Title: POLYPEPTIDES, COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

Abstract: The present invention provides, among other things, a polypeptide, and a pharmaceutically acceptable salt thereof, that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, a nucleic acid that encodes such a polypeptide and can be expressed in a cell, a nucleic acid that comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for such a polypeptide, an antibody that is specific to such a polypeptide, and anti-antibody thereto, a composition comprising such a polypeptide, nucleic acid, antibody or an anti-body and a carrier therefor, a composition comprising a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to a specified polypeptide sequence, a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, a mammal in need thereof, and a method of removing IL-6 ligand from a body fluid of an animal.
POLYPEPTIDES COMPRISING IL-6 LIGAND-BINDING
RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS,
ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to polypeptides
comprising IL-6 ligand-binding receptor domains, nucleic
acids encoding such polypeptides, antibodies,
compositions comprising such polypeptides, nucleic acids,
or antibodies, and methods of use.

BACKGROUND OF THE INVENTION

Interleukin-6 (IL-6) is a cytokine that is produced
in response to various stimulators and is responsible for
a variety of biological activities, including the
stimulation of B- and T-cell growth and differentiation
(Muraguchi et al., J. Exp. Med. 167: 332 (1988)),
production of acute-phase proteins in response to
inflammation or tissue injury (Gauldie et al., PNAS USA
(1988)), multilineage hematopoiesis, osteoclast
formation, maturation of megakaryocytes, and platelet
production. These biological activities are initiated
when IL-6 binds to the extracellular portion of the
interleukin-6 receptor, which is variously referred to as
the interleukin-6 α subunit (IL-6Rα) or B-cell
stimulating factor receptor (BSF-2 receptor). When IL-6
binds to IL-6Rα, a complex is formed. The complex then
binds to the extracellular portion of the interleukin-6
receptor known as gp130, which is also referred to as the
interleukin-6β subunit (IL-6Rβ). The resulting complex then transmits the IL-6 signal intracellularly.

The precursor of the IL-6 receptor reportedly comprises 468 amino acids (Yamasaki et al., Science 241: 825-828 (1988)). The mature IL-6 receptor reportedly comprises 449 amino acids (Yamasaki et al. (1988), supra).

Abnormal expression of IL-6 has been implicated in the pathogenesis of a variety of diseases, including multiple myeloma, plasmacytoma, hematological diseases such as plasma cell dyscrasias, leukemia and lymphoma (including non-Hodgkins's lymphoma and Lennert's T-cell lymphoma (Kishimoto, Blood 74: 1 (1989)), mesangial proliferative glomerulonephritis, polyclonal B-cell activation conditions, allergic diseases (Type I-IV), rheumatoid arthritis (Hirano et al., Eur. J. Immunol. 18: 1797 (1988)), diabetes, multiple sclerosis, SLE, septic shock, bacterial infection, viral infection, post-menopausal osteoporosis, chronic immune deficiency and autoimmune diseases (Med. Immunol. 15: 195-201 (1988)), including organ-specific and systemic diseases and AIDS, inflammatory diseases, and Cattleman's disease. In addition, IL-6 production has been associated with cardiac myxoma and cervical cancer (Kishimoto et al., Ann. Rev. Immunol. 6: 485 (1988)) in vivo and myelomas, histiocytomas and promyelocytic leukemia (Taga et al., J. Exp. Med. 166: 967 (1987)) in vitro. Attempts to abrogate the effects of abnormal expression of IL-6 can be made at its site of production or at its target.

In view of the above, there remains a need for materials and methods for identifying and designing
agents that inhibit IL-signaling and for treating
diseases involving IL-6 signaling prophylactically and
therapeutically. It is an object of the present
invention to provide such materials and methods. This
and other objects and advantages, as well as additional
inventive features, will become apparent from the
detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

The present invention provides, among other things,
a polypeptide, and a pharmaceutically acceptable salt
thereof, that inhibits the binding of IL-6 ligand with
IL-6 receptor under physiological conditions. In one
embodiment, the polypeptide has the formula \( R^1R^2R'^1L'L'L'R^2 \),
and pharmaceutically acceptable salts thereof, in which \( R^1 \)
is hydrogen, \( R^2C(O) - \) or \( R^3 \), and does not comprise an amino
acid residue sequence that is identical to an amino acid
residue sequence of the \( \alpha \)-chain of the IL-6 receptor and
is not linked to the moiety \( -R'^1L'L'L'R^2 \) via a glycyl
residue or via a propionyl residue, \( R^2 \) is hydrogen, a
polypeptide of from 1 to about 100 amino acid residues,
NHR or \( R^3 \), and \( R^3 \) is a pharmaceutically acceptable
substituent group.

In another embodiment, the polypeptide has the
formula \( R^1R'^1XVL'^2L'^2VR'^2 \), in which \( R^1 \) and \( R^2 \),
independently, are pharmaceutically acceptable
substituents, \( R'^1 \) is a naturally-occurring or synthetic
amino acid residue that has an acidic or neutral side-
chain under physiological conditions, \( X \) is any naturally-
occurring or synthetic amino acid residue, and \( L'^2 \) is
leucinyl or isoleucinyl.
In yet another embodiment, the polypeptide has the formula $R^{20}R^{21}L'R'Y'R'A'E'R'S'R^{22}$, in which $R^{20}$ and $R^{22}$ are pharmaceutically acceptable substituents, $R^{21}$ is a naturally-occurring or synthetic amino acid residue that has a basic or neutral side-chain under physiological conditions, $L'$, $Y'$, $E'$ and $S'$ are independently any naturally-occurring or synthetic amino acid residue, $R'$ is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological conditions, and $A'$ is alaninyl, glycynyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, $\beta$-alaninyl or $\alpha$-aminoisobutyryl.

In still yet another embodiment, the polypeptide comprises at least $I'A'I'V'L'R'F'$ but less than about 200 amino acid residues that have a sequence that is identical to an amino acid sequence of the $\alpha$-chain of the IL-6 receptor, in which $I'$, $L'$, and $V'$ are independently a naturally-occurring or synthetic amino acid residue having a side-chain consisting of a $C_1$-$C_4$ straight chain or $C_1$-$C_4$ branched alkyl moiety, $R'$ is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological conditions, $A'$ is alaninyl, glycynyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, $\beta$-alaninyl or $\alpha$-aminoisobutyryl, and $F'$ is tyrosinyl, phenylalaninyl, tryptophanyl or $\alpha$-aminoisobutyryl, with the proviso that at least four of the seven substituents of $I'A'I'V'L'R'F'$ are selected such that $I'$ is isoleucinyl, $A'$ is alaninyl, $V'$ is valinyl, $L'$ is leucinyl, $R'$ is argininyl, and $F'$ is phenylalaninyl.
In a further embodiment, the polypeptide comprises up to 200 amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor and comprises the sequence SVIILKNIQY,

TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL,
QLPVDVQNGFIRNYTIFYRTIIGN, or
IVVPVCLAPLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA, any one of which can comprise from one to about six conservative or neutral replacements. The polypeptide can further comprise a pharmaceutically acceptable substituent.

Also provided by the present invention is a nucleic acid that encodes an above-described polypeptide, wherein the polypeptide preferably consists of naturally-occurring amino acid residues. The nucleic acid encoding the polypeptide can be expressed in a cell. The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes secretion of at least the polypeptide by a cell in which the nucleic acid is expressed. Alternatively, the nucleic acid comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for a nucleotide sequence in a nucleic acid encoding the specified amino acid sequence in an above-described polypeptide.

Further provided by the present invention is a composition comprising an above-described polypeptide or nucleic acid and a carrier therefor. Another composition provided by the present invention is a composition comprising an antibody to an above-described polypeptide, an anti-antibody to an above-described polypeptide, or a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to the
polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIvLRF, SVIIKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIIKYNIQY, KLTWTNPSIKSVIIKYNIQY, TRWKSIIQNYTVNATKLTVLTNDRYLALTVERTEXNLVHKSDEAVL, QLPVDDQDGIRNYTIFYRTIIGN, and IVVPVCLIALLTLLGVLFCFKNKRLIKKHIWPNVPDPSKSHIA.

Also provided by the present invention is a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal. The method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of an above-described polypeptide, a nucleic acid encoding such a polypeptide or an antibody to such a polypeptide.

In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of an animal. The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIvLRF, SVIIKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIIKYNIQY, KLTWTNPSIKSVIIKYNIQY, TRWKSIIQNYTVNATKLTVLTNDRYLALTVERTEXNLVHKSDEAVL, QLPVDDQDGIRNYTIFYRTIIGN, and IVVPVCLIALLTLLGVLFCFKNKRLIKKHIWPNVPDPSKSHIA.

Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the solution can be contacted with a solid support matrix to which is attached a means to remove the polypeptide or
anti-antibody to which is bound IL-6 ligand from the bodily fluid.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 depicts a listing of synthetic amino acids available (from Bachem, King of Prussia, PA) for incorporation into polypeptides and compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, among other things, a polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present invention is predicated in part on a detailed study of a series of synthetic polypeptides having the same or similar amino acid sequence as that of IL-6 receptor, in which the ability of each synthetic polypeptide to bind to the IL-6 ligand was measured first in a high-throughput in vitro assay, and then confirmed (for at least a subpopulation of the synthetic polypeptides of greater interest) by measuring the ability of the synthetic peptide to inhibit the growth, replication, and survival of IL-6-dependent cells grown in a cellular growth medium comprising IL-6 ligand.

Those of skill in the art will recognize that the ability of any particular polypeptide to inhibit IL-6 signaling or function in vivo can be easily and rapidly determined using either the techniques employed in the examples provided below, or by using another suitable testing technique, such as the B9 cell growth and signal transduction assays known in the art (see, e.g., Halimi
et al., Eur. Cytokine Netw. 6: 135-43 (1995)). The skilled artisan would expect the results of such in vitro assays to be reasonably predictive of in vivo utility.

While not intending to be bound by any particular theory, it is believed that the present inventive polypeptide, and compositions comprising the same, inhibit the ability of IL-6 ligand to bind to the soluble IL-6 receptor or the membrane-bound IL-6 receptor, by binding to unbound IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling, IL-6-dependent cellular responses (including changes in one or more of the group consisting of cellular metabolism, cellular growth, cellular replication, and cellular survival; the term "cellular metabolism" includes the ability of the cell to affect neighboring cells by secretion of biomolecules (e.g., paracrines, or exocrines), and/or display of cell-surface biomolecules (e.g., proteins or lipids)).

In each embodiment provided herein, a letter indicates the standard amino acid designated by that letter, and a letter followed directly by an asterisk (*) preferably represents the amino acid represented by the letter (e.g., N represents asparaginyln and T represents threonyln), or a synthetic or naturally-occurring conservative or neutral substitution therefor, unless otherwise specified. Additionally, in accordance with convention, all amino acid sequences provided herein are given from left to right, such that the first amino acid is amino-terminal and the last is carboxyl-terminal. The synthesis of polypeptides, whether synthetic (i.e., chemical) or biological, is within the skill in the art.
It is within the skill of the ordinary artisan to select synthetic and naturally-occurring amino acids that effect conservative or neutral substitutions for any particular naturally-occurring amino acids. The skilled artisan desirably will consider the context in which any particular amino acid substitution is made, in addition to considering the hydrophobicity or polarity of the side-chain, the general size of the side chain and the pK value of side-chains with acidic or basic character under physiological conditions. For example, lysine, arginine, and histidine are often suitably substituted for each other, and more often arginine and histidine. As is known in the art, this is because all three amino acids have basic side chains, whereas the pK value for the side-chains of lysine and arginine are much closer to each other (about 10 and 12) than to histidine (about 6). Similarly, glycine, alanine, valine, leucine, and isoleucine are often suitably substituted for each other, with the proviso that glycine is frequently not suitably substituted for the other members of the group. This is because each of these amino acids are relatively hydrophobic when incorporated into a polypeptide, but glycine's lack of an α-carbon allows the phi and psi angles of rotation (around the α-carbon) so much conformational freedom that glycyl residues can trigger changes in conformation or secondary structure that do not often occur when the other amino acids are substituted for each other. Other groups of amino acids frequently suitably substituted for each other include, but are not limited to, the group consisting of glutamic and aspartic acids; the group consisting of
phenylalanine, tyrosine and tryptophan; and the group consisting of serine, threonine and, optionally, tyrosine. Additionally, the skilled artisan can readily group synthetic amino acids with naturally-occurring amino acids.

In the context of the present invention, a polypeptide is "substantially identical" to another polypeptide if it comprises at least about 80% identical amino acids. Desirably, at least about 50% of the non-identical amino acids are conservative or neutral substitutions. Also, desirably, the polypeptides do not differ in length (i.e., due to deletion mutations) by more than about 10%.

In a first embodiment, the present invention provides a polypeptide of the formula $R^1R^2L^1L^2L^3R^1R^2$ (domain I), and pharmaceutically acceptable salts thereof. In this embodiment, $R^1$ is selected from the group consisting of hydrogen, $R^2C(O)-$, and $R^3$. However, $R^1$ does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α-chain of the IL-6 receptor and is not linked to the moiety $-R^1R^2L^1L^2L^3R^1$ via a glycinyl residue or a propionyl residue. Preferably, $R^1$ is not linked to the moiety $-R^1R^2L^1L^2L^3R^1$ via either a glycyl, propionyl, butyryl, or alaninyl residue, and, more preferably, $R^1$ does not comprise an amino acid residue sequence that is greater than 50% identical to the amino acid residue sequence RWAGM- at the site of linkage to the moiety $-R^1R^2L^1L^2L^3R^1$.

$R^1$ is independently selected from the group consisting of arginyl, naturally-occurring arginyl equivalents, and synthetic arginyl equivalents.
L' is independently selected from the group consisting of leucinyll, naturally-occurring leucinyl equivalents, and synthetic leucinyl equivalents. 

R² is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR³, and R³. 

The substituent R³ is a pharmaceutically acceptable group. R³ is independently selected with respect to size or length and secondary structure so that the present inventive polypeptide is able to bind to the IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling under physiological conditions. 

An amino acid residue equivalent thereof comprises a primary amine linked by one to three, preferably two, and more preferably one, methylenyl group(s) linked to a carboxylic acid, i.e., NH₂-(CHRⁿ)₁₋₃-COO⁻, preferably NH₂-(CHRⁿ)₂-COO⁻ and more preferably NH₂-(CHRⁿ)₃-COO⁻. An amino residue (or its equivalent) is linked via a peptide bond (-C(O)NH-) to another amino acid residue (or its equivalent) or a polypeptide. An amino acid residue equivalent is an amino acid residue in which R⁴ is selected to have the same charge under physiological conditions as the amino acid residue, and, preferably, is selected to have a similar number of atoms as the side-chain substituent of the amino acid residue, i.e., plus or minus 50%, preferably plus or minus 20%. All amino acid residue equivalents preferably have only one R⁴ moiety that is not hydrogen (except for glycinyll equivalents for which R⁴ can be, and preferably is, repetitively selected as hydrogen, e.g., 3-amino proprionic acid; NH₂-(CH₃)₂-COO⁻). By way of example, an
argininyln equivalent residue is preferably selected from the group consisting of argininyln and lysinyln because (1) these residues are naturally-occurring and are encoded by a mammalian gene or genome, and (2) these residues have
(a) similar sizes (arginine having 7 side-chain atoms (excluding hydrogen atoms) and lysine having 5, ((5-7)/(7) x 100% = 28%)), and (b) these residues are bases having similar pK values (about 12 and 10, respectively).

An argininyln residue or an argininyln equivalent residue can be either natural or synthetic. In addition to an argininyln residue per se, a natural amino acid residue equivalent to an argininyln residue includes, but is not limited to, histidinyln and lysinyln, and is preferably lysinyln. A synthetic amino acid residue equivalent to and argininyln residue includes, but is not limited to, d-forms of argininyln, lysinyln, and histidinyln residues, as well as L- and D-, but preferably L-, ornithinyln, citrullinyln, and homoargininyln residues. The skilled artisan will recognize additional argininyln equivalents from Figure 1.

A leucinyln residue or a leucinyln equivalent residue can be either natural or synthetic. Leucinyln equivalents include, but are not limited to, leucinyln, isoleucinyln, alaninyln, valinyln, norleucinyln, norvalinyln, sarcosinyln, β-alaninyln, and α-aminoisobutyryl. The skilled artisan will recognize additional leucinyln equivalents from Figure 1. Of course, in any given polypeptide, substitutions are preferably limited in number. For example, in the polypeptide R'R'L'L'L'R', all of the R' residues and all of the L' residues are most preferably argininyln and leucinyln, respectively; less preferably,
one residue is other than argininy1 or leuciny1, yet less preferably two or three residues are not argininy1 or leuciny1, and least preferably four to six residues are not argininy1 or leuciny1. Accordingly, a most preferred residue for R' is an argininy1 residue.

Similarly, L' can be independently selected from the group consisting of leuciny1, isoleuciny1, and valiny1; preferably L' is leuciny1 or isoleuciny1; and most preferably, L' is leuciny1. Additionally, L' can optionally be a d-form amino acid residue, and/or a synthetic residue such as, e.g., an α-aminoisobutyryl residue.

The substituent R' can be any suitable pharmaceutically acceptable substituent. A pharmaceutically acceptably substituent need not, but can provide a function, such as homing to sites of inflammation, increasing the solubility in water of the present inventive polypeptide, and protecting side-chains of amino acid residues from oxidative or chemical attack.

For example, a pharmaceutically acceptable substituent can be a biopolymer, such as a polypeptide, an RNA, a DNA, or a polysaccharide. Suitable polypeptides comprise fusion proteins, an antibody or fragment thereof, a cell adhesion molecule or a fragment thereof, or a peptide hormone. Suitable polysaccharides comprise polyglucose moieties, such as starch and derivatives thereof, such as heparin. R' also can be any suitable lipid or lipid-containing moiety, such as a lipid of a liposome or a vesicle, saccharide or disaccharide, or even a lipophilic moiety, such as a prostaglandin, a steroid hormone, or a derivative of either of the foregoing. Additionally, R'
can be a nucleotide or a nucleoside, such as nicotine adenine dinucleotide or thymine. $R'$ also can be a vitamin, such as vitamin C, thiamine, or nicotinic acid. A pharmaceutically acceptable substituent can be a synthetic organic moiety, such as t-butyl carbonyl, an acetyl moiety, quinine, or polystyrene and another biologically acceptable polymer. A pharmaceutically acceptable substituent also can be $R'$, wherein $R'$ is selected from the group consisting of a

$C_1-C_{18}$ alkyl, a $C_2-C_{18}$ alkenyl, a $C_2-C_{18}$ alkynyl, a $C_4-C_{18}$ aryl, a $C_2-C_{18}$ alkaryl, a $C_2-C_{18}$ aralkyl, and a $C_3-C_{18}$ cycloalkyl, wherein any of the foregoing $R'$ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

$R'$ can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a $C_1-C_4$ monoalkylamine moiety, a $C_1-C_4$ dialkylamine moiety, and a $C_1-C_4$ trialkylamine moiety.

A preferred polypeptide of the first embodiment $R'R''R''L''L''R''R'^2$ is RRLLLR, wherein $R$ is argininy1 and $L$ is leuciny1. In a more preferred embodiment, $R'$ of the formula $R'R''R''L''L''R''R'^2$ is a - (seriny1-valiny1-$R'^2$), and $R'$ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 98 amino acid residues,
-NHR\(^4\), and R\(^4\), wherein R\(^4\) is as defined above and can be substituted as described above.

In a second embodiment, the present invention provides a polypeptide of the formula R\(^{10}\)R\(^{11}\)XVL\(^2\)L\(^3\)VR\(^{12}\), as well as pharmaceutically acceptable salts thereof. This embodiment is predicated, at least in part, on two surprising and unexpected discoveries. First, that a second domain of the \(\alpha\)-chain of the IL-6 receptor that has the ability to bind to the IL-6 ligand comprises an important amino acid residue sequence -VLLV-, which naturally occurs in the context TKAVLLVRF. Second, that the binding affinity of this second domain is substantially increased if the lysinyl residue (in the larger subsequence) is replaced by an amino acid residue that does not have a side-chain that is basic under physiological conditions.

In this second embodiment, R\(^{10}\) and R\(^{12}\) are pharmaceutically acceptable substituents. Examples of pharmaceutically acceptable substituents are provided above with respect to R\(^3\).

R\(^{11}\) is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or neutral side-chain under physiological conditions. For example, R\(^{11}\) can be selected from either the group consisting of alaninyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glyciny1, isoleucinyl, leucinyl, methioninyl, phenylalaninyl, prolinyl, serinyl, threoninyl, tryptophanyl, tyrosinyl, and valinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, \(\beta\)-alaninyl, \(\alpha\)-aminoisobutyryl, \(\gamma\) aminopentane-1,5-dioyl,
homoserinyl, hydroxyprolinyl, α-carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl.

Similarly, X can be any synthetic or naturally-occurring amino acid residue, such as any synthetic or naturally-occurring amino acid residue that has an acidic or neutral side-chain under physiological conditions. That is, X can be selected from the group consisting of suitable R^11 residues, as well as from among the group consisting of argininyln, lysinyl, and histidinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, γ-aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, γ-carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, O-phosphotyrosinyl, ornithinyl, citrullinyl, and homoargininyl. However, X is preferably independently selected from the group denoted by R^11.

In the context of the formula R^1^2R^1^2XV^L^2L^2V^R^1^2, V is valinyl and L^2 is leucinyl or isoleucinyl, and preferably leucinyl. As noted above, each substituent of the polypeptide is selected such that this present inventive polypeptide inhibits the binding of IL-6 with IL-6 receptor under physiological conditions.

The pharmaceutically acceptable group R^1^2 can optionally be the substituent R^1^3-R^1^4. Where R^1^2 is R^1^3-R^1^4, R^1^3 is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions, including, but not limited to norleucinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, γ-aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, α-
carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. Where R¹² is R¹³-R¹⁴, R¹⁴ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR¹⁵, and R¹⁵. R¹⁵ is a pharmaceutically acceptable substituent group (see R³, supra). Preferably, R¹³ is selected from the group consisting of naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions. Alternatively, R¹³ is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C₁-C₆ straight-chained or branched alkyl moiety; for example, from the group consisting of glycyl, alaninyl, isoleucinyl, leucinyl, valinyl, norleucinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl. The polypeptide in which R¹³ is alaninyl is among the preferred polypeptides of the second embodiment.

In one polypeptide of the second embodiment, R¹⁶ is R¹⁶, and R¹⁶ is selected from the group consisting of hydrogen, a C₁-C₁₆ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₁₅-C₁₈ cycloalkyl, wherein any of the foregoing R¹₆ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

Optionally, R¹⁶ can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate
moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₆-C₈ monoalkylamine moiety, a C₆-C₈ dialkylamine moiety, and a C₇-C₈ trialkylamine moiety.

In another polypeptide of the second embodiment, R¹⁰ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, R³C(Ο)-, and R¹⁷, wherein R¹⁷ is a pharmaceutically acceptable substituent group (see R³, supra).

Similarly to R¹⁶, R¹⁷ can be selected from the group consisting of hydrogen, a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₂-C₁₈ aralkyl, and a C₆-C₁₈ cycloalkyl, wherein any of the foregoing R¹⁷ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur. In a preferred embodiment, R¹⁷ is hydrogen.

Optionally, R¹⁷ can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

In a third embodiment, the present invention provides a polypeptide of the formula R²⁰R²¹L'R'Y'R'A'E'R'S'R²². This embodiment is predicted, at
least in part, on three surprising and unexpected discoveries. First, that a third domain within the IL-6 receptor has the ability to bind to the IL-6 ligand and this domain has the essential core amino acid residue sequence -LRAERS-, which naturally occurs in the larger subsequence -FELRAERSKT. Second, that the affinity of this domain for the IL-6 ligand can be substantially enhanced if the acidic side chain of the first glutamyl residue in the larger sequence is eliminated or preferably is replaced by a small hydrophobic side-chain (e.g., as possessed by alanine). Third, that the lysinyl residue is preferably present and more preferably has a side-chain that is basic under physiological conditions.

In this third embodiment, \( R^{20} \) and \( R^{22} \) are pharmaceutically acceptable substituents. The substituent \( R^{21} \) is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions, which includes, but clearly is not limited to, norleucinyl, norvalinyl, sarcosinyl, \( \beta \)-alaninyl, \( \alpha \)-aminoisobutyryl, homoserinyl, hydroxyprolinyl, ornithinyl, citrullinyl, and homoargininyl. Preferably, \( R^{21} \) is alaninyl.

Additionally, \( L' \), \( Y' \), \( E' \), and \( S' \) are each independently selected from the group consisting of synthetic and naturally-occurring amino acid residues. \( L' \) is preferably leucinyl or isoleucinyl. More preferably, \( L' \) is leucinyl. The substituent \( Y' \) is preferably selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and \( \alpha \)-aminoisobutyryl. More preferably, \( Y' \) is tyrosinyl or phenylalaninyl, and most preferably,
tyrosinyl. The substituent E' is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having acidic side-chains under physiological conditions. For example, E' can be selected from the group consisting of glutamyl, aspartyl, γ-aminopentane-1,5-dioyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. More preferably, E' is selected from the group consisting of glutamyl, aspartyl, and γ-aminopentane-1,5-dioyl. Yet more preferably, E* is glutamyl. The substituent S' is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl, and preferably is serinyl. The substituent A' is selected from the group consisting of alaninyl, glycylinyl, and valinyl, and preferably is alaninyl.

Preferably, R²⁰ is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, R²³C(O)-, and R²³. Similarly, R²² is preferably selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, -NH-R²³, and R²³.

The substituent R²³ can be selected from the group consisting of a C₁-C₈ alkyl, a C₂-C₈ alkenyl, a C₆-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R²³ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

R²³ can be substituted by one to about six substituents, which can be the same or different,
selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₄ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

R' is independently selected from the group consisting of synthetic or naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions; for example, argininyln, lysinyln, ornithinyln, citrullinyln, or homoargininyln. Preferably, R' is selected from the group consisting of argininyln and lysinyln. More preferably, R' is argininyln.

A' is selected from the group consisting of alaninyln, glycinyln, isoleucinyln, leucinyln, valinyln, norleucinyln, norvalinyln, sarcosinyln, β-alaninyln, and α-aminoisobutyryln. Preferably, A' is alaninyln.

Additionally, the polypeptide of the third embodiment of the present invention can comprise additional polypeptides or protein motifs. Preferably, the present inventive polypeptide does not comprise more than about 200, and preferably more than about 50, additional amino acid residues that have an amino acid residue sequence that is identical (or at least 60% identical over a span of five or ten amino acid residues) to another amino acid residue sequence from the same chain of the IL-6 receptor.

In a fourth embodiment, the present invention provides a polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under
physiological conditions. The sequence comprises at least a polypeptide of the formula I'AV'IV'L'R'F'. This embodiment is predicated, at least in part, on the surprising and unexpected discovery that a fourth domain of the IL-6 receptor occurs in the membrane-associated region of the receptor, and this domain is centered about a region of the receptor having an amino acid residue sequence of IAVISLRFK. This embodiment is further predicated on the surprising and unexpected discovery that this domain is highly tolerant of amino acid residue substitutions. For example, the basic residues of this sequence (i.e., argininy1 and lysiny1) can be replaced by a non-conservative alaninyl substitution, which has the surprising effect of increasing the affinity of the domain for the IL-6 ligand.

In this fourth embodiment I', L', and V' are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C₁-C₆ straight-chain or branched alkyl moiety.

R' is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions. For example, R' can be selected from the group consisting of argininy1, lysiny1, ornithiny1, citrulliny1, and homoargininy1. When R' is to be translated from a nucleic acid, R' preferably is selected from the group consisting of argininy1 and lysiny1. R' is more preferably argininy1.

A' is selected from the group consisting of alaninyl, glyciny1, isoleuciny1, leuciny1, valiny1, norleuciny1,
norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl.

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl.

Preferably, at least four of the seven substituents, more preferably at least five substituents, yet more preferably at least six substituents of I'A'I'V'L'R'F', are selected such that I* is isoleucinyl, A* is alaninyl, V* is valinyl, L' is leucinyl, R' is argininyln, and F* phenylalaninyl. Of course, all seven amino acid residues can be selected such that I'A'I'V'L'R'F' is IAIVLRFK. The polypeptide is preferably selected such that it is small enough to bind effectively to IL-6 and does not comprise unnecessary extra atoms (making synthesis and processing of the polypeptide easier). The polypeptide preferably comprises less than about 200 amino acid residues, alternatively less than about 100 amino acid residues, alternatively less than about 30 amino acid residues, and alternatively less than about 16 amino acid residues that have a sequence that is identical to that of a region of the α-chain of the IL-6 receptor.

Surprisingly, the affinity of the polypeptide for binding with IL-6 increases if any one, preferably two, and more preferably three, amino acid residues are bound via peptide bonds to the carboxyl-terminus of the sequence I'A'I'V'L'R'F'. Accordingly, the polypeptide preferably comprises at least the sequence IAIVLRFKXX in which X is any synthetic or naturally-occurring amino acid residue, as defined above, and preferably a synthetic or naturally-occurring amino acid residue of
the formula NH₂-(CHR⁴)-COO⁻. Optionally, the sequence can comprise an amino-terminal tripeptide of the formula LLC-, or conservatively or neutrally substituted equivalents of LLC-. In this regard, the sequence can comprise at least the sequence LLCIAIVLRFK. Additionally, the sequence can comprise at least the sequence FGTLLCIAIVLRFKKT.

A fifth embodiment of the present invention is predicated on the surprising and unexpected discovery that the amino acid sequence SVIILKYNIQY, which is a subsequence of the β-chain amino acid sequence of the IL-6 receptor, is critical in the binding between IL-6 ligand and IL-6 receptor. Accordingly, the present invention also provides a polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present inventive polypeptide of this fifth embodiment comprises the sequence SVIILKYNIQY and has an amino acid residue sequence of up to about 200 amino acid residues, preferably about 100 residues, more preferably about 50 residues, and optionally no or essentially no additional residues, that are identical to the β-chain of the IL-6 receptor or alternatively are at least about 60% identical over a span of about five or ten contiguous amino acid residues.

Biochemical analysis of this sequence revealed that the binding interaction is somewhat stronger if the sequence SVIILKYNIQY is extended on the amino terminus to include the sequence PSIK-. Accordingly, the present invention also provides a polypeptide of this fifth embodiment comprising the sequence PSIKSVIILKYNIQY.
Similar analyses further defined a region governing the binding between IL-6 ligand and its receptor. These analyses resulted in the identification and provision of polypeptides comprising the sequences WTNPSIKSVILKYNIQY and KLTWNPSIKSVILKYNIQY, and up to about 200 amino acid residues that have an identical residue sequence to the sequence of the \( \beta \)-chain of the IL-6 receptor. Preferably, the polypeptides comprising the recited sequences comprise up to about 100 amino acid residues, more preferably, up to about 50 amino acid residues, from the IL-6 receptor \( \beta \)-chain sequence. Optionally, the polypeptide comprises no other, or essentially no other, sequence of amino acid residues that has an identical sequence to the sequence of the IL-6 receptor \( \beta \)-chain over a continuous stretch of five, or more preferably three, amino acid residues other than the sequences explicitly recited above. Additionally, the present inventive sequences preferably do not comprise a region of higher than about 60% homology to the IL-6 receptor over a stretch of at least five or ten contiguous amino acid residues, outside the region of the IL-6 receptor \( \beta \)-chain sequences explicitly recited above.

Alternatively, the present inventive \( \beta \)-chain polypeptides comprise a sequence consisting essentially of the recited sequence and polypeptides from other sources or origins that primarily contribute a function that is not directly related to IL-6 function or signaling.

In additional (sixth, seventh, and eighth) embodiments, the present invention provides a polypeptide of up to about 200 amino acid residues having a sequence
that is identical to a portion of the sequence
TRWKSHLQNYTVNATKLTVLTDNYLTLTVNRNLVGKSDDAVL,
QLPVDVQNGFIRNYTIFYRTIIGN, or
IVVPVCLAFLLLTLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA, and that
inhibits the binding of IL-6 ligand with IL-6 receptor
under physiological conditions. The portion of the
sequence can be any suitable size. For example, the
portion of the amino acid sequence can be about a 6-mer,
about a 12-mer, about an 18-mer, or about a 24-mer. An
"n"-mer, as is understood in the art, is an oligopolymer
consisting of "n" monomeric components or residues.
Thus, a polypeptide comprising a portion of any of the
preceding sequences that is a 6-mer, would comprise an
amino acid sequence of any six adjacent residues of any
one of the three preceding amino acid sequences.
Preferably, the polypeptide comprises no more than about
100 amino acid residues, and more preferably no more than
about 50 amino acid residues, having a sequence identical
to that of the IL-6 receptor β-chain.

Conservative or neutral amino acid substitutions
that do not destroy the ability of any of the above-
described polypeptides to bind to IL-6 can be made. The
replacement residues that substitute for the amino acid
residues explicitly recited above can be either synthetic
or naturally-occurring. Preferably, the number of
substitutions is kept to a minimum, e.g., from 1 to about
6 conservative or neutral substitutions, and more
preferably from 1 to about 3 conservative or neutral
amino acid residue substitutions. While the residues
substituted for the recited amino acid residues can be
natural or synthetic, natural residues are preferred in
those instances in which it is desirable for the amino acid residues to be encoded by a nucleic acid.

Additionally, any embodiment of the foregoing present inventive polypeptide can further comprise a pharmaceutically acceptable substituent, which is selected so that the polypeptide retains the ability to inhibit the binding of IL-6 ligand with IL-6 receptor under physiological conditions.

Also provided by the present invention is a nucleic acid that encodes an above-described polypeptide, which consists of naturally-occurring amino acid residues. The nucleic acid can be expressed in a cell.

In another embodiment, the present invention also provides a vector comprising a nucleic acid molecule as described above. A nucleic acid molecule as described above can be cloned into any suitable vector and can be used to transduce, transform, or transfect any suitable host. The selection of vectors and methods to construct them are commonly known to persons of ordinary skill in the art and are described in general technical references (see, in general, "Recombinant DNA Part D," Methods in Enzymology, Vol. 153, Wu and Grossman, eds., Academic Press (1987)). Desirably, the vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host (e.g., bacterium, fungus, plant, or animal) into which the vector is to be inserted, as appropriate and taking into consideration whether the vector is DNA or RNA. Preferably, the vector comprises regulatory sequences that are specific to the genus of the host. Most preferably, the vector comprises
regulatory sequences that are specific to the species of the host and is optionally optimized for the expression of an above-described polypeptide.

Constructs of vectors, which are circular or linear, can be prepared to contain an entire nucleic acid sequence as described above or a portion thereof ligated to a replication system that is functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived from ColEl, 2 μ plasmid, λ, SV40, bovine papilloma virus, and the like.

Suitable vectors include those designed for propagation and expansion, or for expression, or both. A preferred cloning vector is selected from the group consisting of the pUC series, the pBluescript series (Stratagene, LaJolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clonetech, Palo Alto, CA). Examples of animal expression vectors include pEUK-CI, pMAM and pMAMneo (Clonetech, Palo Alto, CA).

An expression vector can comprise a native or nonnative promoter operably linked to a nucleic acid molecule encoding an above-described polypeptide. The selection of promoters, e.g., strong, weak, inducible, tissue-specific and developmental-specific, is within the skill in the art. Similarly, the combining of a nucleic acid molecule as described above with a promoter is also within the skill in the art.

The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes secretion of at least the polypeptide by a cell in which the nucleic acid is expressed. Signal sequences
(alternatively called secretion sequences) are well-known in the art.

Alternatively, the nucleic acid comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for a naturally-occurring, specified amino acid sequence of an above-described polypeptide. A nucleic acid sequence introduced in antisense suppression generally is substantially identical to at least a portion of the endogenous gene or gene to be repressed, but need not be identical. Thus, the vectors can be designed such that the inhibitory effect applies to other proteins within a family of genes exhibiting homology or substantial homology to the target gene. The introduced sequence also need not be full-length relative to either the primary transcription product or fully processed mRNA. Generally, higher homology can be used to compensate for the use of a shorter sequence. Furthermore, the introduced sequence need not have the same intron or exon pattern, and homology of non-coding segments will be equally effective.

Ribozymes also have been reported to have use as a means to inhibit expression of endogenous genes. It is possible to design ribozymes that specifically pair with virtually any target RNA and cleave the phosphodiester backbone at a specific location, thereby functionally inactivating the target RNA. In carrying out this cleavage, the ribozyme is not itself altered and is, thus, capable of recycling and cleaving other molecules, making it a true enzyme. The inclusion of ribozyme sequences within antisense RNAs confers RNA-cleaving activity upon them, thereby increasing the activity of
the constructs. The design and use of target RNA-specific ribozymes is described in Haseloff et al.,

Further provided by the present invention is a
composition comprising an above-described polypeptide or
nucleic acid and a carrier therefor. Another composition
provided by the present invention is a composition
comprising an antibody to an above-described polypeptide,
an anti-antibody to an above described polypeptide, or a
solid support matrix to which is attached an above-
described polypeptide or an anti-antibody to the
polypeptide sequence RRLLR, RXVLLV, LRYAERS, IAVLRF,
SVILKNIQY, PSKSIILKNIQY, WTNPSIKSIILKNIQY,
KLTWNPSKSIILKNIQY,
TRWKSBLQNYTVNATKLTVNLTNDRYLAALTVRNLVGKSDAAL,
QLPVDQNGFIRNYTIFYRTIGN, or
IVVPVCLAFLTLTLGVLFCRNKRDLIKKHIWPNVPDPSKSHIA.

Antibodies can be generated in accordance with
methods known in the art. See, for example, Benjamin, *In
436-437; Kuby, *In Immunology*, 3rd. ed., Freeman, NY,
1997, pp. 455-456; Greenspan et al., *FASEB J.* 7: 437-443
antibodies (i.e., anti-idiotypic antibodies) also can be
generated in accordance with methods known in the art
(see, for example, Benjamin, *In Immunology: a short
Immunology*, 3rd. ed., Freeman, NY, 1997, pp. 455-456;
Greenspan et al., *FASEB J.*, 7, 437-443, 1993; Poskitt,
*Vaccine*, 9, 792-796, 1991; and Madiyalakan et al.,
therapy"). Such antibodies can be obtained and employed either in solution-phase or coupled to a desired solid-phase matrix. Having in hand such antibodies, one skilled in the art will further appreciate that such antibodies, using well-established procedures (e.g., such as described by Harlow and Lane (1988, supra), are useful in the detection, quantification, or purification of IL-6 ligand, IL-6 receptor, conjugates of each and host cells transformed to produce IL-6 receptor or a derivative thereof. Such antibodies are also useful in a method of prevention or treatment of a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

In view of the above, the present invention also provides a method of producing an antibody to the specific amino acid sequence of an above-described polypeptide. The method comprises administering an above-described polypeptide to an animal. The animal generates anti-polypeptide antibodies. Such an antibody can be administered to an animal to prevent or treat a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

Although nonhuman antibodies are useful for prophylactic or therapeutic treatment in humans, their favorable properties, in certain instances, can be further enhanced and/or their adverse properties further diminished, through "humanization" strategies, such as those recently reviewed by Vaughan, *Nature Biotech.*, 16, 535-539, 1998.
Prior to administration to an animal, such as a mammal, in particular a human, an above-described polypeptide, nucleic acid or antibody can be formulated into various compositions by combination with appropriate carriers, in particular, pharmaceutically acceptable carriers or diluents, and can be formulated to be appropriate for either human or veterinary applications.

Thus, a composition for use in the method of the present invention can comprise one or more of the aforementioned polypeptides, nucleic acids or antibodies, preferably in combination with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those skilled in the art, as are suitable methods of administration. The choice of carrier will be determined, in part, by whether a polypeptide or a nucleic acid is to be administered, as well as by the particular method used to administer the composition. One skilled in the art will also appreciate that various routes of administering a composition are available, and, although more than one route can be used for administration, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, there are a wide variety of suitable formulations of compositions that can be used in the present inventive methods.

A composition in accordance with the present invention, alone or in further combination with one or more other active agents, can be made into a formulation suitable for parenteral administration, preferably intraperitoneal administration. Such a formulation can include aqueous and nonaqueous, isotonic sterile
injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

The formulations can be presented in unit dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneously injectable solutions and suspensions can be prepared from sterile powders, granules, and tablets, as described herein.

A formulation suitable for oral administration can consist of liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or fruit juice; capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solid or granules; solutions or suspensions in an aqueous liquid; and oil-in-water emulsions or water-in-oil emulsions. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers.

Similarly, a formulation suitable for oral administration can include lozenge forms, which can
comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier; as well as creams, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

An aerosol formulation suitable for administration via inhalation also can be made. The aerosol formulation can be placed into a pressurized acceptable propellant, such as dichlorodifluoromethane, propane, nitrogen, and the like.

A formulation suitable for topical application can be in the form of creams, ointments, or lotions.

A formulation for rectal administration can be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate. A formulation suitable for vaginal administration can be presented as a pessary, tampon, cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Verhoef, Eur. J. Drug Metab. Pharmacokinetics 15, 83-93, 1990). The appropriate delivery system for a given polypeptide will depend upon its particular nature, the particular clinical application, and the site of drug action. As with any protein drug, oral delivery will likely present special problems, due primarily to instability in the gastrointestinal tract and poor absorption and bioavailability of intact, bioactive drug therefrom. Therefore, especially in the case of oral delivery, but also possibly in conjunction with other routes of delivery, it will be necessary to use an absorption-enhancing agent in combination with a given polypeptide. A wide variety of absorption-enhancing agents have been investigated and/or applied in combination with protein drugs for oral delivery and for delivery by other routes (Verhoef (1990), supra; van Hoogdalem, Pharmac. Ther. 44: 407-443, (1989); Davis, J. Pharm. Pharmacol. 44(Suppl. 1): 186-190, (1992). Most commonly, typical enhancers fall into the general categories of (a) chelators, such as EDTA, salicylates, and N-acyl derivatives of collagen, (b) surfactants, such as lauryl sulfate and polyoxyethylene-9-lauryl ether, (c) bile salts, such as glycholate and taurocholate, and derivatives, such as taurodihydrofusidate, (d) fatty acids, such as oleic acid and capric acid, and their derivatives, such as acylcarnitines, monoglycerides, and diglycerides, (e) non-surfactants, such as unsaturated cyclic ureas, (f) saponins, (g) cyclodextrins, and (h) phospholipids.

Other approaches to enhancing oral delivery of protein drugs can include the aforementioned chemical
modifications to enhance stability to gastrointestinal enzymes and/or increased lipophilicity. Alternatively, the protein drug can be administered in combination with other drugs or substances that directly inhibit proteases and/or other potential sources of enzymatic degradation of proteins. Yet another alternative approach to prevent or delay gastrointestinal absorption of protein drugs is to incorporate them into a delivery system that is designed to protect the protein from contact with the proteolytic enzymes in the intestinal lumen and to release the intact protein only upon reaching an area favorable for its absorption. A more specific example of this strategy is the use of biodegradable microcapsules or microspheres, both to protect vulnerable drugs from degradation, as well as to effect a prolonged release of active drug (Deasy, in Microencapsulation and Related Processes, Swarbrick, ed., Marcel Dekker, Inc.: New York, 1984, pp. 1-60, 88-89, 208-211). Microcapsules also can provide a useful way to effect a prolonged delivery of a protein drug, such as an above-described polypeptide, after injection (Maulding, J. Controlled Release 6, 167-176, 1987).

In view of the above, the present invention further provides a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof. The method comprises administering to the mammal an IL-6 signaling-inhibiting effective amount of an above-described polypeptide, nucleic acid, or antibody to an above-described polypeptide or a nucleic acid encoding such a polypeptide.
The dose administered to an animal, such as a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic or prophylactic (which desirably, but not necessarily, means absolute prevention as any degree of inhibition of IL-6 signaling in a mammal in need thereof is deemed beneficial) response in the individual over a reasonable time frame. The dose will be determined by the particular polypeptide, nucleic acid or antibody, administered, the severity of any existing disease state, as well as the body weight and age of the individual. The size of the dose also will be determined by the existence of any adverse side effects that may accompany the use of the particular polypeptide, nucleic acid or antibody employed. It is always desirable, whenever possible, to keep adverse side effects to a minimum.

The dosage can be in unit dosage form, such as a tablet or capsule. The term "unit dosage form" as used herein refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a vector, alone or in combination with other active agents, calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the unit dosage forms of the present invention depend on the particular embodiment employed and the effect to be achieved, as well as the pharmacodynamics associated with each polypeptide, nucleic acid or antibody in the host.

The dose administered should be an "IL-6 signaling-inhibiting effective amount" of an above-described active
agent to achieve an "effective level" in the individual patient.

With respect to the above methods, sufficient amounts can be determined in accordance with methods known in the art. Similarly, the sufficiency of an immune response in an animal also can be assessed in accordance with methods known in the art. Either one of the above methods can further comprise concurrent, pre- or post-treatment with an adjuvant to enhance the immune response (see, for example, Harlow et al. (1988), supra).

Since the "effective level" is used as the preferred endpoint for dosing, the actual dose and schedule can vary, depending on interindividual differences in pharmacokinetics, drug distribution, and metabolism. The "effective level" can be defined, for example, as the blood or tissue level desired in the patient that corresponds to a concentration of one or more polypeptides, nucleic acids or antibodies according to the invention. The "effective level" for a polypeptide, nucleic acid or antibody of the present invention also can vary when the compositions of the present invention are used in combination with other known active agents.

One skilled in the art can easily determine the appropriate dose, schedule, and method of administration for the exact formulation of the composition being used, in order to achieve the desired "effective level" in the individual patient. One skilled in the art also can readily determine and use an appropriate indicator of the "effective level" of a polypeptide, nucleic acid or antibody of the present invention by a direct or indirect
analysis of appropriate patient samples (e.g., blood and/or tissues).

It also will be appreciated by one skilled in the art that an above-described nucleic acid can be inserted ex vivo into animal cells, such as mammalian cells, in particular human cells, previously removed from such an animal. Such transformed autologous or homologous host cells, reintroduced into the animal or human, will express directly the corresponding polypeptide in vivo.

The feasibility of such a therapeutic strategy to deliver a therapeutic amount of an agent in close proximity to the desired target cells has been demonstrated in studies with cells engineered ex vivo to express sCD4 (Morgan et al., (1994), supra). As an alternative to ex vivo insertion of the DNA sequences of the present invention, such sequences can be inserted into cells directly in vivo, such as by use of an appropriate viral or other suitable vector. Such cells transfected in vivo are expected to produce effective amounts of an above-described polypeptide directly in vivo.

Given the present disclosure, it will be additionally appreciated that an above-described nucleic acid sequence can be inserted into suitable nonmammalian host cells, and that such host cells will express therapeutic or prophylactic amounts of the desired polypeptide directly in vivo within a desired body compartment of an animal, in particular a human.

In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of a mammal. The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to
which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKNIQY, PSIKSVIILKNIQY, WTNPSIKSVIILKNIQY, KLTWTPSIKSVIILKNIQY,
TRWKSHLQNYTVNATKLTVNLTNDRLATLTVNLVGKSDAHL, QLPVDVQNGFIRNYTFYRTIIGN, or IVVPVCLAFLLTLTLGVLFCFNKRDLIKKHIWNPVPDPSKSIA. Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the solution can be contacted with a solid support matrix to which is attached a means to remove the polypeptide or anti-antibody to which is bound IL-6 ligand from the bodily fluid. The method further comprises separating the bodily fluid and the solid support matrix by any suitable means.

Methods of attaching an above-described polypeptide or an anti-antibody to a solid support matrix are known in the art. "Attached" is used herein to refer to attachment to (or coupling to) and immobilization in or on a solid support matrix. See, for example, Harris, in Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York (1992), pp. 1-14 and international patent application WO 91/02714 (Saxinger). Diverse applications and uses of functional polypeptides attached to or immobilized on a solid support matrix are exemplified more specifically for poly(ethylene glycol) conjugated proteins or peptides in a review by Holmberg et al. (In Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York, 1992, pp. 303-324).
EXAMPLES

The following examples further illustrate the present invention but, of course, should not be construed as limiting the scope of the claimed invention in any way.

Synthetic peptide arrays were constructed in 96-well microtiter plates in accordance with the method set forth in WO 91/02714 (Saxinger), and used to test the binding of recombinant human IL-6 that had been labeled with radioactive iodine (radiolabeling by standard methods). After incubating the radiolabeled IL-6 ligand in a well with each synthetic peptide, a washing step was performed to remove unbound label, and the relative level of radioactivity remaining in each well of the plate was evaluated to determine the relative affinity of each peptide for IL-6 ligand. The synthesis of the peptides and the quantity of binding between the synthetic peptides and IL-6 ligand were found to be suitably reproducible, precise, and sensitive. Initial screening of the entire primary sequence of the IL-6 receptor molecule, taken 21 amino acid residues at a time, identified active binding sequences in four regions of the receptor corresponding to amino acid residues 66-86 (AAGSHPSRWAGMRRLLLSRV), 136-156 (PRSTPSLTKAVLLVRKFQNS), 246-266 (SSFYRLRFELRYRAERSKFT), and 371-391 (GGSLAFGTLICAILVRKFKT) (hereinafter domains I, II, III, and IV).

The authenticity of the binding signal was confirmed, at least for domains I-III, by demonstrating that antibodies that specifically bind to IL-6 ligand
were able to inhibit the binding reactions. The binding between domain IV and IL-6 ligand was not similarly shown to be authentic because domain IV resides in the transmembrane region of the protein and is not believed to have been present in the soluble receptor used as an immunogen to raise the antibodies to IL-6 ligand.

Each of the four binding domains was analyzed in detail, which is set forth in these examples. First, serial truncations (or nested truncations) were performed from each end of the peptides to determine the location of the critical binding residues within each domain. Second, each amino acid residue in the critical regions of each domain were serially replaced by an alaninyl residue to indicate whether the side-chain of the residue at each particular location is likely to be essential or important to the mechanism of binding.

Example 1

This example provides data identifying domain I, as well as amino acid residues that are essential and/or important in the binding of domain I to human IL-6.

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<th>Counts/minute bound</th>
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These data indicate that the sequence RRLLLR is a critical binding region within domain I, that domain I is preferably flanked on the amino-terminus by a pharmaceutically acceptable substituent equivalent in size to three amino acid residues, e.g., any three amino acid residues, and is preferably flanked on the carboxyl-
terminus by a pharmaceutically acceptable substituent equivalent in size to at least one amino acid residue, and preferably two or three or more amino acid residues.

Example 2

This example provides data identifying the critical binding regions of domain II, as well as which residues within the critical binding domain that are essential and/or important in the binding of human IL-6 to IL-6 receptor within domain II.

<table>
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<tr>
<th>Peptide Identifier</th>
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<th>Counts/minute bound</th>
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These data indicate that the sequence VLLV is a critical binding region within domain II, that domain II is preferably flanked on the amino-terminus by an amino acid sequence R^{II}-X-, wherein R^{II} is a synthetic or naturally-occurring amino acid residue that is neutral or acidic under physiological conditions and X is any amino acid residue. More preferably, the sequence includes LTTR^{II}-XVLLV, wherein X can optionally be alaninyl.

Additionally, these data indicate that the sequence VLLV is preferably flanked on the carboxyl-terminus by a pharmaceutically acceptable substituent equivalent in size to 1 to 3 amino acid residues, or more preferably, by 4 to 6 amino acid residues.

Example 3

This example provides data identifying the critical binding regions of domain III, as well as which residues
within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 receptor within domain III.

<table>
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These data indicate that the sequence LRYRAERS is a critical binding region within domain III, that domain III is preferably flanked on the amino-terminus by an amino acid residue R^21, wherein R^21 is a synthetic or naturally-occurring amino acid residue that has a side-chain that is neutral or basic under physiological conditions. Additionally, these data show that any of the amino acid residues of the critical binding domain can be replaced, preferably by a conservative substitution, and that the arginanyl residues of the critical binding region are most important to the binding of the peptide. Moreover, while not meaning to be bound by any particular theory, it is apparent that this region of the protein exists in a pleated-sheet motif. Accordingly, substitutions of amino acid residues by structure-breaking amino acid residues, e.g., prolinyl, is less preferred.

**Example 4**

This example provides data identifying the critical binding regions of domain IV, as well as which residues within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 receptor within domain IV. In the following tabulation
of data, rows D1-D10 were examined in one experiment, and rows D11-D57 were examined in a separate experiment. Thus, the numerical data obtained from rows D1-D10 should not be directly compared to the numerical data from rows D11-D57.

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<td>1153</td>
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<tr>
<td>D20:</td>
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</tr>
<tr>
<td>D22:</td>
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</tr>
<tr>
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</tr>
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<tr>
<td>D31:</td>
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<td>24047</td>
</tr>
<tr>
<td>D32:</td>
<td>FGTLCAIVLRFKK</td>
<td>21799</td>
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</table>
These data indicate that the sequence IAIVLRF is a critical binding region within domain IV, that this critical binding domain is preferably flanked on the carboxyl-terminus by one or two lysinyl residues, or at least a pharmaceutically acceptable substituent comparable in size to one to three amino acid residues, which are -KKT in the sequence of the human IL-6 receptor. These data also show that the sequence is preferably flanked on the amino-terminus by a pharmaceutically acceptable substituent comparable in size to one, two, three, four, five, or six or more amino
acid residues. Of course, the pharmaceutically acceptable substituents could be synthetic or naturally-occurring amino acid residues. Moreover, the data show that any one of the amino acid residues can be replaced by an alaninyl residue, resulting in an increase in affinity for IL-6. One skilled in the art will also appreciate that multiple (e.g., two or three) substitutions can be made in the critical binding region, and that when multiple replacements or substitutions are made, then the substitutions are preferably conservatively selected. Additionally, the skilled artisan will note that the critical amino acid sequence IAIYLRF resides in an extended region that has high affinity for the IL-6 ligand and that four of the seven amino acid residues of this critical region can be found at either the amino- or carboxyl terminus of a polypeptide comprising the sequence.

Example 5

This example employs essentially the same techniques as Examples 1-4 except that fragments of the β-chain of the IL-6 receptor are used. As is known in the art, the β-chain is shared by multiple receptors. Thus, the identified fragments here are effective inhibitors of a multiplicity of binding reactions in addition to the IL-6 ligand:IL-6 receptor interaction.

<table>
<thead>
<tr>
<th>Peptide Identifier</th>
<th>Peptide Sequence</th>
<th>Counts/minute bound</th>
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</thead>
<tbody>
<tr>
<td>E1:</td>
<td>MLTLQTWVQALFIFLTESTGEL</td>
<td>3365</td>
</tr>
<tr>
<td>E2:</td>
<td>ALFIFLTTESTGELLDPCGYISPE</td>
<td>1531</td>
</tr>
<tr>
<td>E3:</td>
<td>TGE LLDP CGYISPESPVQVLHSNF</td>
<td>1300</td>
</tr>
<tr>
<td>E4:</td>
<td>ISPESPVQVLHSNFPTAVCVLKEKC</td>
<td>1499</td>
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</tbody>
</table>
HSNFTAHCVLKEKCMDYFHVNANY
KEKCMDFYHNANYIVWKTNHFTI
NANYIVWKTNHFTIKEQYTIINR
HFTIPKEQYTIINRTASSVFTFDI
IINRTASSVFTFDIALNQIQLCN
FTDIASLNQLTCNILTFQGQLEQN
LTCNILTFQGQLEQNYVGYITISGL
LEQNVYGITISGLPPEKPNLSC
ISLGPPEKPKNLSCIVNEGKMRC
NLSCIVNEGKMRCWGDGREQH
KMRCWGDGREQHLETNFTLKEW
ETHLETNFTLKEWATHKFADECA
KEWATHKFADECAKRDTPTCTV
DCKAKRDTPTCTVDYSTVYFVNI
SCTVDYSTVYFVNIEVERVAENAL
FVNEVVEAENALGKVTSHDINF
ENALKKVTSHDINFDPVYKVPNP
HINFDPVYKVPNPNNLSVINSE
KNNPVHNLSSVINEEELSSILKTLW
INSEELSSILKLTWNTNPSIKSVII
KLWTNPSIKSVIILKYNIQYRTK
SVIILKYNIQYRTKDASTWSQIPP
YRTKDASTWSQIPPEDTASTRSSF
QIPPEDTASTRSSFQTLQVFDPFTE
RSSVTQDLKFYEVYFRIRCMKE
PPTEFYFRIRCMKEDGKGYWSDWS
CMKEDGKGYWSDWSEASAGITYED
SDWSEEASAGITYEDRPSKAPSFYY
TYEDRPSKAPSFYYKIDSHTQGY
SFWKIDSHTQGYRTQVQLWKLTL
TQGYRTQVQLWKLTPPFEEANGKIL
WKTLPPFEANGKILDYEVTLTRWK
GKILDYEVTLTRWKSHLQNYTVNA
TRWKSHELQNYTVNATKLTVNLTD
TVNATKLTVNLTDYRLATLTVRN
LTNDRYLATLTVRNWGLKASV
TVRNGLKASVAELTIPACDFQAT
AAVLTIQACDFQATHPVMDLKAFF
FQATHPVMDLKAFFKDNMLWVEWT
KFPKDNMLWVEWTTPRESVVKYI
VEWTPRESVVKYILEWCVLSDKA

51

1292
1443
1327
1143
1628
3376
1816
1669
1202
1171
1573
1035
1409
1548
3317
1413
1122
1728
1414
1007
10331
2832
1162
1202
1318
1263
1732
1161
1215
1145
1169
1465
1791
3652
4360
4802
1104
1121
1299
1175
1389
| E46: | KKYILEWCVLSDKAPCITDWDQQED | 1712 |
| E47: | SDKAPCITDWDQQEDGTVHRTLYLRG | 2079 |
| E48: | QQEDGTVHRTYLRGNAESKCYLI | 1082 |
| E49: | YLRGNLAESKCYLTVTPVYADGP | 1541 |
| E50: | CYLTITVTPVYADGPSESISYKAYL | 1259 |
| E51: | ADGPGSPESIKAYLKVQAPPSKGPT | 1194 |
| E52: | KAYLQAPPSKGTVTCKVKGKE | 1816 |
| E53: | KGPSVRKKVKVKEANASEWDLQPV | 1636 |
| E54: | GNEAVLEWDQLPVDVQNGFIRNY | 1307 |
| E55: | QLPVQNGFIRNYTLYRFFIGN | 4355 |
| E56: | IRNYTIFYRITIGNETAVNVDSSE | 1635 |
| E57: | IIGNETAVNVDSSEHTYTLSSLTS | 1232 |
| E58: | DSSHTETYTLSSLTSDTLYMVRAA | 1353 |
| E59: | SLSTSLTLTMYMVRAAYTDEGGKGDGP | 1270 |
| E60: | RMAAYTDEGGKGDPEFTFTPFPFA | 1447 |
| E61: | KDGEFPTFTPFPFAQGEIEIAIVVP | 1393 |
| E62: | PKFAQGEIEIAIVVPVCLAFLLTTL | 2794 |
| E63: | IVVPVCLAFLLTLLGLVLFCCNKR | 4519 |
| E64: | LTTLLGVLFCCNFNDLKLKHIPWN | 4501 |
| E65: | FNKRDLIKKLHWPVPNPDPSKSHA | 5741 |
| E66: | IWPVPDPSKSHINIAQSWPHTPRH | 1203 |
| E67: | SHIAQWSHPHPRHNFSKDQMYSS | 1199 |
| E68: | PPRHNFSKDQMYSDNSFDTSVDVSV | 1231 |
| E69: | QMYSDGNTDTSVVEIEANDKFF | 1194 |
| E70: | VSVVEIEANDKFPEDLKSCLDLF | 1305 |
| E71: | KDPEDLKLSDLFKKKEKINTEGH | 2694 |
| E72: | LDLFKKEKINTEGHSSGIGSSCM | 1443 |
| E73: | TEGHSSGIGGSSCMSGSSRPSISSS | 1060 |
| E74: | SCCMSRSSPSIISSSDENESSQNTS | 1131 |
| E75: | ISSSDEESSQNTSTTVYQSYTSTV | 1118 |
| E76: | QTTSSTTVSYQTSTVHSYRQVPSV | 1197 |
| E77: | TVVHSVSRHQPSPQVFSRSESTQ | 1247 |
| E78: | VPSVQFSRSESTQPLLDSERPE | 1229 |
| E79: | ESTQPLDSEERPDLQVLDHVGD | 1384 |
| E80: | ERPEDLQLVDHVGDGDGILPRQY | 1214 |
| E81: | HVVDGGDGILPRQYFKQNCSCQHE | 1097 |
| E82: | RRQYFKQNCSCQHESSPDISHCFERS | 1087 |
| E83: | QHESSPDISHFERSKQVSVNEED | 1250 |
| E84: | FERSKQVSVNEEDFVRLKQQISD | 1015 |
| E85: | NEEDFVRLKQQISDHSISQSCGSGQ | 1113 |
| E86: | QISDHSISQSCGSGQMKMFQEVSA | 1239 |
These data demonstrate that the sequence SVIIKYNIQY is sufficient to bind to IL-6 ligand; however, better binding can be obtained by a sequence comprising the sequence PSIKSVIIKYNIQY and the sequence can optionally comprise either WTNPSIKSVIIKYNIQY or even KLTWTNPSIKSVIIKYNIQY.

These data also indicate that the sequence TRWKSHLQNYTVNATKLTVNLNDRTLTLTVNLVGKSDAAVL comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand. Similarly, QLPVDVQNGFIRNYTIFYRTIGN comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand. Additionally, the sequence IVVPVCLAFLLLLTLGLVLFCKNRDLIKKHINPNVPDPSKSHIA comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand.

For example, one skilled in the art will appreciate that any segment of the foregoing sequences comprising about six, twelve, eighteen, or twenty-four amino acid residues is expected to bind with IL-6 ligand. Moreover, these data indicate to the skilled artisan that a multiplicity of amino acid substitutions, particularly conservative amino acid substitutions, within any of the above-described polypeptides can yield additional polypeptides having a substantial ability to bind with IL-6 ligand and to inhibit the binding of IL-6 ligand to
IL-6 receptor and thereby inhibit IL-6 signaling under physiological conditions.

All publications cited herein are hereby incorporated by reference to the same extent as if each publication were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred polypeptides, nucleic acids, compositions and methods, and the like can be used and that it is intended that the invention can be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.
WHAT IS CLAIMED IS:

1. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions and has the formula R'R'L'LL'R'IR', and pharmaceutically acceptable salts thereof, wherein R' does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α-chain of the IL-6 receptor and is not linked to the moiety -R'R'L'LL'R' via a glycinyl residue or via a propionyl residue and is selected from the group consisting of hydrogen, R'C(O) -, and R';

    R' is independently selected from the group consisting of argininyl, naturally-occurring argininyl equivalents, and synthetic argininyl equivalents;

    L' is independently selected from the group consisting of leucinyl, naturally-occurring leucinyl equivalents, and synthetic leucinyl equivalents;

    R² is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR³, and R¹; and

    R³ is a pharmaceutically acceptable substituent group.

25 2. The polypeptide of claim 1, wherein R' is independently selected from the group consisting of argininyl and lysinyl.

3. The polypeptide of claim 1, wherein R' is argininyl.
4. The polypeptide of any of claims 1-3, wherein 
   L' is independently selected from the group 
   consisting of leucinyl, isoleucinyl, and valinyl.

5. The polypeptide of any of claims 1-3, wherein L' 
   is leucinyl.

6. The polypeptide of any of claims 1-5, wherein R' 
   is R', and 
   R' is independently selected from the group 
   consisting of a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ 
   alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, 
   and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R' 
   groups that are cyclic comprise from 0 to 2 atoms per 
   carbocyclic ring, which can be the same or different, 
   selected from the group consisting of nitrogen, oxygen, 
   and sulfur,

   any of the foregoing R' groups can be substituted by 
   one to about six substituents, which can be the same or 
   different, selected from the group consisting of an amino 
   moiety, a carbamate moiety, a carbonate moiety, a 
   phosphamate moiety, a phosphate moiety, a phosphonate 
   moiety, a pyrophosphate moiety, a triphosphate moiety, a 
   sulfamate moiety, a sulfate moiety, a sulfonate moiety, a 
   C₁-C₆ monoalkylamine moiety, a C₁-C₆ dialkylamine moiety, 
   and a C₁-C₆ trialkylamine moiety.

7. The polypeptide of claim 1, wherein said 
   polypeptide is RRLLLR, wherein R is argininyln and L is 
   leucinyl.
8. The polypeptide of any of claims 1-6, wherein \( R^2 \) is a -(serinyl-valinyl-\( R^3 \)), and \( R^4 \) is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 98 amino acid residues, -NH\( R^4 \), and \( R^4 \), and

\( R^4 \) is independently selected from the group consisting of a \( C_1-C_{18} \) alkyl, a \( C_2-C_{18} \) alkenyl, a \( C_2-C_{18} \) alkynyl, a \( C_6-C_{18} \) aryl, a \( C_7-C_{18} \) alkaryl, a \( C_7-C_{18} \) aralkyl, and a \( C_7-C_{18} \) cycloalkyl, wherein any of the foregoing \( R^3 \) groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur,

any of the foregoing \( R^4 \) groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a \( C_1-C_9 \) monoalkylamine moiety, a \( C_1-C_9 \) dialkylamine moiety, and a \( C_1-C_9 \) trialkylamine moiety.

9. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions and has the formula \( R^{10} R^{11} X V L^{2} L^{2} V R^{12} \), and pharmaceutically acceptable salts thereof, wherein

\( R^{10} \) is a pharmaceutically acceptable substituent;

\( R^{11} \) is selected from the group consisting of synthetic and naturally-occurring amino acid residues having an acidic or neutral side-chain under physiological conditions;
X is any synthetic or naturally-occurring amino acid residue;
V is valinyl;
L\textsuperscript{2} is leucinyl or isoleucinyl; and
R\textsuperscript{12} is a pharmaceutically acceptable substituent.

10. A polypeptide of claim 9, wherein X is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or neutral side-chain under physiological conditions.

11. A polypeptide of claim 9 or 10, wherein L\textsuperscript{2} is leucinyl.

12. A polypeptide of any of claims 9-11, wherein R\textsuperscript{12} is R\textsuperscript{13}-R\textsuperscript{14};
R\textsuperscript{13} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions; and
R\textsuperscript{14} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR\textsuperscript{15}, and R\textsuperscript{15}; and
R\textsuperscript{15} is a pharmaceutically acceptable substituent group.

13. The polypeptide of any of claims 9-12, wherein R\textsuperscript{13} is selected from the group consisting of naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions.
14. The polypeptide of any of claims 9-13, wherein R^{13} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1-C_6 straight-chain or branched alkyl moiety.

15. The polypeptide of claim 12, wherein R^{13} is alaninyl.

16. The polypeptide of any of claims 9-15, wherein R^{15} is R^{16}, and

R^{16} is selected from the group consisting of hydrogen, a C_1-C_18 alkyl, a C_2-C_18 alkenyl, a C_2-C_18 alkynyl, a C_6-C_18 aryl, a C_7-C_18 alkaryl, a C_7-C_18 aralkyl, and a C_3-C_18 cycloalkyl, wherein any of the foregoing R^{16} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R^{16} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphoramate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_6 monoalkylamine moiety, a C_1-C_6 dialkylamine moiety, and a C_1-C_6 trialkylamine moiety.
17. The polypeptide of any of claims 9-16, wherein \( R^{10} \) is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, \( R^{17} \) C(O) -, and \( R^{17} \); and

\( R^{17} \) is a pharmaceutically acceptable substituent group.

18. The polypeptide of claim 17, wherein \( R^{17} \) is selected from the group consisting of hydrogen, a \( C_{1-18} \) alkyl, a \( C_{2-18} \) alkenyl, a \( C_{2-18} \) alkynyl, a \( C_{1-18} \) aryl, a \( C_{2-18} \) alkaryl, a \( C_{2-18} \) aralkyl, and a \( C_{2-18} \) cycloalkyl, wherein any of the foregoing \( R^{17} \) groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and any of the foregoing \( R^{17} \) groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a \( C_{1-18} \) monoalkylamine moiety, a \( C_{1-8} \) dialkylamine moiety, and a \( C_{1-8} \) trialkylamine moiety.

19. The polypeptide of claim 17, wherein \( R^{17} \) is hydrogen.
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20. A polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions having the formula $R^{20}R^{22}L'R'Y'R'A'E'R'S'R^{22}$, wherein $R^{20}$ and $R^{22}$ are pharmaceutically acceptable substituents;

$R^{21}$ is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions;

$L'$, $Y'$, $E'$, and $S'$ are each independently selected from the group consisting of synthetic or naturally-occurring amino acid residues;

$R'$ is independently selected from the group consisting of synthetic or naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions; and

$A'$ is selected from the group consisting of alaninyl, glycynyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, $\beta$-alaninyl, and $\alpha$-aminoisobutyryl.

21. The polypeptide of claim 20, wherein $R^{20}$ is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, $R^{23}C(O)\cdot$, and $R^{23}$; and wherein

$R^{23}$ is selected from the group consisting of a $C_1$-$C_{18}$ alkyl, a $C_2$-$C_{18}$ alkenyl, a $C_2$-$C_{18}$ alkynyl, a $C_6$-$C_{18}$ aryl, a $C_7$-$C_{18}$ alkaryl, a $C_7$-$C_{18}$ aralkyl, a $C_7$-$C_{18}$ cycloalkyl, wherein any of the foregoing $R^{23}$ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which
can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur and any of the foregoing R^{23} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_{1-6} monoalkylamine moiety, a C_{1-6} dialkylamine moiety, and a C_{1-6} trialkylamine moiety.

22. The polypeptide of claim 20 or 21, wherein R^{22} is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, -NHR^{23}, and R^{23}; and wherein

R^{23} is selected from the group consisting of a C_{1-18} alkyl, a C_{2-18} alkenyl, a C_{2-18} alkynyl, a C_{6-18} aryl, a C_{7-18} alkaryl, a C_{7-18} aralkyl, a C_{1-18} cycloalkyl, wherein any of the foregoing R^{23} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and any of the foregoing R^{23} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a
C₁-C₅ monoalkylamine moiety, a C₁-C₅ dialkylamine moiety, and a C₁-C₅ trialkylamine moiety.

23. The polypeptide of any of claims 20-22, wherein R²⁺ is alaninyl.

24. The polypeptide of any of claims 20-23, wherein R' is argininyl.

25. The polypeptide of any of claims 20-24, wherein L' is isoleucinyl or leucinyl.

26. The polypeptide of claim 25, wherein L' is leucinyl.

27. The polypeptide of any of claims 20-26, wherein Y' is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl.

28. The polypeptide of any of claims 20-27, wherein Y' is tyrosinyl.

29. The polypeptide of any of claims 20-28, wherein E' is selected from the group consisting of synthetic and naturally-occurring amino acid residues having an acidic side-chain under physiological conditions.

30. The polypeptide of claim 29, wherein E' is selected from the group consisting of glutamyl, aspartyl, and γ-aminopentane-1,5-dioyl.
31. The polypeptide of claim 30, wherein E* is glutamyl.

32. The polypeptide of any of claims 20-31, wherein A' is alaninyl, glycynyl, or valinyl.

33. The polypeptide of claim 32, wherein A' is alaninyl.

34. The polypeptide of any of claims 20-33, wherein S' is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl.

35. The polypeptide of claim 34, wherein S' is serinyl.

36. A polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under physiological conditions, wherein said sequence comprises at least I'A'I'V'L'R'F',

wherein I', L', and V' are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C<sub>1</sub>-C<sub>6</sub> straight-chain or branched alkyl moiety;

R' is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions;

A' is selected from the group consisting of alaninyl, glycynyl, isoleucinyl, leucinyl, valinyl, norleucinyl,
norvalinyln, sarcosinyl, β-alaninyl, and α-aminoisobutyryl;

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl,

and wherein at least four of the seven substituents of I'A'I'V'L'R'F' are selected such that I* is isoleucinyl, A* is alaninyl, V' is valinyl, L' is leucinyl, R' is argininyl, and F* is phenylalaninyl;

and said polypeptide comprises less than about 200 contiguous amino acid residues that have a sequence that is identical to an amino acid sequence of the α-chain of the IL-6 receptor.

37. The polypeptide of claim 36, wherein said sequence comprises IAIVLRFK.

38. The polypeptide of claim 36, wherein said sequence comprises at least IAIVLRFXXX in which X is any synthetic or naturally-occurring amino acid residue.

39. The polypeptide of claim 36, wherein said sequence comprises at least LLCIAIVLRFK.

40. The polypeptide of claim 36, wherein said sequence comprises at least FGTLLCIAIVLRFKKT.

41. The polypeptide of any of claims 36-40, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span
of less than about 100 contiguous amino acid residues of
the α-chain of the IL-6 receptor.

42. The polypeptide of claim 41, wherein said
polypeptide has an amino acid residue sequence that is
identical to the amino acid residue sequence of a span of
less than about 30 contiguous amino acid residues of the
α-chain of the IL-6 receptor.

43. The polypeptide of claim 42, wherein said
polypeptide has an amino acid residue sequence that is
identical to the amino acid residue sequence of a span of
less than about 16 contiguous amino acid residues of the
α-chain of the IL-6 receptor.

44. A polypeptide, which inhibits the binding of
IL-6 ligand with IL-6 receptor under physiological
conditions, comprises up to about 200 contiguous amino
acid residues that are identical to an amino acid residue
sequence of the β-chain of the IL-6 receptor and
comprises the sequence SVIILKYNIQY.

45. The polypeptide of claim 44, comprising the
sequence PSIKSVIIKYNIQY.

46. The polypeptide of claim 44, comprising the
sequence WTNPSIKSVIIKYNIQY.

47. The polypeptide of claim 44, comprising the
sequence KLIWTNPSIKSVIIKYNIQY.
48. The polypeptide of any of claims 44-47, having up to about 100 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor.

49. The polypeptide of any of claims 44-47, having up to about 50 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor.

50. The polypeptide of any of claims 44-47 consisting of the recited sequence.

51. The polypeptide of any of claims 44-50 comprising from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue, and wherein the polypeptide inhibits the binding of human IL-6 ligand to human IL-6 receptor under physiological conditions.

52. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino residue sequence of the β-chain of the IL-6 receptor, and comprises a portion of the sequence TRWKSHLQNYTVNATKLTVNLINDRYLATLTVRNLVGVKSDAVAL.

53. The polypeptide of claim 52, wherein said portion is about a 6-mer.
54. The polypeptide of claim 52, wherein said portion is about a 12-mer.

55. The polypeptide of claim 52, wherein said portion is about an 18-mer.

56. The polypeptide of claim 52, wherein said portion is about a 24-mer.

57. The polypeptide of any of claims 52-56, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

58. The polypeptide of any of claims 52-57, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

59. The polypeptide of any of claims 52-58, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.

60. The polypeptide of any of claims 53-59, further comprising a pharmaceutically acceptable substituent.

61. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological
conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor, and comprises a portion of the sequence QLPVDVQNGFIRNYTIFYRTIIGN.

62. The polypeptide of claim 61, wherein said portion is about a 6-mer.

63. The polypeptide of claim 61, wherein said portion is about a 12-mer.

64. The polypeptide of claim 61, wherein said portion is about an 18-mer.

65. The polypeptide of any of claims 61-64, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

66. The polypeptide of any of claims 61-65, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

67. The polypeptide of any of claims 61-66, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.
68. The polypeptide of any of claims 61-67, further comprising a pharmaceutically acceptable substituent.

69. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor, comprises a portion of the sequence IVVPCLAFLLTLLGVLFCFNKRDLIKKHWWPNVPDPSSHA.

70. The polypeptide of claim 69, wherein said portion is about a 6-mer.

71. The polypeptide of claim 69, wherein said portion is about a 12-mer.

72. The polypeptide of claim 69, wherein said portion is about an 18-mer.

73. The polypeptide of claim 69, wherein said portion is about a 24-mer.

74. The polypeptide of any of claims 69-73, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

75. The polypeptide of any of claims 69-73, having up to about 50 contiguous amino acid residues that have
an identical sequence to an amino acid residue sequence
of the β-chain of the IL-6 receptor.

76. The polypeptide of any of claims 69-75, wherein
said portion comprises from 1 to about 6 conservative or
neutral substitutions, wherein any indicated amino acid
residue can be substituted with a synthetic or naturally-
occurring amino acid residue.

77. The polypeptide of any of claims 69-76, further
comprising a pharmaceutically acceptable substituent.

78. The polypeptide of any of claims 1-77, wherein
said polypeptide consists of naturally-occurring amino
acid residues.

79. A nucleic acid that encodes the polypeptide of
any of claims 1-78 and can be expressed in a cell.

80. The nucleic acid of claim 79, in which the
nucleic acid encoding the polypeptide is operably linked
to a signal sequence, wherein said signal sequence is
translated as a fusion protein with the polypeptide to
form a signal sequence-polypeptide fusion, and wherein
said signal sequence can cause secretion of at least the
polypeptide by a cell in which the nucleic acid is
expressed.

81. A composition comprising the polypeptide of any
of claims 1-78 or a nucleic acid of claim 79 or 80 and a
carrier therefor.
82. The composition of claim 81, wherein said composition comprises an agent or substituent that increases the solubility of the polypeptide.

83. The composition of claim 82, wherein said agent that increases the solubility of the polypeptide is a liposome.

84. The composition of claim 82, wherein said substituent is a saccharide.

85. A composition comprising a solid support matrix to which is attached a polypeptide of any of claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLR, RXVLLV, LRYRAERS, IAIIVLRF, SVIILKNIQY, PSIKSVIIKNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIIKNIQY, KLTWNPSIKSVIIKNIQY, TRWKSHTQNYTVNTKTLVNLTDRLTLTVNRNLVGSAAVL, QLFVDVQNGFRNYTIFYRTIGN, and IVVPVCALFLTLTLLGVLFCFNKRDILIKKHWPNPVPDPSKSHIA.

86. A method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, which method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of a polypeptide of any of claims 1-78, a nucleic acid of claim 79 or 80, or an antibody to a polypeptide of any of claims 1-78.
87. A method of removing IL-6 ligand from a bodily fluid of a mammal, which method comprises extra-corporeally contacting said bodily fluid with a solid support to which is attached a polypeptide of any of claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKNIQY, PSIKSIVILKNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIIKNIQY, KLTWTPSIKSVIIKNIQY, TRWKSHELQNVTNATKLTVNLTDQRYLALTAVRLNVGKSAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLLTLGVLFCFNKRDLIKKHIWPVPDPSPSISIA.
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**Fig. 1**
special amino acids and amino acid derivatives

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F-3755  H-γ-Abu-OtBu·HCl
E-2660  Ac-p-aminohippuric acid
F-1015  Ac-p-amino-Phe-OMe
F-2275  Ac-p-bromo-DL-Phe-OH
F-3265  Ac-p-Bz-D-Phe-OH
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F-2930  Ac-Cys(farnesyl)-OMe
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F-3175  Ac-4,5 dehydro-Leu-OH
F-1030  Ac-3,5-dinitro-Tyr-OEt
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F-1170  H-DL-allo-Ile-OH
F-1175  H-allo-Thr-OH
F-1180  H-D-allo-Thr-OH
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[ L-2-Aminohexanedioic acid ]
F-2575  D-α–Aminoadipic acid  
[ D-2-Aminohexanedioic acid ]
F-1185  DL-α-Aminoadipic acid  
[ DL-2-Aminohexanedioic acid ]
F-3150  L-2-Aminoadipic acid-δ-2-buty1 ester  
[ L-2-Aminohexanedioic acid-δ-2-buty1 ester ]
F-3130  L-α-Aminoadipic acid-δ-methyl ester · HCl  
[ L-2-Aminohexanedioic acid-δ-methyl ester · HCl ]
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F-3805  1-Aminocyclopropane-1-carboxylic acid
F-1200  H-4-Amino-3,5-diodo-Phe-OH
F-1205  7-Aminoheptanoic acid
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[ DL-2-Aminoheptandioic acid ]
H-3605  4-Aminopiperidine-4-carboxylic acid  
[ H-Pip-OH ]
F-2740  L-2-Aminosuberic acid  
[ L-2-Aminoocotandioic acid/H-Asu-OH ]
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F-3305  DL-a-Aminosuberic acid
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E-1700  n-Aminovaleric acid-benzyl ester • p-tosylate
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F-1281  L-Azetidine -2-carboxylic acid
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F-2485  H-ß-(3-Benzathienyl)-D-Ala-OH
F-1215  Bestatin
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A-3610  Boc-Homocys(Trt)-OH  
A-1190  Boc-Homophe-OH  
A-1195  Boc-D-Homophe-OH  
A-2830  Boc-Homopro-OH  
A-3125  Boc-D-Homopro-OH  
A-4165  Boc-7-hydroxy-Tic-OH  
A-4170  Boc-7-hydroxy-D-Tic-OH  
A-1800  Boc-p-iodo-Phe-OH  
A-3640  Boc-p-iodo-D-Phe-OH  
A-1805  Boc-p-iodo-DL-Phe-OH  
A-3815  Boc-isonipecotic acid  
[Boc-piperidine-4-carboxylic acid]  
A-3715  Boc-N-Me-Abz-OH  
A-2025  Boc-N-Me-allo-Ile-OH  
A-3730  Boc-N-Me-D-allo-Ile-OH  
A-2880  Boc-N-Me-p-chloro-D-Phe-OH  
A-2070  Boc-N-Me-p-nitro-Phe-OH · DCHA  
A-4495  Boc-p-Me-Phe-OH  
A-4500  Boc-p-Me-D-Phe-OH  
A-1965  Boc-Met(O)-OH  
A-2885  Boc-Met(O₂)-OH  
A-4145  Boc-α-Me-DL-Val-OH  
A-3225  Boc-1-Nal-OH  
A-4305  Boc-D-1-Nal-OH  
A-2850  Boc-2-Nal-OH  
A-2575  Boc-D-2-Nal-OH
A-3110  Boc-Neopentylgly-OH
A-4210  Boc-D-Neopentylgly-OH
A-2125  Boc-p-nitro-Phe-OH
A-2130  Boc-p-nitro-D-Phe-OH
A-3645  Boc-Oic-OH
[Boc-L-octohydroindole-2-carboxylic acid]
A-2965  Boc-Pen(Acm)-OH
A-2970  Boc-D-Pen(Acm)-OH
A-3660  Boc-Pen(Mbzl)-OH · DCHA
A-3665  Boc-D-Pen(Mbzl)-OH · DCHA
A-2900  Boc-Pen(Mob)-OH
A-3990  Boc-D-Pen(Mob)-OH
A-3650  Boc-Pen(NPys)-OH
A-3655  Boc-D-Pen(NPys)-OH
A-3550  Boc-Pen(Trt)-OH
A-3555  Boc-D-Pen(Trt)-OH
A-3915  Boc-pentafluoro-Phe-OH
A-3960  Boc-pentafluoro-D-Phe-OH
A-4385  Boc-p-phenyl-Phe-OH
[Boc-β-(4-biphenyl)-Ala-OH; Boc-Bip-OH]
A-4390  Boc-p-phenyl-D-Phe-OH
[Boc-β-(4-biphenyl)-D-Ala-OH; Boc-D-Bip-OH]
A-4100  N-Boc-phenylstatine
[N-Boc-(3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid]
B-3115  1-Boc-piperidine-4-Fmoc-amino-4-carboxylic acid
[Fmoc-Pip(Boc)-OH]
A-3745  Boc-β-(3-pyridyl)-Ala-OH
A-2855  Boc-β-(3-pyridyl)-D-Ala-OH
A-4395  Boc-β-(2-quinoly1)-Ala-OH
A-4400  Boc-β-(2-quinoly1)-D-Ala-OH
A-1180  N-Boc-statine  
[N-Boc-(3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid]

A-3945  Boc-L-thiazolidine-4-carboxylic acid  
[Boc-L-thioproline]

A-3940  Boc-D-thiazolidine-4-carboxylic acid  
[Boc-D-thioproline]

A-2290  Boc-β-(2-thienyl)-Ala-OH

A-2295  Boc-β-(2-thienyl)-D-Ala-OH

A-2300  Boc-β-(2-thienyl)-DL-Ala-OH

A-3700  Boc-L-thiocitulline-OtBu

A-4360  Boc-Thiomaala-1-(6-nitro)benzotriazolide

A-4345  Boc-Thionoleu-1-(6-nitro)benzotriazolide

A-4355  Boc-Thionoph-1-(6-nitro)benzotriazolide

A-4365  Boc-Thionoser(BzI)-1-(6-nitro)benzotriazolide

A-4350  Boc-Thionoval-1-(6-nitro)benzolriazolide

A-3070  Boc-Tic-OH

A-3075  Boc-D-Tic-OH

A-4090  Boc-D-Tpi-OH  
[Boc-D-1,2,3,4-tetrahydroarman-3-carboxylic acid]

F-1305  H-p-Bromo-Phe-OH

F-3700  H-p-Bromo-D-Phe-OH

F-1310  H-p-Bromo-DL-Phe-OH

F-3790  H-p-tBu-Phe-OH

F-3795  H-p-tBu-D-Phe-OH

F-3250  n-Butyloxy carbonyl-Dap-OH

F-2800  H-p-Bz-Phe-OH  
[H-Bpa-OH]

F-2810  H-p-Bz-D-Phe-OH  
[H-D-Bpa-OH]
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>F-2345</td>
<td>Carbamoyl-DL-Ala-OH</td>
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<td>F-1375</td>
<td>Carbamoyl-β-Ala-OH</td>
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<tr>
<td>M-2240</td>
<td>Carbamoyl-Asp-OH · magnesium salt</td>
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<tr>
<td>F-2430</td>
<td>Carbamoyl-Leu-OH</td>
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<tr>
<td>Q-1140</td>
<td>β-Carboline-3-carboxylic acid-ethyl ester</td>
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<tr>
<td>Q-1145</td>
<td>β-Carboline-3-carboxylic acid-propyl ester</td>
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<td>F-3590</td>
<td>H-p-Carboxy-Phe-OH</td>
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<tr>
<td>F-3585</td>
<td>H-p-Carboxy-Phe(OtBu)-OH</td>
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<tr>
<td>F-2700</td>
<td>L-Carnitine</td>
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<tr>
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<td>[(R)-β-Hydroxy-γ-(trimethylammonio)butyrate]</td>
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<td>F-1425</td>
<td>H-β-Chloro-Ala-OH</td>
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<tr>
<td>F-1430</td>
<td>H-β-Chloro-Ala-OH · HCl</td>
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<tr>
<td>F-1435</td>
<td>H-β-Chloro-D-Ala-OH · HCl</td>
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<td>F-1440</td>
<td>H-β-Chloro-DL-Ala-OH</td>
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<td>F-2325</td>
<td>H-β-Chloro-DL-Ala-OH · HCl</td>
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<td>F-3380</td>
<td>H-β-Chloro-Ala-NHOH</td>
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<td>H-β-Chloro-Ala-OMe · HCl</td>
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<td>F-1450</td>
<td>H-p-Chloro-DL-Phe-OH</td>
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<td>F-2690</td>
<td>H-p-Cloro-D-Phe-OMe · HCl</td>
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<td>F-1455</td>
<td>H-p-Chloro-DL-Phe-OMe · HCl</td>
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<td>F-1460</td>
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<td>F-2500</td>
<td>H-β-Cyclohexyl-Ala-OH · HCl</td>
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<tr>
<td>F-2505</td>
<td>H-β-Cyclohexyl-D-Ala-OH · HCl</td>
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<tr>
<td>F-3760</td>
<td>H-Cyclohexyl-Gly-OH · salt</td>
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<tr>
<td>F-3765</td>
<td>H-Cyclohexyl-D-Gly-OH · salt</td>
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</tbody>
</table>
F-2830  Cyclohexylstatine
        [(3S,4S)-4-Amino-5-cyclohexyl-3-hydroxypentanoic acid]
F-1470  H-β-(1-Cyclopentenyl)-DL-Ala-OH
F-1465  H-β-(1-Cyclopentenyl)-DL-Ala-OH
F-3470  H-β-Cyclopropyl-Ala-OH
F-1475  L-Cycloserine
F-1480  D-Cycloserine
F-1485  DL-Cycloserine
F-3050  H-Dob-OH · 2 HCl
F-3055  H-D-Dob-OH · 2 HCl
A-3305  H-Dob(Boc)-OH
E-3360  H-Dob(Boc)-OMe · HCl
F-3040  H-Dop-OH · HCl
F-3045  H-D-Dop-OH · HCl
F-3420  H-Dop(Boc)-OMe · HCl
F-2985  H-4,5-Dehydro-Leu-OH
F-2970  H-trans-4,5-Dehydro-Lys-OH
        [DL-trans-2,6-Diamino-4-hexenoic acid]
F-1490  H-3,4 Dehydro-Pro-OH
F-2705  H-3,4-Dehydro-DL-Pro-OH
F-1495  H-3,4-Dehydro-Pro-NH₂ · HCl
F-1500  H-3,4-Dehydro-Pro-OMe · HCl
F-1505  2,6-Diaminopimelic (LL,DD and Meso)
        [2,6-Diaminoheptanedioic acid]
F-1510  H-6-Diazo-5-oxo-Nle-OH
        [L-DON]
F-2185  H-6-Diazo-5-oxo-D-Nle-OH
        [D-DON]
F-1520  H-3,5-Dibromo-Tyr-OH
F-3395  H-3,4-Dichloro-Phe-OH
F-3400  H-3,4-Dichloro-D-Phe-OH
F-3695  H-β,β, Dicyclocexyl-DL-Ala-OH
F-2395  H-α-Difluoro-Me-DL-Orn-OH
        [DFMO]
F-1525  H-β-(3,4-Dihydroxyphenyl)-DL-Ser-OH
        [DL-Threo-DOPS]
F-3460  H-2,5-Diido-His-OH · HCL
F-2225  H-3,5-Diido-Tyr-OH
F-3005  H-3,5-Diido-D-Tyr-OH
E-2385  H-3,5-Diido-Tyr-OMe · HCL
M-1925  FA-Cys(farnesyl)-OH
M-1920  FA-Cys(farnesyl)-OMe
F-2530  H-β-Fluoro-DL-Ala-OH
F-3285  H-m-Fluoro-Phe-OH
F-3290  H-m-Fluoro-D-Phe-OH
F-2135  H-m-Fluoro-DL-Phe-OH
F-1530  H-p-Fluoro-Phe-OH
F-2320  H-p-Fluoro-D-Phe-OH
F-1535  H-p-Fluoro-DL-Phe-OH
F-3820  H-p-Fluoro-Phe-OEt · HCL
F-3295  H-m-Fluoro-D-Phe-OMe · HCL
F-1540  H-p-Fluoro-DL-Phe-OMe · HCL
B-1780  Fmoc-Abu-OH
B-2920  Fmoc-D-Abu-OH
B-1910  Fmoc-γ-Abu-OH
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<tr>
<td>B-3260</td>
<td>Fmoc-Abz-OH</td>
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<tr>
<td>B-2985</td>
<td>Fmoc-4-Abz-OH</td>
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<td>B-1860</td>
<td>Fmoc-Aib-OH</td>
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<tr>
<td>B-2880</td>
<td>Fmoc-allo-Ile-OH</td>
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<td>B-2230</td>
<td>Fmoc-D-allo-Ile-OH</td>
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<td>B-3100</td>
<td>Fmoc-allo-Thr-OH</td>
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<td>B-3090</td>
<td>Fmoc-D-allo-Thr-OH</td>
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<td>B-1815</td>
<td>Fmoc-allo-Thr(tBu)-OH</td>
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<td>B-1810</td>
<td>Fmoc-allo-Thr(tBu)-Odbhbt</td>
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<td>B-3280</td>
<td>Fmoc-α-allyl-DL-Gly-OH</td>
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<td>[Fmoc-DL-2-amino-4-pentanoic acid]</td>
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<td>B-2440</td>
<td>Fmoc-L-α-amino adipic acid-δ-t-butyl ester</td>
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<td>[Fmoc-L-2-amino hexanedioic acid-δ-t-butyl ester]</td>
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<td>Fmoc-e-aminocoproic acid</td>
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<td>B-3310</td>
<td>2-(Fmoc-amino)-3-(2,2-dimethyl-4H-benzol[1,3]dioxin-6-yl)-propionic acid</td>
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<td>B-2070</td>
<td>Fmoc-p-amino-Phe-OH</td>
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<td>B-1995</td>
<td>Fmoc-p-amino-Phe-(Boc)-OH</td>
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<td>B-2930</td>
<td>Fmoc-p-amino-D-Phe-(Boc)-OH</td>
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<td>B-2360</td>
<td>Fmoc-p-azido-Phe-OH</td>
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<td>B-2830</td>
<td>Fmoc-β-(3-benzothienyl)-Ala-OH</td>
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<td>B-3320</td>
<td>Fmoc-p-tBu-Phe-OH</td>
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<td>Fmoc-p-tBu-D-Phe-OH</td>
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<td>Fmoc-p-Bz-Phe-OH</td>
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<td>[Fmoc-D-Bpa-OH]</td>
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<td>B-3070</td>
<td>Fmoc-p-carboxy-Phe(OtBu)-OH</td>
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<td>B-2115</td>
<td>Fmoc-p-chloro-Phe-OH</td>
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B-1900 Fmoc-p-chloro-D-Phe-OH  
B-3125 Fmoc-p-cyano-Phe-OH  
B-1975 Fmoc-β-cyclohexyl-Ala-OH  
B-2345 Fmoc-β-cyclohexyl-D-Ala-OH  
B-3270 Fmoc-cyclohexyl-Gly-OH  
B-3275 Fmoc-cyclohexyl-D-Gly-OH  
B-2905 Fmoc-β-cyclopropyl-Ala-OH  
B-3120 Fmoc-Cys(Boc-3-aminopropyl)-OH  
B-2300 Fmoc-Dab-OH  
B-2365 Fmoc-D-Dab-OH  
B-2860 Fmoc-Dab-(Adpoc)-OH  
B-2850 Fmoc-Dab-(aloc)-OH  
B-1800 Fmoc-Dab-(Boc)-OH  
B-2960 Fmoc-D-Dab(Boc)-OH  
B-2270 Fmoc-D-Dab(Fmoc)-OH  
B-3250 Fmoc-Dab(Z)-OH  
B-2385 Fmoc-Dap-OH  
B-3055 Fmoc-D-Dap-OH  
B-2865 Fmoc-Dap(Adpoc)-OH  
B-2845 Fmoc-Dap(Aloc)-OH  
B-2380 Fmoc-Dap(Boc)-OH  
B-2965 Fmoc-D-Dap(Boc)-OH  
B-2995 Fmoc-Dap(Dnp)-OH  
B-2265 Fmoc-Dap(Fmoc)-OH  
B-2255 Fmoc-4,5-dehydro-Leu-OH  
B-1660 Fmoc-3,4-dehydro-Pro-OH
B-1275 Fmoc-3,5-dibromo-Tyr-OH
B-1285 Fmoc-3,5-Diiodo-Tyr-OH
B-3265 Fmoc-3,5-dinitro-Tyr-OH
B-2595 Fmoc-m-fluoro-Phe-OH
B-2835 Fmoc-p-fluoro-Phe-OH
B-3210 Fmoc-p-fluoro-D-Phe-OH
B-1550 Fmoc-p-fluoro-DL-Phe-OH
B-3130 Fmoc-Homoarg(Pmc)-OH
B-2250 Fmoc-Homocit-OH
B-2390 Fmoc-D-Homocit-OH
B-2405 Fmoc-Homocys(Trt)-OH
B-1535 Fmoc-Homophe-OH
B-2810 Fmoc-D-Homophe-OH
B-2285 Fmoc-Homoprop-OH
B-2290 Fmoc-D-Homoprop-OH
B-2750 Fmoc-p-iodo-Phe-OH
B-1740 Fmoc-3-iodo-Tyr-OH
B-3190 Fmoc-isonipecotic acid
B-2590 Fmoc-DL-Isoser-OH
B-3335 Fmoc-p-Me-Phe-OH
B-3330 Fmoc-p-Me-D-Phe-OH
B-2130 Fmoc-Met(O)-OH
B-1905 Fmoc-Met(O_2)-OH
B-1965 Fmoc-1-Nal-OH
B-3020 Fmoc-D-1-Nal-OH
B-2100 Fmoc-2-Nal-OH
B-1950  Fmoc-D-2-Nal-OH
B-2690  Fmoc-m-nitro-p-hydroxy-Phe-OH
  [Fmoc-m-nitro-Tyr-OH]
B-1395  Fmoc-p-nitro-Phe-OH
B-2350  Fmoc-p-nitro-D-Phe-OH
B-2690  Fmoc-m-nitro-Tyr-OH
  [Fmoc-m-nitro-p-hydroxy-Phe-OH]
B-2425  Fmoc-Oic-OH
  [Fmoc-L-actahydroindole-2-carboxylic acid]
B-1885  Fmoc-Pen(Acm)-OH
B-1915  Fmoc-D-Pen(Acm)-OH
B-1545  Fmoc-D-Pen(Bzl)-OH
B-2315  Fmoc-Pen-(Trt)-OH
B-2320  Fmoc-D-Pen(Trt)-OH
B-3155  Fmoc-p-phenyl-Phe-OH
  [Fmoc-ß-(4-biphenyl)-Ala-OH; Fmoc-Bip-OH]
B-3160  Fmoc-p-phenyl-D-Phe-OH
  [Fmoc-ß-(4-biphenyl)-D-Ala-OH; Fmoc-D-Bip-OH]
B-3195  1-Fmoc-piperidine-4-Fmoc-amino-4-carboxylic acid
  [Fmoc-Pip(Fmoc)-OH]
B-3175  Fmoc-4-piperidylacetic acid
  [Fmoc-4-carboxymethyl-piperidine]
B-2005  Fmoc-ß-(3-pyridyl)-Ala-OH
B-2040  Fmoc-ß-(3-pyridyl)-D-Ala-OH
B-3165  Fmoc-ß-(2-quinolyl)-Ala-OH
B-3170  Fmoc-ß-(2-quinolyl)-D-Ala-OH
B-1665  Fmoc-ß-(2-thienyl)-Ala-OH
B-2120  Fmoc-ß-(2-thienyl)-D-Ala-OH
B-1920  Fmoc-Tic-OH
B-1925  Fmoc-D-Tic-OH
B-2470  Fmoc-Tyr(PO₃H₂)-OH
B-1990  Fmoc-Tyr(PO₃Me₂)-OH
B-2275  Fmoc-D-Tyr(PO₃Me₂)-OH
E-2870  Glutaryl-Leu-OH · 2DCHA
G-4490  Hippuryl-Cys(2-aminoethyl)-OH
         [Bz-Gly-Cys(2-aminoethyl)-OH; BZ-Gly-4-thia-Lys-OH]
F-3815  H-α-Homoethyl-Gly-OH
F-2780  H-Homoarg-OH
F-2995  H-HomoCit-OH
F-2735  H-D-HomoCit-OH
F-1610  H-Homophe-OH
F-1615  H-D-Homophe-OH
F-1620  H-DL-Homophe-OH
F-1625  H-Homopro-OH
F-1630  H-D-Homopro-OH
F-2915  H-DL-Homopro-OH
F-2465  H-Homopro-OMe · HCl
F-3125  H-D-Homopro-OMe · HCl
F-3330  H-(2S,4S)-γ-Hydroxy-Glu-OH
F-3335  H-(2S,4R)-γ-Hydroxy-Glu-OH
Q-1420  o-Hydroxyhippuric acid
         [Salicyluric acid]
E-2655  p-Hydroxyhippuric acid
F-1650  H-DL-δ-Hydroxy-DL-Lys-OH · HCl
F-2335  H-DL-δ-Hydroxy-DL-Lys(Boc)-OH
F-3685  H-α-Hydroxy-nor-L-arginine
         [L-2-Amino-(4-2'-hydroxyguanidino) butyric acid]
F-2935  H-7-Hydroxy-Tic-OH
F-2990  H-7-Hydroxy-D-Tic-OH
F-1665  H-p-lodo-Phe-OH
F-1670  H-p-lodo-D-Phe-OH
F-1675  H-p-lodo-DL-Phe-OH
F-3350  H-m-lodo-Tyr-OH
F-1695  H-DL-Isoser-OH
       [H-DL-β-Amino-α-hydroxypropionic acid]
F-1195  Lysinoalanine-2 HCl (diastereomeric mixture: LL + LD)
       H-Lys(DL-2-amino-2-carboxyethyl)-OH · 2HCl
F-1765  N-Me-Aib-OH
F-1760  N-Me-allo-ile-Obzl · P-tosylate
F-1795  H-α-Me-DL-His-OH · 2HCl
Q-1585  Melphalan-methyl esler · 2HCl
       [H-p-Dl(2-chloroethyl)amino-Phe-OMe · 2HCl]
F-1800  H-α-Me-DL-Leu-OH
F-1780  N-Me-p-nitro-Phe-OH
E-3150  H-α-Me-Phe-OH
F-3115  H-α-Me-D-Phe-OH
F-1805  H-α-Me-DL-Phe-OH
F-2805  H-α-Me-DL-Phe-OMe · HCl
F-3780  H-p-Me-Phe-OH
F-3785  H-p-Me-D-Phe-OH
F-3440  H-α-Me-Pro-OH
F-3615  H-2-Mercapto-His-OH
F-3620  H-2-Mercapto-His-OMe
M-2345  H-β-(7-Methoxycoumarin-4yl)-Ala-OH
       [L-2-Amino-3-(7-methoxycoumarin-4-yl)-propionic acid]
F-3810  1-Methylaminocyclopropone-1-carboxylic acid
F-1815  H-γ-Methylene-DL-Glu-OH
Q-1645  (2-Methyl-1-indolyl)acetic · DCHA
F-3180  S-Methyl-L-thiocitrulline · acetate
F-2945  H-Met(O)-OH
F-2895  H-Met(O₂)-OH
F-1810  H-α-Me-DL-Trp-OH
F-2240  H-α-Me-DL-Trp-OMe
F-1820  H-1-Me-DL-Trp-OH
F-3535  H-α-Me-Val-OH
F-3540  H-α-Me-D-Val-OH
F-3355  H-α-Me-DL-Val-OH
F-2550  Myristoyl-Gly-OH
F-1840  H-1-Nal-OH
F-1845  H-D-1-Nal-OH
F-1850  H-DL-1-Nal-OH
F-1855  H-2-Nal-OH
F-1860  H-D-2-Nal-OH
F-1865  H-DL-2-Nal-OH
F-3710  H-2-Nal-Obzl · salt
F-1315  H-Neopentylgly-OH
F-1320  H-D-Neopentylgly-OH
F-1325  H-DL-Neopentylgly-OH
F-3340  H-m-Nitro-p-hydroxy-Phe-OH
    [H-m-Nitro-Tyr-OH]
F-1895  H-p-Nitro-Phe-OH
F-1900  H-p-Nitro-D-Phe-OH
F-1905  H-p-Nitro-DL-Phe-OH
F-1910  H-p-Nitro-Phe-OMe · HCl
F-3340  H-m-Nitro-Tyr-OH  
         [H-m-Nitro-p-hydroxy-Phe-OH]
F-3105  H-Oic-OH  
         [L-Octahydroindole-2-carboxylic acid]
F-2515  H-Pan-OH
F-3065  H-Pan(Trt)-OH
F-3645  H-β-Phenyl-Phe-OH  
         [H-β-(4-Biphenyl)-Ala-OH; H-Bip-OH]
F-3650  H-p-Phenyl-D-Phe-OH  
         [H-β-(4-Biphenyl)-D-Ala-OH; H-D-Bip-OH]
F-2040  H-Propargyl-Gly-OH
F-2900  H-D-Propargyl-Gly-OH
F-2860  H-DL-Propargyl-Gly-OH
F-2075  H-Propargyl-Gly-OMe · HCl
F-2825  H-β-(2-Pyridyl)-Ala-OH
F-2790  H-β-(2-Pyridyl)-D-Ala-OH
F-2825  H-β-(2-Pyridyl)-DL-Ala-OH
F-3195  H-β-(3-Pyridyl)-Ala-OH
F-2640  H-β-(3-Pyridyl)-D-Ala-OH
F-3705  H-β-(3-Pyridyl)-DL-Ala-OH
F-3655  H-β-(2-Quinolyl)-Ala-OH
F-3660  H-β-(2-Quinolyl)-D-Ala-OH
F-2030  H-Ser(PO₃H₂)-OH
F-2035  H-D-Ser(PO₃H₂)-OH
F-3365  H-Ser(SO₃H)-OH
F-3370  H-D-Ser(SO₃H)-OH
F-1220  Statine
[(3S,4S)-4-Amino-3-hydroxy-6-methylheptanoic acid]
F-3665  L-4,5,6,7-Tetrahydro-1H-imidazo(4,5-c)pyridine-6-carboxylic acid
Q-1535  L-Thiazolidin-2-one-4-carboxylic acid
[L-2-Oxothiazolidine-4-carboxylic acid]
F-2955  H-β-(2-Thiazolyl)-DL-Ala-OH
F-2110  H-β-(2-Thienyl)-Ala-OH
F-2115  H-β-(2-Thienyl)-D-Ala-OH
N-1150  H-β-(2-Thienyl)-DL-Ala-OH
F-2120  H-β-(2-Thienyl)-DL-Ser-OH
N-1195  DL-Thiorphan
[(DL-3-Mercapto-2-benzylproponoyl)-Gly-OH]
F-2460  L-Thyronine
[H-p-(p-Hydroxyphenoxy)-Phe-OH]
F-2405  DL-Thyronine
[H-p-(p-Hydroxyphenoxy)-DL-Phe-OH]
F-2580  H-Tic-OH
F-2585  H-D-Tic-OH
F-3310  H-D-Tic-OctBu · HCl
Q-1700  H-Tpi-OH
[L-1,2,3,4-Tetrahydronorharman-3-carboxylic acid]
F-3225  H-β-(1,2,4-Triozol-1-yl)-DL-Ala-OH
F-3670  H-β-(Ureido)-Ala-OH
[H-β-((Aminocarbonyl)amino)-Ala-OH; L-Albizzine]
C-1260  Z-Abu-OH
C-3160  Z-γ-Abu-OH
C-1265  Z-Abu-OSu
C-3350  Z-3-Abz-OSu
C-3680  Z-Aib-OH
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<td>Z-allo-Thr(tBu)-OH · DCHA</td>
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<td>Z-L-α-amino adipic acid</td>
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<td>Z-L-2-amino adipic acid-δ-t-butyl ester · DCHA</td>
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<td>Z-Dob(Boc)-OH · DCHA</td>
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<td>C-3500</td>
<td>Z-2-Nal-OH</td>
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C-2255  Z-D-2-Nal-OH
C-2260  Z-Neopentylgly-OH • DCHA
C-2265  Z-D-Neopenlylgly-OH
C-4030  Z-p-phenyl—Phe-OH
       [Z-β-(4-biphenyl)-Ala-OH; Z-Bip-OH]
C-4035  Z-p-phenyl-D-Phe-OH
       [Z-β-(4-biphenyl)-D-Ala-OH; Z-D-Bip-OH]
C-3870  Z-D-Tic-OH