GCC TCC CGG GCC TGG GCC CGG GCC TGG GCC CGG

Gly Val Gly Gly Gly Gly Ser Gly Ser Arg Arg Arg Arg Arg Arg

25  30  35

GCC TGC TGC TGC CAG CGG CTA AAC TGC ACG GTC AAG AAT AGT

Ala Leu Val Cys Ser Gly Leu Arg Cys Thr Val Lys Arg Asp

40  45  50  55

ACC TGC GTG GAT GAC AGC TGG ATT CAC CCA AAC CTC AGC ACC CCC

Thr Cys Leu Met Asp Asp Ser Trp Ile His Pro Arg Asn Leu Thr Pro

60  65  70

TCC CCA AAG GAC CTG CAG ATC CAG CTG CAG TCT GCA ACC CAA

Ser Pro Lys Asp Leu Glu Ile Glu His Asp Leu His Glu Glu

75  80  85

GGA GAC CTG TCC CCC TGT CAC ATC GAA AGT ACG CTG CAG ACA GAC

Gly Asp Leu Pro Val Ala His Ile Glu Trp Thr Leu Asp Thr

90  95  100

GCC AGC ATC CTG TAC TCT GAG GCC GCA CAG TTA TGT GTC CTG CAG CTG

Ala Ser Ile Leu Tyr Leu Gly Ala Ser Leu Leu Leu Gly Leu

105  110  115

AAC ACC AAT GAG CTT TGG TGC TGC AGG TGT CTC TGC TGC CAA CCC

Aam Thr Asn Leu Arg Leu Cys Val Arg Phe Glu Leu Ser Lys Leu

120  125  130  135

AGG CAT CAC AGC AGG CGG TGG CAG TTT ACC TCC AGC TGG CTA ACC

Arg His His Asp Arg Trp Arg Phe Thr Phe Ser His Phe Val

140  145  150

GAC CCT GAA GAC TGG TAA GAC ACC GTT CAC CGG ATG CTC ATG CAC

Glu Asp Glu Leu Tyr Thr Val His Leu His Leu Pro Lys Pro

155  160  165

ATC CCT GAT GCG GAC CAA CAC CGG TGG AAG ATG TCT CTT GCT TCT

Ile Pro Asp Gly Asp Pro Asn His Glu Ser Lys Asn Phe Leu Val Pro

170  175  180

GAC TGG GAC GCC AGG ATG AAG GTA ACC AGC CGA TAC ATG AGC TCA

Asp Cys Glu His Ala Arg Met Lys Val Thr Thr Pro Cys Met Ser Ser

185  190  195

GCC AGC CTG TGG GAC CCC AAC ATC ACC GTG GAG ACC CTG GAG GCC CAC

Gly Ser Leu Trp Asp Pro Asn Ile Thr Val Glu Thr Leu Ala His

200  205  210  215

CAG CTG GTG AGC TCC CTG TAG ACG GAA TCT ACC CAT TAC CAG

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ATC CTG CTG ACC AGT TTG CCG CAC ATG GAG AAC CAC AGT TGC TTT TAG
Ile Leu Leu Ser Phe Pro His Met Glu Asn Ser Cys Phe Glu
  235  240  245
CAC ATG CAC ATA CCT GCG CCC AGA CCA GAA GAC TTC CAC CAG CAA
His Met His Ile Pro Ala Pro Arg Pro Glu Phe His Glu Arg
  250  255  260
TCC AAC GTC ACA CTC ACT CTA CAC AAC CTT AAA GGG TGG TCG TGC CGC CAC
Ser Asn Val Thr Leu Thr Leu Arg Asn Leu Lys Gly Cys Cys Arg His
  265  270  275
CAA GTC CAG ATC CAG CCC TCC TTC AGC AGC TGC CTC AAT GAC TGC TCT
Glu Val Gln Ile Glu Pro Phe Ser Ser Cys Leu Asn Asp Cys Leu
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AGA CAC TCC GCC ACT GTT TCC TGC CCA GAA ATG CCA GAC ACT CCA GAA
Arg His Ser Ala Val Ser Cys Pro Met Asp Thr Pro Glu
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CAG ATT CCG GAC TAC ATG CCC CTG TGG GTG TAC TGG TCC TGC TAC ATC AGC GGC
Pro Ile Pro Asp Tyr Met Pro Leu Val Tyr Trp Phe Ile Thr Gly
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ATC TCC ATC CTG CTG GGC TGC TCT ATC ATC CTC ATC GTG GAG
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ACC TGG AGG CTA GCT GGG CCT GAA AGA AAA TAC AGT GAT GAC ACC
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AAA TAC ACC GAT GCC CTG CCT GCG CTC GCT AAC ATC CCC CCA CGG CTG
Lys Tyr Thr Asp Glu Lys Ala Ala Asn Ala Thr Pro Pro Leu
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AGA CCC AGG AGC GTG ATC TAC TGG TAC ATG GCC GAC ACC CCC CTC TAC
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GTG GAC GTG GTC CTG AAA TTC GCC CGG TTC CTG CTC ACC GCC TTC GCC
Val Asp Val Leu Lys Phe Ala Glu Phe Leu Leu Thr Ala Cys Gly
  395  400  405
AGA GAA GTG GCC CTG GAC CTC CAG CTG GCC GAC ACC TGG GAG GCA
Thr Glu Ala Leu Asp Leu Leu Glu Glu Ala Ile Ser Glu Ala
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GA A GTC ATG ACC TGG GTC GCC CTT GAA GAG GAG ATG GTG GAG AGC
Gly Val Met Thr Trp Val Gly Arg Glu Gly Gln Met Val Glu Ser
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Aam Ser Lys Ile Ile Val Leu Cys Ser Arg Gly Thr Arg Ala Lys Trp
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CAG GCC CTC CGG CCN GCC GCC ATT GCC GCC GCC GCC GCC GCC GCC GCC GCC
Gln Ala Leu Leu Asn Met Leu Leu Gly Arg Gly Ala Pro Arg Leu Arg Asp His
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GAA AAG CCC GTG GCC GCC GCC TGG TCC ACT GCC GTC TCC ACC ATG AGC
Gly Lys Pro Val Gly Asp Leu Phe Thr Ala Ala Met Met Ile Leu
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CGG GTC TTG AGG CCA GCC TGC GCC GCC GCC ACC TAG GTA GTC TGC TAC
Pro Asp Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr
  490  495  500
TTC ACG GAG GTC TCG GCC GCC GCC GCC GCC GCC GCC GCC GCC GCC GCC
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GAG CTG TCG GGG GAC AAC TAC CTG CGG AGC CGC GGC GCC AGG CAG CTC
Glu Leu Ser Gly Asp Asn Tyr Leu Arg Ser Pro Gly Gly Arg Glu Leu
555 560 565

GCC GCC CTG GAC AGG TCC CGG GCC TGG CAG GTC GCC TGT CCC GAC
Arg Ala Ala Leu Arg Phe Arg Asp Trp Glu Val Arg Cys Pro Asp
570 575 580

TGG TTC GAA TGT GAG AAC CTC TAC TCA GCA GAT GAC CAG GAT GCC CCG
Trp Phe Glu Cys Glu Asp Leu Tyr Ser Ala Asp Asp Gln Asp Ala Pro
595 598

TCC CTG GAC GAA GAG GTG TTT GAG CGG GTG CTG CCG GCC GCA ACC
Ser Leu Asp Gly Leu Phe Glu Pro Leu Leu Pro Gly Thr
600 605 610 615

GCC ATC GTG AAG CGG GCC CTG GAG CCT GCC GAG GCT GCC TCC CAG GCC
Gly Ile Val Lys Arg Leu Val Pro Val Ser Gly Ser Glu Ala
620 625 630

TGC CTG GCC AYA GAC CGG CTG GTC GGG GAG GAA GGA GGA GCA GCC GTC
Cys Leu Ala Ile Asp Pro Leu Val Gly Glu Gly Ala Ala Val
635 640 645

GCA AAG CTG GAA CCT CAC CTG CGA CCC CGG GGT CAG CCA GCG CCG CAG
Ala Lys Leu Glu Pro Leu Gly Leu Glu Pro Arg Gly Gly Pro Ala Pro
650 655 660

CCC CTC CAC ACC CTG GTG CTC GCC GAG GAG GCC GGC CTT GTG GCC
Pro Leu His Thr Leu Val Ala Ala Gly Glu Gly Ala Leu Val Ala
665 670 675

GCC GAG CTC CTG GCC CGT GCT GCC GGC GCA GTC GCC GAG GCC GCC GGC GCT
Glu Val Gly Gly Pro Gly Pro Leu Asp Gly Ala Ala Val Arg Leu Ala
680 685 690 695

CTG GCG GGG GAG GCC GGC GCC TGC GTG CTC GCC GCG ACG GCC GCC GCT
Leu Ala Gly Glu Gly Ala Cys Pro Leu Leu Gly Ser Pro Gly Ala
700 705 710

GGG CCA AAT AGC GTC CTC TTC GCC GTC GAC CCC GAG GAC TCG CCC
Gly Arg Asn Ser Val Phe Leu Pro Val Asp Pro Gly Arg Ser Pro
715 720 725

CTT GCC GAC ACC ACC CCT ATG CGG TCT CCT GAC GTC CTT CCA GAG GAC
Leu Gly Ser Ser Thr Pro Met Ala Ser Pro Asp Leu Leu Pro Gly Asp
730 735 740

GTA AAG GAG GAC CTC GAA GAC TGG ATG CTC TCG CTG TCC GAG CAG
Val Arg Glu His Leu Glu Gly Leu Met Leu Ser Leu Phe Glu Glu Ser
745 750 755

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(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 866 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(x) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

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Trp Gln Val Arg Cys Pro Asp Trp Phe Glu Cys Glu Asn Leu Tyr Ser
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We claim:
1. An isolated DNA selected from the group consisting of:
   (a) a DNA having a nucleotide sequence encoding an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2; and
   (b) DNA molecules capable of hybridization to the clones of (a) under stringent conditions and which encode CTLA-8R capable of binding CTLA-8.
2. An isolated DNA according to claim 1 which encodes a soluble CTLA-8R.
3. An isolated DNA selected from the group consisting of:
   (a) a DNA having a nucleotide sequence encoding an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2; and
   (b) DNA molecules encoding peptides that are at least about 70% identical in amino acid sequence to the amino acid sequence of SEQ ID NO.2.

4. A recombinant expression vector comprising a DNA sequence according to claim 1.
5. A recombinant expression vector comprising a DNA sequence according to claim 2.
6. A recombinant expression vector comprising a DNA sequence according to claim 3.
7. A host cell transformed or transfected with an expression vector according to claim 4.
8. A host cell transformed or transfected with an expression vector according to claim 5.
9. A host cell transformed or transfected with an expression vector according to claim 6.
10. A process for preparing a CTLA-8R or an analog thereof, comprising culturing a host cell according to claim 7 under conditions promoting expression.
11. A process for preparing a CTLA-8R or an analog thereof, comprising culturing a host cell according to claim 8 under conditions promoting expression.

12. A process for preparing a CTLA-8R or an analog thereof, comprising culturing a host cell according to claim 9 under conditions promoting expression.

13. An isolated and purified biologically active CTLA-8 receptor (CTLA-8R) protein.

14. An isolated and purified CTLA-8R protein according to claim 13, consisting essentially of human CTLA-8R.

15. An isolated and purified CTLA-8R according to claim 13, consisting essentially of soluble CTLA-8R.

16. A composition comprising a CTLA-8R protein according to claim 13, and a suitable diluent or carrier.

17. A method for regulating an immune or inflammatory response in a mammal, comprising administering an effective amount of a composition according to claim 16.

18. An assay method for detection of CTLA-8 and homologs thereof, or CTLA-8R and homologs thereof, or the interaction thereof, comprising use of a protein composition according to claim 16.

19. Antibodies immunoreactive with CTLA-8R.

* * * * *