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The invention pertains to methods for treating medical disorders characterized by elevated levels or abnormal expression of IL-1 by administering an IL-1 antagonist, such as soluble type II IL-1 receptor and/or IL-1RacP.

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INTERLEUKIN-1 RECEPTORS IN THE TREATMENT OF DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 of U.S. Provisional Application Serial Number 60/310,789, filed August 7, 2001, the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention pertains to methods for treating certain diseases and disorders associated with inflammatory and immunoregulatory responses. More particularly, the present invention involves treating diseases characterized by IL-1 production by administering an IL-1R, alone or in combination with other cytokines or IL-1 inhibitors, to an individual afflicted with such a disease.

Description of Related Art

The Interleukin-1 (IL-1) pathway is a cellular signaling pathway that plays a crucial role in the mammalian inflammatory response and is associated with a wide range of immunologic, metabolic, physiological and hematopoietic activities. The IL-1 family includes three structurally related cytokines: IL-1 alpha, IL-1 beta and IL-1 receptor antagonist (IL-1ra). Of the three, IL-1 alpha and IL-1 beta are proinflammatory agonists while IL-1 receptor antagonist (IL-1ra) functions to block IL-1 alpha and IL-1 beta activity. All known biological functions of IL-1 are mediated through a complex composed of integral membrane proteins: the type I IL-1Receptor (IL-1R I) and the IL-1 Receptor Accessory Protein (IL-1RacP). IL-1 alpha, IL-1 beta and IL-1ra bind the type I IL-1R with high affinity. In contrast, IL-1 beta binds the type II IL-1R with high affinity and IL-1 alpha and IL-1ra bind the type II IL-1R with a low affinity. The type II IL-1R has a severely truncated cytoplasmic domain and upon binding to IL-1 does not transduce signal to a cell, but instead is involved in regulating an IL-1-mediated response by acting as a decoy receptor.

IL-1 production is triggered by infections, microbial toxins, inflammatory agents and allergic reactions. Overall the main functions of IL-1 is to regulate the amplitude and duration of the immune and inflammatory response at the sites of inflammation or allergic immune reaction. When excess IL-1 is produced or IL-1 expression is not appropriately regulated disease states can develop. Accordingly, IL-1 has been implicated in a variety of inflammatory and immunoregulatory diseases and conditions. It has been proposed

that a systemic or localized excess of IL-1 contributes to the incidence of numerous medical disorders. Further to this proposal, it has been shown that IL-1ra, which blocks IL-1 alpha and IL-1 beta activity, has varying degrees of efficacy in treating some diseases thought to be mediated by IL-1 signaling. For example, a peptidomimetic that binds IL-1R and blocks IL-1 binding is reportedly clinically useful for suppressing IL-1 (Yanofsky, S.D. et al. Proc Natl Acad Scie USA 93(14):7381-6, 1996; Akeson A.L. et al. J Biol Chem. 271(48):30517-23, 1996). Additionally, inhibitors of Interleukin-1 Converting Enzyme (ICE), an essential component in the formation of active IL-1 beta, are thought to be effective therapeutics for treating disease states associated with IL-1 activity. Further, a peptidomimetic that binds IL-1R and blocks IL-1 binding is reportedly clinically useful for suppressing IL-1 (Yanofsky, S.D. et al. Proc Natl Acad Scie USA 93(14):7381-6, 1996; Akeson A.L. et al. J Biol Chem. 271(48):30517-23, 1996).

It has been suggested that the suppression of IL-1 might be beneficial in patients suffering from various disorders characterized by abnormal or excessive IL-1 expression or IL-1 activity. The IL-1ra and ICE inhibitors have met with limited degrees of success as therapeutics for diseases associated with IL-1 activity. Although progress has been made in devising effective treatment for such diseases, improved medicaments and methods of treatment are needed.

SUMMARY OF THE INVENTION

Provided herein are methods for treating medical disorders associated with IL-1 mediated inflammatory reactions or IL-1 mediated immunoregulatory reactions. In part, the methods of the present invention are based upon the discovery that soluble IL-1 Accessory Protein (IL-1AcP) enhances the inhibitory ability of IL-1R and particularly type II IL-1R. The methods of the present invention include administering an IL-1 antagonist, or IL-1 inhibitor, that inhibits IL-1 inflammatory or immunoregulatory signaling, to an individual afflicted with an inflammatory or immunoregulatory disease mediated by IL-1. More particularly, the present invention involves administering an IL-1 antagonist such as type II IL-1 receptor, type I IL-1 receptor and/or IL-1RAcP, to such an individual, for a period of time sufficient to induce a sustained improvement in the patient's condition. The present invention further encompasses administering IL-1 inhibitors, particularly type II IL-1R and/or IL-1AcP in combination with additional therapeutics, including TNF inhibitors, i.e. TNFR:Fc, cytokines and cytokine receptors.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for treating an individual including a human, who is suffering from a medical disorder that is associated with IL-1 mediated inflammatory reactions or IL-1 mediated immunoregulatory reactions. For purposes of this disclosure, the terms "illness," "disease," "medical condition" or "abnormal condition" are used interchangeably with the term "medical disorder."

The subject methods involve administering to the patient an IL-1 antagonist or IL-1 inhibitor that is capable of reducing the effective amount of endogenous biologically active IL-1, such as by reducing the amount of IL-1 alpha, or IL-1 beta produced, or by preventing the binding of IL-1 to its cell surface receptor type I IL-1R and/or the receptor accessory protein IL-1RAcP. Such antagonists include receptor-binding peptide fragments of IL-1, antibodies directed against IL-1 (including IL-1 beta and IL-1alpha), IL-1 receptor type I, IL-1RAcP and recombinant proteins comprising all or portions of receptors for IL-1 or modified variants thereof e.g. soluble forms of IL-1R and soluble forms of IL-1RAcP, including genetically-modified muteins, multimeric forms and sustained-release formulations. Particular antagonists include IL-1ra polypeptides, IL-1 beta converting enzyme (ICE) inhibitors, antagonistic type I IL-1 receptor antibodies, IL-1 binding forms of type I IL-1 receptor and type II IL-1 receptor and IL-1RAcP, antibodies to IL-1, including IL-1 alpha and IL-1 beta, antibodies to IL-1RAcP, and other IL-1 family members, and therapeutics known as IL-1 traps.

IL-1 binding forms of type I IL-1 receptor and type II IL-1 receptor are described in U.S. 4,968,607, US 4,968,607, US 5,081,228, U.S. Re 35,450, U.S. 5,319,071, and 5,350,683. IL-1 traps are described in WO 018932. IL-1RAcP, soluble forms of IL-1RAcP and antibodies to IL-1RAcP are described in WO 96/23067. All of the foregoing identified US patents and PCT publications are incorporated in their entirety herein by reference.

Further, suitable IL-1 antagonists encompass chimeric proteins that include all or portions of both an antibody molecule and an IL-1 antagonist molecule. Such chimeric molecules may form monomers, dimers or higher order multimers. Other suitable IL-1 antagonists include peptides derived from IL-1 that are capable of binding competitively to the IL-1 signaling receptor, IL-1 R type I. Suitable dimeric antagonists include all or soluble portions of the IL-1R type I and all or soluble forms of IL-1RAcP. Similarly, suitable dimeric antagonists include all of soluble portions of the IL-1R type II and all or soluble forms of IL-1RAcP. Soluble forms of the type II and type I IL-1R and IL-1RAcP include those that are capable of binding IL-1, including IL-1 alpha and IL-1 beta. A particularly suitable dimeric antagonist includes all or soluble portions of the type II IL-1R and all or soluble portions of the IL-1RAcP. Such dimeric compounds may take the form of the C-terminal portion of soluble type II IL-1R linked to the C-terminal portion of

soluble IL-1RAcP and can further include a spacer compound separating the two C-terminal links.

Preferred methods of the invention utilize type II IL-1 receptor in a form that binds IL-1, including IL-1 beta and IL-1 alpha, in combination with IL-1RAcP in a form that enhances the binding of type II IL-1R to IL-1 beta and IL-1 alpha. The combination results in an enhanced ability of type II IL-1R to block IL-1 signal transduction, thereby interrupting the proinflammatory and immunoregulatory effects of IL-1, including IL-1 alpha and IL-1 beta. U.S. Patent No. 5,350,683 describes type II IL-1 receptor polypeptides. The receptor polynucleotide sequence and the amino acid sequence that it encodes are provided herein as SEQ ID NO:1 and SEQ ID NO:2, respectively. Preferable forms of the type II IL-1 receptor polypeptide are truncated soluble fragments that retain the capability of binding IL-1 and particularly IL-1 beta. Soluble type II IL-1 receptor molecules include, for example, analogs or fragments of native type II IL-1 receptor having at least 20 amino acids, that lack the transmembrane region of the native molecule, and that are capable of binding IL-1, particularly IL-1 beta. A preferred soluble fragment of type II IL-1 receptor for use in the methods of the present invention includes amino acids 1-333 of SEQ ID NO:2. Publication WO 96/23067 describes IL-1RAcP and IL-1 binding portions of IL-1RAcP.

PCT Publication WO 96/23067, incorporated herein by reference, describes IL-1RAcP polypeptides and a soluble form of IL-1RAcP and polynucleotides that encode these polypeptides. The polynucleotide and the amino acid that it encodes are provided herein as SEQ ID NO:3 and SEQ ID NO:4, respectively. One soluble form of IL-1RAcP polynucleotide and the sequence of amino acids that it encodes are shown in SEQ ID NO:5 and SEQ ID NO:6, respectively. Preferred forms of the IL-1RAcP are truncated soluble fragments that enhance the capability of type II IL-1R to bind IL-1 beta and IL-1 alpha. One such truncated form includes SEQ ID NO:6 or amino acids 21 through 359 of SEQ ID NO:6, which is a soluble form absent the signal peptide..

The preferred soluble type II IL-1 receptor is also the preferred IL-1 inhibitor for use in the methods of the present invention, used in combination with IL-1RAcP as in the foregoing description. It is recognized, however, that other inhibitors, including soluble forms of type I IL-1 receptor, IL-1ra, the foregoing mentioned antibodies, and derivative of IL-1 family members that bind cell bound receptors and inhibit signal transduction are useful in the practice of the present invention and in combination with IL-1RAcP in forms described above. Further it is recognized that soluble forms of IL-1RAcP are useful as a sole therapeutic in the practice of this invention.

Antagonists derived from type II IL-1 receptors (e.g. soluble forms that bind IL-1) compete for IL-1 with IL-1 receptors on the cell surface, thus inhibiting IL-1 from binding to cells, thereby preventing it from manifesting its biological activities. Binding

of soluble type II IL-1 receptor or fragments to IL-1including IL-1 beta and IL-1 alpha can be assayed using ELISA or any other convenient assay. Antagonists derived from IL-1RAcP enhance the capability of type II IL-1R and other antagonist to bind IL-1 beta and IL-1 alpha. Such enhanced activity is described in the examples that follow and can be assayed using methods described below or any other convenient assay.

This invention additionally provides for the use of soluble forms of type II IL-1 receptor and/or soluble forms of type I IL-1R, or other IL-1 antagonists in combination with IL-1RAcP, or soluble IL-1RAcP, in the manufacture of a medicament for the treatment of numerous diseases. This invention additionally provides for the use of DNA encoding type II IL-1 receptor, DNA encoding soluble type II IL-1R, DNA encoding IL-1RAcP or soluble IL-1RAcP and/or DNA encoding other IL-1 antagonists described above, in the manufacture of polypeptides for use in the manufacture of a medicament for the treatment of diseases disclosed herein.

Soluble type II IL-1 receptor polypeptides or fragments, soluble IL-1RAcP polypeptides or fragments and other IL-1 antagonists including soluble type I IL-1R that are suitable in the practice of this invention may be fused with a second polypeptide to form a chimeric protein. In one embodiment of such a chimeric protein, the second polypeptide may promote the spontaneous formation by the chimeric protein of a dimer, trimer or higher order multimer that is capable of binding IL-1 molecule and preventing it from binding to a cell-bound receptor that promotes IL-1 signaling. Chimeric proteins used as antagonists may be proteins that contain portions of both an antibody molecule and a soluble type II IL-1 receptor and a soluble IL-1RAcP polypeptide. A suitable IL-1 antagonist for treating diseases in humans and other mammals is type II IL-1 receptor having amino acids 1-333 of SEQ ID NO:2 and soluble IL-1RAcP fused to an Fc, antibody heavy and/or light chain polypeptides.

One embodiment of the invention encompasses sustained-release forms of IL-1 antagonists described herein. For example soluble IL-1 receptors, and in particular, soluble type II IL-1 receptor combined with IL-1RAcP can be formulated to release in a controlled manner and provide optimized polypeptide availability over time. Sustained-release forms suitable for use in the disclosed methods include, but are not limited to, IL-1 receptors and IL-1RAcP that are encapsulated in a slowly-dissolving biocompatible polymer, admixed with such a polymer, and or encased in a biocompatible semi-permeable implant. In addition, the soluble IL-1 receptors and soluble IL-1RAcP may be conjugated with polyethylene glycol (pegylated) to prolong its serum half-life or to enhance protein delivery. Soluble forms of IL-1 receptors and IL-1RAcP, including monomers, fusion proteins (also called "chimeric proteins), dimers, trimers or higher order multimers, are particularly useful in formulating IL-1 antagonists.

To treat a medical disorder characterized by abnormal or excess expression of IL-1 or abnormal or excess IL-1 signaling, a composition that including an IL-binding soluble IL-1 receptor, preferably a soluble type II IL-1 receptor, other IL-1 antagonists described herein and a soluble IL-1RAcP, is administered to the patient in an amount and for a time sufficient to induce a sustained improvement in at least one indicator that reflects the severity of the disorder. An improvement is considered "sustained" if the patient exhibits the improvement on at least two occasions separated by one to four weeks. The degree of improvement is determined based on signs or symptoms, and may also employ questionnaires that are administered to the patient, such as quality-of-life questionnaires.

Various indicators that reflect the extent of the patient's illness may be assessed for determining whether the amount and time of the treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient prior to administration of the first dose of the composition of soluble type II IL-1 receptor or other IL-1 inhibitor and IL-1RAcP. Preferably, the baseline examination is done within about 60 days of administering the first dose. If the IL-1 antagonist is being administered to treat acute symptoms, such as, for example, to treat traumatic injuries (traumatic knee injury, stroke, head injury, etc.) the first dose is administered as soon as practically possible after the injury or event has occurred.

Improvement is induced by repeatedly administering a dose of soluble type II IL-1 receptor and/or soluble IL-1RAcP or other IL-1 antagonist in combination with IL-1RAcP until the patient manifests an improvement over baseline for the chosen indicator or indicators. In treating chronic conditions, this degree of improvement is obtained by repeatedly administering this medicament over a period of at least a month or more, e.g., for one, two, or three months or longer, or indefinitely. A period of one to six weeks, or even a single dose, often is sufficient for treating acute conditions.

Although the extent of the patient's illness after treatment may appear improved according to one or more indicators, treatment may be continued indefinitely at the same level or at a reduced dose or frequency. Once treatment has been reduced or discontinued, it later may be resumed at the original level if symptoms should reappear.

Any efficacious route of administration may be used to therapeutically administer the compositions described herein. If injected, a combination of soluble type II IL-1 receptor, IL-1 antagonist and IL-1RAcP can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal, intracranial, inhalation or subcutaneous routes by bolus injection or by continuous infusion. For example, pulmonary diseases can involve intranasal and inhalation methods. Other suitable means of administration include sustained release from implants, aerosol inhalation, eyedrops, oral preparations, including pills, syrups, lozenges or chewing gum, and topical

preparations such as lotions, gels, sprays, ointments or other suitable techniques. Administration by inhalation is particularly beneficial when treating diseases associated with pulmonary disorders. Alternatively, IL-1 inhibitor polypeptides, such as a soluble IL-1 receptors, including type II and type I IL-1R, and IL-1RAcP may be administered by implanting cultured cells that express the protein; for example, by implanting cells that express a soluble type II IL-1 receptor and/or IL-1RAcP, separately or on the same cell. In one embodiment, the patient's own cells are induced to produce by transfection *in vivo* or *ex vivo* with a DNA that encodes an IL-1 inhibitor or IL-1 antagonist, and particularly soluble type II IL-1 receptor and IL-1RAcP. This DNA can be introduced into the patient's cells, for example, by injecting naked DNA or liposome-encapsulated DNA that encodes soluble type II IL-1 receptor or selected IL-1 antagonist, or by other means of transfection. When soluble type II IL-1 receptor is administered in combination with one or more other biologically active compounds, e.g. IL-1RAcP. these may be administered by the same or by different routes, and may be administered simultaneously, separately or sequentially.

IL-1 inhibitors used in the methods of this invention, e.g. soluble type II IL-1 receptor or other soluble IL-1 receptors that are antagonists of IL-1 in combination with IL-1RAcP, preferably are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers are nontoxic to recipients at the dosages and concentrations employed. Ordinarily, preparing such compositions entails combining the IL-1 antagonist with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. The IL-1 antagonist compositions described herein are preferably formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in standard dosing trials, and may vary according to the chosen route of administration. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the age and condition of the patient, and so forth.

In one embodiment of the invention, soluble type II IL-1 receptor in combination with soluble IL-1RAcP is administered one time per week to treat the various medical disorders disclosed herein, in another embodiment is administered at least two times per week, and in another embodiment is administered at least once per day. An adult patient

is a person who is 18 years of age or older. If injected, the effective amount, per adult dose, ranges from 1-200 mg/m^2, or from 1-40 mg/m^2 or about 5-25 mg/m^2 of each antagonist Alternatively, a flat dose may be administered, whose amount may range from 2-400 mg/dose, 2-100 mg/dose or from about 10-80 mg/dose of each antagonist. If the dose is to be administered more than one time per week, an exemplary dose range is the same as the foregoing described dose ranges or lower. Preferably, a therapeutic composition is administered two or more times per week at a per dose range of 25-100 mg/dose of each antagonist. In one embodiment of the invention, the various indications described below are treated by administering a preparation acceptable for injection containing type II IL-1 receptor and/or IL-1RAcP at 80-100 mg/dose each, or alternatively, containing 80 mg per dose. The dose is administered repeatedly. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices. For example, if the route of administration is inhalation, dosing may be one to seven times per week at dose ranges from 10 mg/dose to 50 mg per dose.

In many instances, an improvement in a patient's condition will be obtained by injecting a dose of up to about 100 mg of type II IL-1 receptor and IL-1RAcP one to three times per week over a period of at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of improvement. For incurable chronic conditions, the regimen may be continued indefinitely.

For pediatric patients (age 4-17), a suitable regimen involves the subcutaneous injection of 0.4 mg/kg to 5 mg/kg of type II IL-1 receptor and IL-1RAcP administered by subcutaneous injection one or more times per week.

The administration of type II IL-1 receptor concurrently with IL-1RAcP and other drugs to the same patient includes each drug being administered according to a regimen suitable for that medicament. This encompasses pre-treatment, simultaneous treatment, sequential treatment and alternating regimens. Examples of such drugs include but are not limited to antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines, DMARDs and non-steroidal anti-inflammatories. Additionally, the administration of type II IL-1 receptor and IL-1RAcP may be combined with a second IL-1 antagonist, including an antibody against IL-1 or an IL-1 receptor, additional IL-1 receptor derivatives, or other molecules that reduce endogenous IL-1 levels, such as inhibitors of the IL-1 beta converting enzyme and peptidomimetic IL-1 antagonists. In further embodiments, compositions are administered in combination with pentoxifylline or thalidomide.

In an embodiment of the invention, the various medical disorders disclosed herein as being treatable with IL-1 inhibitors including soluble type II IL-1 receptor in combination with IL-1RAcP are treated in combination with another cytokine or cytokine

inhibitor. For example, type II IL-1 receptor and IL-1RAcP may be administered in a composition that also contains a compound that inhibits the interaction of other inflammatory cytokines with their receptors. The type II IL-1 receptor and IL-1RAcP and other cytokine inhibitors may be administered as separate compositions, and these may be administered by the same or different routes. Examples of cytokine inhibitors used in combination with type II IL-1 receptor and IL-1RAcP include those that antagonize, for example, TGFβ, IFNγ, IL-6 or IL-8, IL-17 and TNF, particularly TNFα. The combination of IL-1 inhibitors, e.g. type II IL-1R and IL-1RAcP and IL-6 can be used to treat and prevent the recurrence of seizures, including seizures induced by $GABA_A$ receptor antagonism, seizures associated with EEG ictal episodes and motor limbic seizures occurring during status epilepticus. Further, the combination of type II IL-1 receptor and IL-1RAcP and IFNγ-1b is useful in treating idiopathic pulmonary fibrosis and cystic fibrosis.

As demonstrated in the examples that follow, IL-17 inhibitors, e.g. IL-17R and soluble forms of IL-17R are useful in treating inflammatory diseases are may be used in combination therapies described herein, particularly for the treatment of rheumatoid arthritis, psoriatic arthritis, stroke, neurological diseases, including MS, Alzheimer's. IL-17R is described in US 5,869,286, incorporated herein by reference.

Other combinations for treating the hereindescribed diseases include the use of type II IL-1 receptor and IL-1RAcP with compounds that interfere with the binding of RANK and RANK-ligand, such as RANK-ligand inhibitors, or soluble forms of RANK, including RANK:Fc. For example, the combination of type II IL-1 receptor, IL-1RAcP and RANK:Fc is useful for preventing bone destruction in various settings including but not limited to various rheumatic disorders, osteoporosis, multiple myeloma or other malignancies that cause bone degeneration, or anti-tumor therapy aimed at preventing metastasis to bone, or bone destruction associated with prosthesis wear debris or with periodontitis. IL-1 inhibitors such as type II IL-1 receptor and IL-1RAcP also may be administered in combination with G-CSF, GM-CSF, IL-2 and inhibitors of protein kinase A type 1 to enhance T cell proliferation in HIV-infected patients who are receiving anti-retroviral therapy. In addition, type II IL-1 receptor and IL-1RAcP may be administered in combination with soluble forms of an IL-17 receptor (such as IL-17R:Fc), IL-18 binding protein, soluble forms of IL-18 receptors, and IL-18 antibodies, antibodies against IL-18 receptors or antibodies against CD30-ligand or against CD4.

Importantly, the present invention further encompasses methods for treating the herein disclosed medical disorders with a combination of one or more IL-1 inhibitors, preferably soluble type II IL-1 receptor (amino acids 1-333 of SEQ ID NO:2) and IL-1RAcP (SEQ ID NO:6, a TNF inhibitor, preferably TNFR:Fc (ENBREL marketed for clinical uses by Immunex Corp) and any combination of the above described cytokines or

cytokine inhibitors that are active agents in combination therapies. For example, in accordance with the present invention, combination therapy methods for treating rheumatoid arthritis, stroke, and congestive heart failure, include administering type II IL-1 receptor, IL-1RAcP and ENBREL. Thus, the present invention also relates to the using IL-1 inhibitors and TNF inhibitors in combination therapies for use in medicine and in particular in therapeutic and preventive therapies for the medical disorders described herein. The use in medicine may involve the treatment of any of the medical disorders as described herein with a combination therapy that includes administering a combination of type II IL-1R and ENBREL. The IL-1 inhibitors (e.g. type II IL-1 receptor) and TNF inhibitor (ENBREL) may be in the form of compounds, compositions or combination therapies. Where the compounds are used together with one or more other components, the compound and the one or more other components may be administered simultaneously, separately or sequentially (usually in pharmaceutical format).

In addition, the subject invention provides methods for treating a human patient in need thereof, the method involving administering to the patient a therapeutically effective amount of one or more IL-1 inhibitors, including the aforementioned IL-1 inhibitors, an IL-4 inhibitor, and optionally, a TNFα inhibitor, e.g. ENBREL, and any of the aforementioned combination therapies.

IL-4 antagonists that may be employed in accordance with the present invention include, but are not limited to, IL-4 receptors (IL-4R) and other IL-4-binding molecules, IL-4 muteins and antibodies that bind specifically with IL-4 or IL-4 receptors thereby blocking signal transduction, as well as antisense oligonucleotides and ribozymes targeted to IL-4 or IL-4R. Antibodies specific for IL-4 or IL-4 receptor may be prepared using standard procedures. Among the IL-4 receptors suitable for use as described herein are soluble fragments of human IL-4R that retain the ability to bind IL-4. Such fragments are capable of binding IL-4, and retain all or part of the IL-4R extracellular region.

IL-4 antagonists useful for the hereindescribed combination methods of treatment include molecules that selectively block the synthesis of endogenous IL-4 or IL-4R. IL-4 receptors are described in U.S. Patent 5,599,905; Idzerda et al., *J. Exp. Med.* 171:861-873, March 1990 (human IL-4R); and Mosley et al., *Cell* 59:335-348, 1989 (murine IL-4R), each of which is hereby incorporated by reference in its entirety. The protein described in those three references is sometimes referred to in the scientific literature as IL-4R□. Unless otherwise specified, the terms "IL-4R" and "IL-4 receptor" as used herein encompass this protein in various forms that are capable of functioning as IL-4 antagonists, including but not limited to soluble fragments, fusion proteins, oligomers, and variants that are capable of binding IL-4, as described in more detail below. Suitable IL-4Rs include variants in which valine replaces isoleucine at position 50 (see Idzerda et al., 1990), and include slow-release formulations, and PEGylated derivatives (modified

with polyethylene glycol) are contemplated, as well as recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an IL-4R polypeptide, including signal peptides, immunoglobulin Fc regions, poly-His tags or the FLAG® polypeptide described in Hopp et al., *Bio/Technology* 6:1204, 1988, and U.S. Patent 5,011,912, as well as fusions of IL-4 receptors with oligomer-promoting leucine zipper moieties. Soluble recombinant fusion proteins comprising an IL-4R and immunoglobulin constant regions are described, for example, in EP 464,533.

Various IL-4 antagonists that may be used for the hereindescribed methods of treatment can be identified, for example, by their ability to inhibit ^{3}H-thymidine incorporation in cells that normally proliferate in response to IL-4, or by their ability to inhibit binding of IL-4 to cells that express IL-4R. In one assay for detecting IL-4 antagonists, one measures the ability of a putative antagonist to block the IL-4-induced enhancement of the expression of CD23 on the surfaces of human B cells. For example, B cells isolated from human peripheral blood are incubated in microtiter wells in the presence of IL-4 and the putative antagonist. Following the incubation, washed cells are then incubated with labeled monoclonal antibody against CD23 (available from Pharmingen) to determine the level of CD23 expression. An anti-huIL-4R murine mAb (R&D Systems), previously shown to block the binding and function of both hIL-4 and hIL-13, may used as a positive control for neutralization of CD23 induction by IL-4. Alternatively, suitable IL-4 antagonists may be identified by determining their ability to prevent or reduce the impaired the barrier function of epithelium that results when IL-4 is incubated with the epithelium. For this purpose, one may use confluent monolayers of human epithelial cell lines such as Calu-3 (lung) or T84 (intestinal epithelium). Incubation of such monolayers with IL-4 causes significant damage to their barrier function within about 48 hours. To assay IL-4 antagonists, monolayers may be tested for their permeability, for example, by adding radiolabeled mannitol to cells incubated with IL-4 in the presence or absence of an antagonist. Alternatively, transepithelial resistance (indicating an intact barrier) may be determined using a voltmeter.

Combinations of one of more IL-1 inhibitors (e.g. soluble type II IL-1R and soluble IL-1RAcP and IL-4 inhibitors, and optionally TNFα inhibitors, e.g. ENBREL, preferably are administered one or more times per week. The mode of administration of IL-4 inhibitors and IL-1 inhibitors can depend upon the medical condition treated and include modes described above including subcutaneous injection and by inhalation nasally. Suitable dose ranges for IL-4 antagonists include doses of from about 1 ng/kg/day to about 10 mg/kg/day, more preferably from about 500 ng/kg/day to about 5 mg/kg/day, and most preferably from about 5 μg/kg/day to about 2 mg/kg/day, administered to adults one time per week, two times per week, or three or more times per week. If injected, suitable doses may range from 1-20 mg/m^2, and preferably is about 5-

12 mg/m^2. Alternatively, a flat dose of about 5-100 mg/dose may be used, preferably about 20-30 mg per dose. For pediatric patients (age 4-17), one suitable regimen involves subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of IL-4R, administered two or three times per week. Another embodiment is directed to aerosol pulmonary administration, for example by nebulizer, which optimally will deliver a dose of 3 or more mg of a soluble IL-4R, and is taken at least once a week. Aeresolized IL-4R may be administered orally or nasally. One illustrative embodiment involves subcutaneous injection of a soluble human IL-4R once a week, at a dose of 1.5 to 3 mg. Doses will be adjusted as needed by the patient's physician in accord with standard medical practices.

Conditions effectively treated by a combination of IL-1 inhibitors and an IL-4 inhibitor include conditions in which IL-1 and IL-4 play a role in the inflammatory response. Lung disorders in which IL-4 plays a role include asthma, chronic obstructive pulmonary disease, pulmonary alveolar proteinosis, bleomycin-induced pneumopathy and fibrosis, radiation-induced pulmonary fibrosis, cystic fibrosis, collagen accumulation in the lungs, and ARDS, all of which may be treated with combinations of IL-1 inhibitors and an IL-4 inhibitor. Combinations of IL-1 inhibitors and IL-4 inhibitors also are useful for treating patients suffering from various skin disorders, including but not limited to dermatitis herpetiformis (Duhring's disease), atopic dermatitis, contact dermatitis, urticaria (including chronic idiopathic urticaria), and autoimmune blistering diseases, including pemphigus vulgaris and bullous pemphigoid. Other diseases treatable with the combination of IL-1 inhibitors and IL-4 inhibitors include myesthenia gravis, sarcoidosis, including pulmonary sarcoidosis, scleroderma, reactive arthritis, hyper IgE syndrome, multiple sclerosis and idiopathic hypereosinophil syndrome. The combination is used also for treating allergic reactions to medication and as an adjuvant to allergy immunotherapy. In connection with combination therapies, the combination of IL-1 inhibitors and IL-4 inhibitors, e.g. soluble type II IL-1R, soluble IL-1RAcP and soluble IL-4R, the aforementioned combination methods can further include the administration of TNFα inhibitors.

The present invention also relates to the use of IL-1 inhibitors (as disclosed), such as soluble type II IL-1 receptor and soluble IL-1RAcP, in the manufacture of a medicament for the prevention or therapeutic treatment of each medical disorder disclosed herein.

The disclosed IL-1 inhibitors, compositions and combination therapies described herein are useful in medicines for treating and/or preventing bacterial, viral or protozoal infections, and complications resulting therefrom. One such disease is *Mycoplasma pneumonia*. In addition, provided herein is the use of soluble type II IL-1 receptor and soluble IL-1RAcP compositions or combinations, particularly in combination with

ENBREL to treat AIDS and conditions associated with AIDS and/or related to AIDS, such as AIDS dementia complex, AIDS associated wasting, lipidistrophy due to antiretroviral therapy; CMV (cytomegalovirus) and Kaposi's sarcoma. Furthermore provided herein is the use of soluble type II IL-1 receptor and soluble IL-1RAcP compositions or combinations for treating protozoal diseases, including malaria and schistosomiasis. Additionally provided is the use of IL-1 inhibitors such as soluble type II IL-1 receptor and soluble IL-1RAcP to treat erythema nodosum leprosum; bacterial or viral meningitis; tuberculosis, including pulmonary tuberculosis; and pneumonitis secondary to a bacterial or viral infection. Provided also herein is the use of soluble type II IL-1 receptor compositions or combinations to prepare medicaments for treating louse-borne relapsing fevers, such as that caused by *Borrelia recurrentis*. Soluble type II IL-1 receptor and soluble IL-1RAcP can also be used to prepare a medicament for treating conditions caused by *Herpes* viruses, such as herpetic stromal keratitis, corneal lesions; and virus-induced corneal disorders. In addition, soluble type II IL-1 receptor compositions and soluble IL-1RAcP combinations can be used in treating human papillomavirus infections. Soluble type II IL-1 receptor and soluble IL-1RAcP combinations can be used also to prepare medicaments and to treat influenza infection and infectious mononucleosis.

Cardiovascular disorders and injuries are treatable and/or preventable with the disclosed IL-1 inhibitors, pharmaceutical compositions or combination therapies. In particularly cardiovascular disorders are treatable with soluble type II IL-1 receptor and soluble IL-1RAcP compositions, alone or in combination with TNF inhibitors (e.g. ENBREL) and or other agents as described above. Cardiovasuclar disorders thus treatable include aortic aneurysms; including abdominal aortic aneurysms, acute coronary syndrome, arteritis; vascular occlusion, including cerebral artery occlusion; complications of coronary by-pass surgery; ischemia/reperfusion injury; heart disease, including atherosclerotic heart disease, myocarditis, including chronic autoimmune myocarditis and viral myocarditis; heart failure, including chronic heart failure, congestive heart failure, cachexia of heart failure; myocardial infarction; restenosis and/or atherosclerosis after heart surgery or after carotid artery balloon angioplastic procedures; silent myocardial ischemia; left ventricular pump dysfunction, post implantation complications of left ventricular assist devices; Raynaud's phenomena; thrombophlebitis; vasculitis, including Kawasaki's vasculitis; veno-occlusive disease, giant cell arteritis, Wegener's granulomatosis; mental confusion following cardio pulmonary by pass surgery, and Schoenlein-Henoch purpura. Combinations of IL-1 inhibitors, TNF inhibitors and angiogenesis inhibitors (e.g. anti-VEGF) are useful for treating certain cardiovascular diseases such as aortic aneurysms and tumors.

In addition, the subject IL-1 inhibitors, including soluble type II IL-1R and soluble IL-1RAcP compositions, and combination therapies are used to treat chronic pain conditions, such as chronic pelvic pain, including chronic prostatitis/pelvic pain syndrome. As a further example, soluble type II IL-1 receptor and soluble IL-1RAcP and the compositions and combination therapies of the invention are used to treat post-herpetic pain.

Provided also are methods for using IL-1 inhibitors, compositions or combination therapies to treat various disorders of the endocrine system. For example, type II IL-1 receptor and soluble IL-1RAcP compositions or other IL-1 inhibitor compositions, with or without TNF inhibitors (ENBREL) or other active agents described above, are suitable for use to treat juvenile onset diabetes (includes autoimmune diabetes mellitus and insulin-dependent types of diabetes) and also to treat maturity onset diabetes (includes non-insulin dependent and obesity-mediated diabetes). In addition, the subject compounds, compositions and combination therapies are used to treat secondary conditions associated with diabetes, such as diabetic retinopathy, kidney transplant rejection in diabetic patients, obesity-mediated insulin resistance, and renal failure, which itself may be associated with proteinurea and hypertension. Other endocrine disorders also are treatable with these compounds, compositions or combination therapies, including polycystic ovarian disease, X-linked adrenoleukodystrophy, hypothyroidism and thyroiditis, including Hashimoto's thyroiditis (i.e., autoimmune thyroiditis). Further, IL-1 inhibitors, including type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with other cytokines, including TNF inhibitors such as ENBREL, are useful in treating or preventing medical conditions associated with thyroid cell dysfunction, including euthyroid sick syndrome.

Conditions of the gastrointestinal system are treatable or preventable with IL-1 inhibitors, compositions or combination therapies, including coeliac disease. For example, type II IL-1 receptor and soluble IL-1RAcP compositions, with or without TNF inhibitors (ENBREL) or other active agents described above are suitable for treating or preventing coeliac disease. In addition, the compounds, compositions and combination therapies of the invention are suitable for treating or preventing Crohn's disease; ulcerative colitis; idiopathic gastroparesis; pancreatitis, including chronic pancreatitis; acute pancreatitis, inflammatory bowel disease and ulcers, including gastric and duodenal ulcers.

Included also are methods for using the subject IL-1 inhibitors, compositions or combination therapies for treating disorders of the genitourinary system. For example, type II IL-1 receptor and soluble IL-1RAcP compositions, alone or in combination with TNF inhibitors (ENBREL) or other active agents described above are suitable for treating or preventing glomerulonephritis, including autoimmune glomerulonephritis,

glomerulonephritis due to exposure to toxins or glomerulonephritis secondary to infections with haemolytic streptococci or other infectious agents. Also treatable with the compounds, compositions and combination therapies of the invention are uremic syndrome and its clinical complications (for example, renal failure, anemia, and hypertrophic cardiomyopathy), including uremic syndrome associated with exposure to environmental toxins, drugs or other causes. IL-1 inhibitors, particularly type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with TNF inhibitors, particularly ENBREL, are useful in treating and preventing complications that arise from inflammation of the gallbladder wall that leads to alteration in absorptive function. Included in such complications are cholelithiasis (gallstones) and choliedocholithiasis (bile duct stones) and the recurrence of cholelithiasis and choliedocholithiasis. Further conditions treatable with the compounds, compositions and combination therapies of the invention are complications of hemodialysis; prostate conditions, including benign prostatic hypertrophy, nonbacterial prostatitis and chronic prostatitis; and complications of hemodialysis.

Also provided herein are methods for using IL-1 inhibitors, compositions or combination therapies to treat various hematologic and oncologic disorders. For example, soluble type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with a TNF inhibitor (ENBREL) or other active agents as described above, may be used to treat various forms of cancer, including acute myelogenous leukemia, chronic myelogenous leukemia leukemia, Epstein-Barr virus-positive nasopharyngeal carcinoma, glioma, colon, stomach, prostate, renal cell, cervical and ovarian cancers, lung cancer (SCLC and NSCLC), including cancer-associated cachexia, fatigue, asthenia, paraneoplastic syndrome of cachexia and hypercalcemia. Additional diseases treatable with the subject IL-1 inhibitors, compositions or combination therapies are solid tumors, including sarcoma, osteosarcoma, and carcinoma, such as adenocarcinoma (for example, breast cancer) and squamous cell carcinoma. In addition, the subject compounds, compositions or combination therapies are useful for treating esophogeal cancer, gastric cancer, gall bladder carcinoma, leukemia, including acute myelogenous leukemia, chronic myelogenous leukemia, myeloid leukemia, chronic or acute lymphoblastic leukemia and hairy cell leukemia. Other malignancies with invasive metastatic potential, including multiple myeloma, can be treated with the subject compounds, compositions and combination therapies, and particularly combination therapies that include soluble type II IL-1 receptor and soluble TNF receptor (ENBREL). In addition, the disclosed IL-1 inhibitors, compositions and combination therapies can be used to treat anemias and hematologic disorders, including chronic idiopathic neutropenia, anemia of chronic disease, aplastic anemia, including Fanconi's aplastic anemia; idiopathic thrombocytopenic purpura (ITP); thrombotic thrombocytopenic purpura, myelodysplastic

syndromes (including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation); myelofibrosis/myeloid metaplasia; and sickle cell vasocclusive crisis.

Various lymphoproliferative disorders also are treatable with the disclosed IL-1 inhibitors, compositions or combination therapies. Type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with a TNF inhibitor, such as ENBREL, or other active agents are useful for treating or preventing autoimmune lymphoproliferative syndrome (ALPS), chronic lymphoblastic leukemia, hairy cell leukemia, chronic lymphatic leukemia, peripheral T-cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt's lymphoma, Epstein-Barr virus-positive T cell lymphoma, histiocytic lymphoma, Hodgkin's disease, diffuse aggressive lymphoma, acute lymphatic leukemias, T gamma lymphoproliferative disease, cutaneous B cell lymphoma, cutaneous T cell lymphoma (i.e., mycosis fungoides) and Sézary syndrome.

In addition, the subject IL-1 inhibitors, compositions and combination therapies are used to treat hereditary conditions. In particular, type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with a TNF inhibitor such as ENBREL, is useful to treat diseases such as Gaucher's disease, Huntington's disease, linear IgA disease, and muscular dystrophy.

Other conditions treatable or preventable by the disclosed IL-1 inhibitors, compositions and combination therapies include those resulting from injuries to the head or spinal cord including subdural hematoma due to trauma to the head. For example, soluble type II IL-1 receptor and soluble IL-1RAcP alone or in combination with a TNF inhibitor such as ENBREL are useful in treating head injuries and spinal chord injuries. In connection with this therapy, the compositions and combinations described are suitable for preventing cranial neurologic damage and preventing and treating cervicogenic headache. The compositions and combinations described are further suitable for treating neurological side effects associated with brain irradiation.

The disclosed IL-1 inhibitors, compositions and combination therapies are further used to treat conditions of the liver. For example soluble type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with a TNF inhibitor such as ENBREL or other active agents, can be used to treat hepatitis, including acute alcoholic hepatitis, acute drug-induced or viral hepatitis, hepatitis A, B and C, sclerosing cholangitis and inflammation of the liver due to unknown causes. In connection with liver inflammation, IL-1 inhibitors are further useful in treating hepatic sinusoid epithelium

In addition, the disclosed IL-1 inhibitors, compositions and combination therapies are used to treat various disorders that involve hearing loss and that are associated with abnormal IL-1 expression. For example, soluble type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with TNF inhibitors, can be used to treat or prevent

cochlear nerve-associated hearing loss that is thought to result from an autoimmune process, i.e., autoimmune hearing loss. This condition currently is treated with steroids, methotrexate and/or cyclophosphamide. Also treatable or preventable with the disclosed IL-1 inhibitors, compositions and combination therapies is Meniere's syndrome and cholesteatoma, a middle ear disorder often associated with hearing loss.

In addition, the subject invention provides IL-1 inhibitors, e.g. soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies (e.g. soluble type II IL-1 receptor, soluble IL-1RAcP and a TNF inhibitor such as ENBREL or other active agents) for the treatment of non-arthritic medical conditions of the bones and joints. This encompasses osteoclast disorders that lead to bone loss; such as but not limited to osteoporosis, including post-menopausal osteoporosis, osteoarthritis, periodontitis resulting in tooth loosening or loss, and prosthesis loosening after joint replacement (generally associated with an inflammatory response to wear debris). This latter condition also is called "orthopedic implant osteolysis." Another condition treatable with the compounds, compositions and combination therapies of the invention is temporal mandibular joint dysfunction (TMJ).

The following pulmonary disorders also can be treated or prevented with the disclosed IL-1 inhibitors, in particular soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies (e.g. in combination with a TNF inhibitor such as ENBREL or other active agents): adult respiratory distress syndrome (ARDS), acute respiratory distress syndrome and acute lung injury caused by a variety of conditions, including exposure to toxic chemicals, pancreatitis, trauma or other causes of inflammation. The disclosed compounds, compositions and combination therapies of the invention also are useful for treating broncho-pulmonary dysplasia (BPD); chronic obstructive pulmonary diseases (e.g. emphysema and chronic bronchitis), and chronic fibrotic lung disease of preterm infants. In addition, the compounds, compositions and combination therapies of the invention are used to treat occupational lung diseases, including asbestosis, coal worker's pneumoconiosis, silicosis or similar conditions associated with long-term exposure to fine particles. In other aspects of the invention, the disclosed compounds, compositions and combination therapies are used to treat bronchioliterans organizing pneumonia, pulmonary fibrosis, including idiopathic pulmonary fibrosis and radiation-induced pulmonary fibrosis; pulmonary sarcoidosis; and allergies, including allergic rhinitis, contact dermatitis, atopic dermatitis and asthma.

Other embodiments of the present invention include methods for using the disclosed IL-1 inhibitors, in particular soluble type II IL-1 receptor and soluble IL-1RAcP compositions or combination therapies, e.g. soluble type II IL-1 receptor, soluble IL-1RAcP and ENBREL, to treat or prevent a variety of rheumatic disorders. These include adult and juvenile rheumatoid arthritis; scleroderma; systemic lupus erythematosus; gout;

osteoarthritis; polymyalgia rheumatica; seronegative spondylarthropathies, including ankylosing spondylitis, and Reiter's disease. The subject IL-1 inhibitors, compositions and combination therapies are used also to treat psoriatic arthritis and chronic Lyme arthritis. Also treatable or preventable with these compounds, compositions and combination therapies are Still's disease and uveitis associated with rheumatoid arthritis. In addition, the compounds, compositions and combination therapies of the invention are used in treating disorders resulting in inflammation of the voluntary muscle and other muscles, including dermatomyositis, inclusion body myositis, polymyositis, and lymphangioleimyomatosis.

The IL-1 inhibitors, e.g. soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies (e.g. in combination with ENBREL or other TNF inhibitor or active agent) of the invention are useful for treating or preventing primary amyloidosis. In addition, the secondary amyloidosis that is characteristic of various conditions also are treatable with IL-1 inhibitors such as soluble type II IL-1 receptor and soluble IL-1RAcP and the compositions and combination therapies described herein. Such conditions include: Alzheimer's disease, secondary reactive amyloidosis; Down's syndrome; and dialysis-associated amyloidosis. Also treatable with the compounds, compositions and combination therapies of the invention are inherited periodic fever syndromes, including familial Mediterranean fever, hyperimmunoglobulin D and periodic fever syndrome and TNF-receptor associated periodic syndromes (TRAPS).

Disorders involving the skin or mucous membranes also are treatable using the disclosed IL-1 inhibitors, such as soluble type II IL-1 receptor and soluble IL-1RAcP compositions or combination therapies, e.g. in combination with ENBREL. Such disorders include acantholytic diseases, including Darier's disease, keratosis follicularis and pemphigus vulgaris. Also treatable with the subject IL-1 inhibitors, especially soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies are acne; acne rosacea; alopecia areata; aphthous stomatitis; bullous pemphigoid; burns; eczema; erythema, including erythema multiforme and erythema multiforme bullosum (Stevens-Johnson syndrome); inflammatory skin disease; lichen planus; linear IgA bullous disease (chronic bullous dermatosis of childhood); loss of skin elasticity; mucosal surface ulcers, including gastric ulcers; neutrophilic dermatitis (Sweet's syndrome); dermatomyositis, pityriasis rubra pilaris; psoriasis; pyoderma gangrenosum; multicentric reticulohistiocytosis; and toxic epidermal necrolysis. Other skin related conditions treatable by the therapies and combination therapies of the present invention include dermatitis herpetiformis

Disorders associated with transplantation also are treatable or preventable with the disclosed IL-1 inhibitors, such as soluble type II IL-1 receptor and soluble IL-1RAcP

compositions or combination therapies, including compositions of soluble type II IL-1 receptor and soluble IL-1RAcP and ENBREL. Such disorders include graft -versus-host disease, and complications resulting from solid organ transplantation, such as heart, liver, skin, kidney, lung (lung transplant airway obliteration) or other transplants, including bone marrow transplants.

Ocular disorders also are treatable or preventable with the disclosed IL-1 inhibitors, especially soluble type II IL-1 receptor and soluble IL-1RAcP compositions or combination therapies, including rhegmatogenous retinal detachment, and inflammatory eye disease, including inflammatory eye disease associated with smoking and macular degeneration.

IL-1 inhibitors such as soluble type II IL-1 receptor and soluble IL-1RAcP and the disclosed compositions and combination therapies also are useful for treating disorders that affect the female reproductive system. Examples include, but are not limited to, multiple implant failure/infertility; fetal loss syndrome or IV embryo loss (spontaneous abortion); preeclamptic pregnancies or eclampsia; endometriosis, chronic cervicitis, and pre-term labor.

In addition, the disclosed IL-1 inhibitors, particularly soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies, such as combinations of IL-1 inhibitors and ENBREL are useful for treating obesity, including to bring about a decrease in leptin formation. Also, the compounds, compositions and combination therapies of the invention are used to treat or prevent sciatica, symptoms of aging, severe drug reactions (for example, Il-2 toxicity or bleomycin-induced pneumopathy and fibrosis), or to suppress the inflammatory response prior, during or after the transfusion of allogeneic red blood cells in cardiac or other surgery, or in treating a traumatic injury to a limb or joint, such as traumatic knee injury. Various other medical disorders treatable with the disclosed IL-1 inhibitors, compositions and combination therapies include; multiple sclerosis; Behcet's syndrome; Sjogren's syndrome; autoimmune hemolytic anemia; beta thalassemia; amyotrophic lateral sclerosis (Lou Gehrig's Disease); Parkinson's disease; and tenosynovitis of unknown cause, as well as various autoimmune disorders or diseases associated with hereditary deficiencies, including x-linked mental retardation.

The disclosed IL-1 inhibitors, particularly soluble type II IL-1 receptor and soluble IL-1RAcP compositions and combination therapies, e.g. soluble type II IL-1 and soluble IL-1RAcP receptor and ENBREL, are useful for treating central nervous system (CNS) injuries, including the effects of neurotoxic neurotransmitters discharged during excitation of inflammation in the central nervous system and to inhibit or prevent the development of glial scars at sites of central nervous system injury. In connection with central nervous system medical conditions, IL-1 inhibitors, alone or in combination with

TNF inhibitors and particularly type II IL-1 receptor and soluble IL-1RAcP and/or ENBREL are useful in treating temporal lobe epilepsy. In connection with epilepsy and the treatment of seizures, reducing the severity and number of recurring seizures, and reducing the severity of the deleterious effects of seizures. IL-1 inhibitors, in particular soluble type II IL-1R and soluble IL-1RAcP, alone or in combination with agents described herein, e.g. IL-6, is useful for reducing neuronal loss, neuronal degeneration, and gliosis associated with seizures.

Furthermore, the disclosed IL-1 inhibitors, particularly soluble type II IL-1 receptor and soluble IL-1RAcP, compositions and combination therapies, e.g. IL-1 inhibitors and ENBREL, are useful for treating critical illness polyneuropathy and myopathy (CIPNM) acute polyneuropathy; anorexia nervosa; Bell's palsy; chronic fatigue syndrome; transmissible dementia, including Creutzfeld-Jacob disease; demyelinating neuropathy; Guillain-Barre syndrome; vertebral disc disease; Gulf war syndrome; chronic inflammatory demyelinating polyneuropathy, myasthenia gravis; silent cerebral ischemia; sleep disorders, including narcolepsy and sleep apnea; chronic neuronal degeneration; and stroke, including cerebral ischemic diseases. Other diseases and medical conditions that may be treated or prevented by administering IL-1 inhibitors, such as soluble type II IL-1 receptor and soluble IL-1RAcP, alone or in combination with a herein described active agents, particularly a TNF inhibitor such as ENBREL, include anorexia and/or anorexic conditions, peritonitis, endotoxemia and septic shock, granuloma formation, heat stroke, Churg-Strauss syndrome, chronic inflammation following acute infections such as tuberculosis and leprosy, systemic sclerosis and hypertrophic scarring. In addition to IL-1 inhibitors in combination with TNF inhibitors, IFN-alpha beta or gamma and/or IL-4 inhibitors are suitable for treating hypertrophic scarring.

The IL-1 inhibitors discloses herein, and particularly soluble forms of type II IL-1R, soluble IL-1RAcP, IL-1ra and variants, and IL-1 traps, are useful for reducing the toxicity associated with antibody therapies, chemotherapy, radiation therapy and the effects of other apoptosis inducing agents, e.g. TRAIL and TRADE, and therapies that target IL-1 producing cells or illicit an inflammatory response. Monoclonal antibody therapies, chemotherapies and other apoptosis inducing therapies that target IL-1 producing cells induce the production and/or release of IL-1. By administering therapies that inhibit the effects of IL-1 by interfering with its interaction with its receptor and/or receptor accessory, the proinflammatory effects and medical conditions associated with IL-1 are reduced or eliminated.

In addition to human patients, soluble type II IL-1 receptor and soluble IL-1RAcP combinations are useful in the treatment of non-human animals, such as pets (dogs, cats, birds, primates, etc.), domestic farm animals (horses cattle, sheep, pigs, birds, etc.), or any

animal that suffers from an IL-1-mediated inflammatory or arthritic condition. In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the dose is determined according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m^2, or more preferably, from 5-12 mg/m^2. For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. Soluble type II IL-1 receptor (preferably constructed from genes derived from the recipient species), or another soluble IL-1 receptor mimic or IL-1 inhibitor, e.g. IL-1RAcP, is administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

Provided herein are methods of treating or preventing psoriatic lesions that involve administering to a human patient a therapeutically effective amount of a soluble IL-1 receptor and soluble IL-1RAcP. A preferred soluble for this purpose is soluble type II IL-1 receptor. The treatment is effective against psoriatic lesions that occur in patients who have ordinary psoriasis or psoriatic arthritis.

Patients are defined as having ordinary psoriasis if they lack the more serious symptoms of psoriatic arthritis (e.g., distal interphalangeal joint DIP involvement, enthesopathy, spondylitis and dactylitis), but exhibit one of the following: 1) inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris); 2) small red dots appearing on the trunk, arms or legs (guttate psoriasis); 3) smooth inflamed lesions without scaling in the flexural surfaces of the skin (inverse psoriasis); 4) widespread reddening and exfoliation of fine scales, with or without itching and swelling (erythrodermic psoriasis); 5) blister-like lesions (pustular psoriasis); 6) elevated inflamed scalp lesions covered by silvery white scales (scalp psoriasis); 7) pitted fingernails, with or without yellowish discoloration, crumbling nails, or inflammation and detachment of the nail from the nail bed (nail psoriasis).

In treating ordinary psoriasis, soluble type II IL-1 receptor and soluble IL-1RAcP composition is administered in an amount and for a time sufficient to induce an improvement in the patient's condition as measured according to any indicator that reflects the severity of the patient's psoriatic lesions. One or more such indicators may be assessed for determining whether the amount of IL-1 inhibitor and duration of treatment is sufficient. In one preferred embodiment of the invention, the soluble type II IL-1 receptor and soluble IL-1RAcP composition is administered in an amount and for a time sufficient to induce an improvement over baseline in either the psoriasis area and severity index (PASI) or the Target Lesion Assessment Score. In another embodiment, both indicators are used. When PASI score is used as the indicator, treatment is regarded as sufficient when the patient exhibits an at least 50% improvement in his or her PASI score, or alternatively, when the patient exhibits an at least 75% improvement in PASI score.

Using the Psoriasis Target Lesion Assessment Score to measure sufficiency of treatment involves determining for an individual psoriatic lesion whether improvement has occurred in one or more of the following, each of which is separately scored: plaque elevation; amount and degree of scaling or degree of erythema; and target lesion response to treatment. Psoriasis Target Lesion Assessment Score is determined by adding together the separate scores for all four of the aforementioned indicia, and determining the extent of improvement by comparing the baseline score the score after treatment has been administered.

A satisfactory degree of improvement in psoriasis patients is obtained by administering the soluble type II IL-1 receptor and soluble IL-1RAcP composition one or more times per week. For example, soluble type II IL-1 receptor and soluble IL-1RAcP may be administered one time, two times or three or more times per week. Treatment may be continued over a period of at least one week, for two weeks, three weeks, four weeks or longer. Treatment may be discontinued after the patient improves, then resumed if symptoms return, or alternatively, the treatment may be administered continuously for an indefinite period. A preferred route of administration is subcutaneous injection using dosages described above.

Soluble type II IL-1 receptor may be used to treat ordinary psoriasis in combination with one, two, three or more other medications that are effective against psoriasis. These additional medications may be administered before, simultaneously with, or sequentially with the soluble type II IL-1 receptor and soluble IL-1RAcP. Drugs suitable for combination therapies of psoriasis include pain medications (analgesics), including but not limited to acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. In addition, ENBREL or other IL-1 inhibitor may be administered in combination with methotrexate, sulfasalazine, gold salts, azathioprine, cyclosporine, antimalarials, oral steroids (e.g., prednisone) or colchicine. Non-steroidal anti-inflammatories may also be coadministered with the IL-1 inhibitors, including but not limited to: salicylic acid (aspirin); ibuprofen; indomethacin; celecoxib; rofecoxib; ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and COX-2 inhibitors, salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories.

Moreover, soluble type II IL-1 receptor and soluble IL-1RAcP compositions may be used to treat psoriasis in combination with topical steroids, systemic steroids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, anthralin, coal tar, vitamin D3 and its analogs (including 1,25-dihydroxy vitamin D3 and calcipotriene), topical retinoids, oral retinoids (including but not limited to etretinate,

acitretin and isotretinoin), topical salicylic acid, methotrexate, cyclosporine, hydroxyurea and sulfasalazine. In addition, it may be administered in combination with one or more of the following compounds; minocycline; misoprostol; oral collagen; penicillamine; 6-mercaptopurine; nitrogen mustard; gabapentin; bromocriptine; somatostatin; peptide T; anti-CD4 monoclonal antibody; fumaric acid; polyunsaturated ethyl ester lipids; zinc; and other drugs that may be used to treat psoriasis.

Psoriasis moreover may be treated by soluble type II IL-1 receptor and soluble IL-1RAcP compositions administered in combination with one or more of the following topically applied compounds: oils, including fish oils, nut oils and vegetable oils; aloe vera; jojoba; Dead Sea salts; capsaicin; milk thistle; witch hazel; moisturizers; and Epsom salts.

In addition, psoriasis may be treated by soluble type II IL-1 receptor and soluble IL-1RAcP in combination with the following therapies: plasmapheresis; phototherapy with ultraviolet light B; psoralen combined with ultraviolet light A (PUVA); and sunbathing.

It is understood that the response by individual patients to the aforementioned medications or combination therapies may vary, and the most efficacious combination of drugs for each patient will be determined by his or her physician.

In connection with the above-identified therapeutic indications, it has been discovered that soluble IL-1RAcP is found in circulating blood at significant levels. In view of the ability of IL-1RAcP to enhance binding of type II IL-1R to IL-1α and IL-1β, determining the level of circulating IL-1RAcP may be used to determine the level of IL-1RAcP to administer to an individual. Accordingly, the present invention encompasses methods for treating individuals in which the level of circulating IL-1RAcP is assayed, in accordance with standard procedures, and the dose of IL-1RAcP is determined in accordance with the level of circulating soluble IL-1RAcP.

In addition to methods described above that include administering IL-1R Type II and IL-1RAcP in combination to treat the above identified IL-1 mediated diseases and medical conditions, the present invention encompasses methods for treating the diseases by administering fusion proteins, oligomers, and combinations of IL-1R Type II and IL-1RAcP in which the compounds are complexed, covalently, by hydrogen bonds, through disulfide bonds and ionic bonds. Accordingly, this invention includes fusion proteins and complexes of IL-1R Type II and IL-1RAcP. Such fusion proteins and complexes can involve full length IL-1R Type II and full length IL-1RAcP or soluble forms of IL-1R Type II and IL-1RAcP. The soluble forms may be the full extracellular portion of the molecules or fragments of the molecules that together enhance the binding of IL-1α or IL-1β to the IL-1R Type II.

More particularly, the present invention provides multimeric polypeptides that include an IL-1R Type II polypeptide, or fragments thereof, and an IL-1RAcP polypeptide, or fragments thereof. The polypeptides may be covalently linked or noncovalently polypeptide by any suitable means. Such means include *via* a cross-linking reagent, a polypeptide linker, and associations such as via disulfide bonds or by use of leucine zippers.. Methods for treating disorders and medicated conditions that are mediated by IL-1 are also include and can be carried out by administering a therapeutically effective amount of this multimeric polypeptide to a patient afflicted with such a disorder.

The multimeric polypeptides that include IL-1R Type II and IL-1RAcP can be prepared by transfecting cells with DNA encoding IL-1R type II:Fc fusion protein and DNA encoding IL-1RAcP:Fc fusion protein and coexpressing the dimers in the same cells. Preferably the IL-1R Type II and IL-1RAcP are the extracellular forms of the molecules or soluble fragments that together enhance the binding of IL-1α or IL-1β to IL-1R Type II. For example, Type II ;IL-1R of the multimer may be amino acids 1-333 of SEQ ID NO:2 and the IL-1RAcP can be SEQ ID NO:6 or amino acids 21-359 of SEQ ID NO:6.

Alternatively, IL-1R Type II and IL-1RAcP dimers can be prepared by fusing one of the polypeptides, preferably the above identified soluble portion, to the constant region of an immunoglobulin heavy chain and fusing the other to the constant region of an immunoglobulin light chain. For example, an IL-1R Type II polypeptide can be fused to the CH_1-hinge-CH_2-CH_3 region of human IgG1 and an IL-1RAcP polypeptide can be fused to the C kappa region of the Ig kappa light chain, or vice versa. Cells transfected with DNA encoding the immunoglobulin light chain fusion protein and the immunoglobulin heavy chain fusion protein express heavy chain/light chain heterodimers containing the IL-1R type II fusion protein and the IL-1RAcP fusion protein. Via disulfide linkages between the heavy chains, the heterodimers further combine to provide

multimers, largely tetramers. Advantageously, in the event homodimers of two heavy or two light chain fusions are expressed, such homodimers can be separated easily from the heterodimers.

In addition to polypeptide complexes, the present invention includes isolated DNA encoding the multimeric polypeptides, expression vectors containing DNA encoding the heteromer polypeptides, and host cells transformed with such expression vectors. Methods for production of recombinant forms of the multimers, including soluble forms of the protein, are also disclosed. Antibodies immunoreactive with the novel polypeptide are provided herein as well.

Alternatively, the multimer may comprise IL-1R Type II or soluble IL-1R Type II fragments non-covalently complexed with IL-1RAcP or soluble IL-1RAcP fragments. Non-covalent bonding of IL-1R Type II to IL-1RAcP may be achieved by any suitable means that does not interfere with the multimer's or the complex's ability to bind IL-1. In one approach, a first compound is attached to IL-1RAcP and a second compound that will non-covalently bond to the first compound is attached to IL-1R Type II. Examples of such compounds are biotin and avidin. The receptor is thus formed through the non-covalent interactions of biotin with avidin. In one embodiment of the invention, IL-R Type II and IL-1RAcP are recombinant polypeptides, each purified from recombinant cells and then non-covalently bonded together to form the receptor. A host cell may be transformed with two different expression vectors such that both IL-1R Type II and IL-1RAcP are produced by the recombinant host cell. Multimers produced by such transformed host cells may associate to form a complex through non-covalent interactions.

The combination therapy methods of the present invention include administering any of the above described IL-1R Type II/IL-1RAcP fusion proteins or complexes to individuals who are afflicted with or any of the above identified IL-1 mediated diseases.

EXAMPLE 1

The following was performed to determine the effect of type II IL-1R, alone or in combination with soluble IL-17R (IL-17R:Fc) or TNF receptor (p75 TNFR:Fc), on the spontaneous release of IL-6 and degradation of type I collagen in synovium and bone explants from patients with rheumatoid arthritis (RA).

Synovium was obtained from 22 patients with RA undergoing synovectomy, and bone samples were obtained at the site of joint surgery from 8 patients with RA. Synovium and bone explants were cultured for 7 days in the presence of human type II IL-1R, murine IL-17R:Fc, human TNFR:Fc (1 μg/mL in each case), or a combination of soluble receptors. Control explants were cultured with immunoglobulin G (IgG) from

healthy humans. Levels of IL-6 and CTX, a C-terminal peptide released during the degradation of type I collagen, in the supernatants of 7-day cultures were measured by ELISA. Data are expressed as the mean ± SEM. Synovium cultures spontaneously released IL-6 (104 ± 20 ng/mL) and CTX (65 ± 25 nM). In cultures exposed to IL-1RII, spontaneous release of IL-6 was significantly inhibited by 36 ± 7% ($p < 0.001$) and spontaneous release of CTX was significantly inhibited by 59 ± 13% ($p < 0.05$) compared to controls exposed to human IgG. The ability of IL-1RII to inhibit release of IL-6 and CTX from synovium was similar to that of TNFR:Fc (IL-6, 39 ± 7% inhibition; CTX, 55 ± 14% inhibition), and IL 17R:Fc (IL-6, 31 ± 6% inhibition; CTX, 53 ± 7% inhibition). Combining type II IL-1R and TNFR:Fc inhibited IL-6 release by 48 ± 9% ($p < 0.05$ vs. control). The combination of type II IL-1R; TNFR:Fc and IL-17R:Fc had the greatest effect, inhibiting release of IL-6 by 71 ± 5% ($p < 0.001$ vs. control) and release of CTX by 70 ± 5% ($p < 0.05$ vs. control).

Bone cultures from RA patients also spontaneously released IL-6 (88 ± 13 ng/mL) and CTX (99 ± 31 nM). In cultures exposed to type II IL-1R, spontaneous release of IL-6 and CTX were both significantly inhibited by 50 ± 11% ($p < 0.05$ in each case) compared to controls exposed to IgG. In contrast to synovium explants, in bone explants type II IL-1R was more effective than TNFR:Fc and IL-17R:Fc in inhibiting release of IL-6 and CTX. TNFR:Fc inhibited IL-6 release from bone explants by 37 ± 10% and CTX release by 38 ± 9%, while IL-17R:Fc inhibited IL-6 release from bone explants by 23 ± 13% and CTX release by 40 ± 10%. The combination of all 3 soluble receptors inhibited release of IL-6.

These results demonstrate that type II IL-1R inhibits the spontaneous release of IL-6, a proinflammatory cytokine with pleiotropic actions that is considered to be a major mediator of the acute phase reaction, from human RA joint tissues in vitro. IL-1RII also inhibited the degradation of type I collagen in synovium and bone explants, and thus has the potential to reduce inflammation and bone destruction in arthritic joints. Furthermore, combination therapy with type II IL-1R and TNFR:Fc to inhibit IL-1 and TNF and/or IL-17R may be more efficacious than inhibiting IL-1 or TNF individually.

EXAMPLE 2

The following experiments were performed to determine the apparent binding constants of recombinant human type II IL-1R:Fc for human and cynomolgus macaque IL-1α, IL-1β,and IL-1 receptor antagonist (IL-1ra) in the presence or absence of recombinant human or cynomolgus IL-1 receptor Accessory Protein (AcP):Fc.

The relative ability of purified soluble type II IL-1R to bind IL-1α, IL-1β and IL-1ra was measured using a BIACORE 3000 instrument with a research grade CM5 sensor chip at 25 degrees C. Soluble recombinant human type II IL-1R was fused to the Fc

portion of human IgG so that the resulting type II IL-1R:Fc construct could be bound to a goat anti-human IgG, Fc chain-specific antibody immobilized to the chip using standard amine coupling chemistry. A similar construct was made using IL-1AcP for the same reason. When IL-1AcP:Fc was used in combination with type II IL-1R:Fc, it was mixed in a 1:1 molar ratio before injection into the BIACORE 3000. Kinetic data were obtained by running a range of concentrations of IL-1α, IL-1β,and IL-1 ra over a flow cell that contained receptor bound to immobilized antibody, and a reference cell of immobilized antibody alone. Data were fit to a 1:1 Langmuir binding interaction model using global analysis with BIAEvaluation 3.1 software, except data for the binding of IL-1α to type II IL-1R:Fc in the presence of IL-1AcP:Fc which were fit to a heterogenous ligand model

In the absence of human IL-1AcP, human type II IL-1R:Fc bound to human IL-1β with a high apparent equilibrium binding constant (1.3 x 10 9 M -1), but the affinity for human IL-1α was ~100-fold lower primarily as a result of the rapid dissociation rate. In the presence of human IL-1AcP:Fc, the apparent equilibrium binding constants of human type II IL-1R:Fc for human IL-1α and IL-1β were increased >100-fold over those measured in the absence of human IL-1AcP. Human IL-1AcP:Fc slowed the dissociation rates of both ligands by ~100-fold. In contrast, human IL-1AcP:Fc had little effect on the affinity of human IL-1RII:Fc for human IL-1ra. In the absence of receptor, no binding of human IL-1α, IL-1β,and IL-1 ra to human IL-1AcP:Fc was detected.

EXAMPLE 3

The following experiments were performed to examine the binding of recombinant cynomolgus ligands to recombinant human and cynomolgus Type II IL-1R:Fc. These experiments were done to establish proof of principle for the use of cynomolgus macaques in pharmacology and toxicology studies. In the absence of cynomolgus IL-1AcP, human type II IL-1R:Fc had very low apparent equilibrium affinity constant for binding cynomolgus IL-1α (1.4 x 10 6 M -1) or cynomolgus IL-1ra (6.2 x 10 7 M -1). In the presence of cynomolgus IL-1AcP:Fc, the apparent affinity of human type II IL-1R:Fc for cynomolgus IL-1β was increased by >100-fold (1.8 x 10 8 M -1) over the apparent equilibrium affinity constant measured in the absence of IL-1AcP. he increased affinity of human type II IL-1R:Fc for cynomolgus IL-1β in the presence of cynomolgus IL-1AcP:Fc results from both an increase in the apparent association rate and a decrease in the apparent dissociation rate. As expected, cynomolgus IL-1AcP:Fc increased the apparent equilibrium affinity constant of cynomolgus type II IL-1R:Fc for cynomolgus IL-1β. As occurred when the human homologs were tested, human type II IL-1R:Fc bound cynomolgus IL-1ra with low affinity and the presence of cynomolgus IL-1AcP:Fc had little effect on the affinity. In the absence of receptor, no binding of cynomolgus IL-1β or IL-1ra to cynomolgus IL-1AcP:Fc was detected. Monkey IL-1β can induce a

biological response in human cells as shown by its ability to induce the death of human cells of the A375 melanoma cell line in a dose-dependent manner.

In conclusion, in the absence of soluble recombinant human IL-1AcP:Fc, soluble recombinant human type II IL 1R:Fc bound human IL-1β with high affinity (apparent equilibrium binding constant = 1.3 x 10 9 M -1. In the presence of soluble recombinant IL-1RAcP:Fc, the apparent equilibrium binding constants of human type II IL-1R:Fc for both human IL-1α and IL-1β were increased >100-fold over those measured in the absence of human IL-1AcP:Fc. Therefore, if sufficient soluble IL-1AcP is present, human type II IL-1R is a good inhibitor of IL-1α signaling as well as a very high affinity inhibitor of IL-1β signaling. A treatment regimen that includes type II IL-R, preferably in soluble form, and IL-1AcP (preferably in soluble form) results in increased IL-1α and IL-1β binding and higher effective IL-1 inhibition.

EXAMPLE 4

The following demonstrates that the increased binding of IL-1 by Type II IL-1 receptor, which is conferred by IL-1RAcP, also results in an enhanced ability of IL-1R Type II to inhibition IL-1. Thus, soluble IL-1R Type II is a better inhibitor in the presence of IL-1RAcP. COS7 cells that were transfected with an NF-κB luciferase reporter plasmid were incubated for four hours with varying concentrations of recombinant rhesus IL-1β in the presence of soluble IL-1R Type II receptor. Cells were lysed and luciferase activity measured to determine NF-κB activation. No NF-κB activation or a decrease in the amount of NF-κB activation indicates that IL-1 activity is inhibited. The results of these experiments showed that in the presence of both IL-1R type II and IL-1RAcP a 25-fold increase in IL-1β was required in order to achieve the same biological response as the IL-1R Type II or IL-1RAcP alone. Additionally, the IL-1R Type II, in the presence of IL-1RAcP, inhibits the action of IL-1α about 25 times more than the modest inhibitory effect of IL-1R Type II alone. The above described experimental results demonstrate that IL-1R Type II, in the presence of IL-1RAcP, has significantly greater IL-1α and IL-1β inhibitory characteristics than IL-1R type II alone or IL-1RAcP alone. Therefore, IL-1RAcP and IL-1R Type II in combination have increased affinity of binding and an increased effectiveness as an inhibitor of IL-1α and IL-1β.

EXAMPLE 5

The following experiments describe the results of experiments designed to determine the level of soluble IL-1RAcP in animal model of inflammation. In a model, DBA/1 mice were primed by immunization with chicken type II collagen, and arthritis induced by a second collagen injection 21 days later. Disease continuously worsened

over the next two weeks, as measured by the arthritis score. The levels of soluble IL-1RAcP in the mice prior to induction were very high, the mean value of 4.04 +/- 0.26 μg/mL. The level diminished as the disease progressed as follows: day 3, 3.56 +/-0.09 μg/mL; day 7, 3.02+/-0.78 μg/mL; day 10, 2.5+/-0.47 μg/mL; day 14, 2.3+/-0.19μg/mL.

In a mouse colitis model, colitis was induced in Balb/c mice by adding DSS to their drinking water for seven days. Intestinal inflammation increased steadily until about day 12. The IL-1RAcP level was determined by an ELISA procedure for untreated mice and at day 8 and day 12 for the DSS treated mice. In the untreated mice, the IL-1RAcP level was 4.08+/-0.72 μg/mL. At day 8, the DSS treated animals had 3.4+/-0.52μg/mL IL-1RAcP and at day 12 the IL-1RAcP level was 2.6+/-0.54μg/mL.

It is evident that changes in serum levels of IL-1RAcP relate to the course of inflammatory diseases. The combination of IL-1RAcP and IL-1R Type II enhance the IL-1 inhibitory effect of IL-1R Type II and IL-1RAcP alone and the involvement of these IL-1 inhibitors in inflammation is demonstrated. Thus, combinations IL-1R Type II and IL-1RAcP are useful for treating IL-1 mediated diseases as disclosed above.

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Sims, John E.
Smith, Dirk E.

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ggc ctt act ctg atc tgg tat tgg act agg cag gac cgg gac ctt gag       240
Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65                  70                  75                  80

gag cca att aac ttc cgc ctc ccc gag aac cgc att agt aag gag aaa       288
Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85                  90                  95

gat gtg ctg tgg ttc cgg ccc act ctc ctc aat gac act ggc aac tat       336
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100                 105                 110
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acc tgc atg tta agg aac act aca tat tgc agc aaa gtt gca ttt ccc      384
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115                 120                 125

ttg gaa gtt gtt caa aaa gac agc tgt ttc aat tcc ccc atg aaa ctc      432
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130                 135                 140

cca gtg cat aaa ctg tat ata gaa tat ggc att cag agg atc act tgt      480
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160

cca aat gta gat gga tat ttt cct tcc agt gtc aaa ccg act atc act      528
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175

tgg tat atg ggc tgt tat aaa ata cag aat ttt aat aat gta ata ccc      576
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190

gaa ggt atg aac ttg agt ttc ctc att gcc tta att tca aat aat gga      624
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195                 200                 205

aat tac aca tgt gtt gtt aca tat cca gaa aat gga cgt acg ttt cat      672
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220

ctc acc agg act ctg act gta aag gta gta ggc tct cca aaa aat gca      720
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240

gtg ccc cct gtg atc cat tca cct aat gat cat gtg gtc tat gag aaa      768
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255

gaa cca gga gag gag cta ctc att ccc tgt acg gtc tat ttt agt ttt      816
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270

ctg atg gat tct cgc aat gag gtt tgg tgg acc att gat gga aaa aaa      864
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285

cct gat gac atc act att gat gtc acc att aac gaa agt ata agt cat      912
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300

agt aga aca gaa gat gaa aca aga act cag att ttg agc atc aag aaa      960
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320

gtt acc tct gag gat ctc aag cgc agc tat gtc tgt cat gct aga agt     1008
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335

gcc aaa ggc gaa gtt gcc aaa gca gcc aag gtg acg cag aaa gtg cca     1056
Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Thr Gln Lys Val Pro
            340                 345                 350
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gct cca aga tac aca gtg gaa ctg gct tgt ggt ttt gga gcc aca gtc     1104
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ctg cta gtg gtg att ctc att gtt gtt tac cat gtt tac tgg cta gag     1152
Leu Leu Val Val Ile Leu Ile Val Val Tyr His Val Tyr Trp Leu Glu
    370                 375                 380

atg gtc cta ttt tac cgg gct cat ttt gga aca gat gaa acc att tta     1200
Met Val Leu Phe Tyr Arg Ala His Phe Gly Thr Asp Glu Thr Ile Leu
385                 390                 395                 400

gat gga aaa gag tat gat att tat gta tcc tat gca agg aat gcg gaa     1248
Asp Gly Lys Glu Tyr Asp Ile Tyr Val Ser Tyr Ala Arg Asn Ala Glu
                405                 410                 415

gaa gaa gaa ttt gtt tta ctg acc ctc cgt gga gtt ttg gag aat gaa     1296
Glu Glu Glu Phe Val Leu Leu Thr Leu Arg Gly Val Leu Glu Asn Glu
            420                 425                 430

ttt gga tac aag ctg tgc atc ttt gac cga gac agt ctg cct ggg gga     1344
Phe Gly Tyr Lys Leu Cys Ile Phe Asp Arg Asp Ser Leu Pro Gly Gly
        435                 440                 445

att gtc aca gat gag act ttg agc ttc att cag aaa agc aga cgc ctc     1392
Ile Val Thr Asp Glu Thr Leu Ser Phe Ile Gln Lys Ser Arg Arg Leu
    450                 455                 460

ctg gtt gtt cta agc ccc aac tac gtg ctc cag gga acc caa gcc ctc     1440
Leu Val Val Leu Ser Pro Asn Tyr Val Leu Gln Gly Thr Gln Ala Leu
465                 470                 475                 480

ctg gag ctc aag gct ggc cta gaa aat atg ggc tct cgg ggc aac atc     1488
Leu Glu Leu Lys Ala Gly Leu Glu Asn Met Gly Ser Arg Gly Asn Ile
                485                 490                 495

aac gtc att tta gta cag tac aaa gct gtg aag gaa acg aag gtg aaa     1536
Asn Val Ile Leu Val Gln Tyr Lys Ala Val Lys Glu Thr Lys Val Lys
            500                 505                 510

gag ctg aag agg gct aag acg gtg ctc acg gtc att aaa tgg aaa ggg     1584
Glu Leu Lys Arg Ala Lys Thr Val Leu Thr Val Ile Lys Trp Lys Gly
        515                 520                 525

gaa aaa tcc aag tat cca cag ggc agg ttc tgg aag cag ctg cag gtg     1632
Glu Lys Ser Lys Tyr Pro Gln Gly Arg Phe Trp Lys Gln Leu Gln Val
    530                 535                 540

gcc atg cca gtg aag aaa agt ccc agg cgg tct agc agt gat gag cag     1680
Ala Met Pro Val Lys Lys Ser Pro Arg Arg Ser Ser Ser Asp Glu Gln
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35 40 45

Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
50 55 60

Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65 70 75 80

Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
85 90 95

Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
100 105 110

Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
115 120 125

Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
130 135 140

Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145 150 155 160

Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
165 170 175

Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
180 185 190

Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
195 200 205

Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
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Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
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Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
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Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270

Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285

Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300

Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320

Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335

Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Thr Gln Lys Val Pro
            340                 345                 350

Ala Pro Arg Tyr Thr Val Glu Leu Ala Cys Gly Phe Gly Ala Thr Val
        355                 360                 365

Leu Leu Val Val Ile Leu Ile Val Val Tyr His Val Tyr Trp Leu Glu
    370                 375                 380

Met Val Leu Phe Tyr Arg Ala His Phe Gly Thr Asp Glu Thr Ile Leu
385                 390                 395                 400

Asp Gly Lys Glu Tyr Asp Ile Tyr Val Ser Tyr Ala Arg Asn Ala Glu
                405                 410                 415

Glu Glu Glu Phe Val Leu Leu Thr Leu Arg Gly Val Leu Glu Asn Glu
            420                 425                 430

Phe Gly Tyr Lys Leu Cys Ile Phe Asp Arg Asp Ser Leu Pro Gly Gly
        435                 440                 445

Ile Val Thr Asp Glu Thr Leu Ser Phe Ile Gln Lys Ser Arg Arg Leu
    450                 455                 460

Leu Val Val Leu Ser Pro Asn Tyr Val Leu Gln Gly Thr Gln Ala Leu
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Leu Glu Leu Lys Ala Gly Leu Glu Asn Met Gly Ser Arg Gly Asn Ile
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caa agt gat gcc tca gaa cgc tgc gat gac tgg gga cta gac acc atg 96
Gln Ser Asp Ala Ser Glu Arg Cys Asp Asp Trp Gly Leu Asp Thr Met
20 25 30

agg caa atc caa gtg ttt gaa gat gag cca gct cgc atc aag tgc cca 144
Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
35 40 45

ctc ttt gaa cac ttc ttg aaa ttc aac tac agc aca gcc cat tca gct 192
Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
50 55 60

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Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65 70 75 80

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Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
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gat gtg ctg tgg ttc cgg ccc act ctc ctc aat gac act ggc aac tat      336
Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100                 105                 110

acc tgc atg tta agg aac act aca tat tgc agc aaa gtt gca ttt ccc      384
Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115                 120                 125

ttg gaa gtt gtt caa aaa gac agc tgt ttc aat tcc ccc atg aaa ctc      432
Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130                 135                 140

cca gtg cat aaa ctg tat ata gaa tat ggc att cag agg atc act tgt      480
Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160

cca aat gta gat gga tat ttt cct tcc agt gtc aaa ccg act atc act      528
Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175

tgg tat atg ggc tgt tat aaa ata cag aat ttt aat aat gta ata ccc      576
Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
            180                 185                 190

gaa ggt atg aac ttg agt ttc ctc att gcc tta att tca aat aat gga      624
Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
        195                 200                 205

aat tac aca tgt gtt gtt aca tat cca gaa aat gga cgt acg ttt cat      672
Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
    210                 215                 220

ctc acc agg act ctg act gta aag gta gta ggc tct cca aaa aat gca      720
Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225                 230                 235                 240

gtg ccc cct gtg atc cat tca cct aat gat cat gtg gtc tat gag aaa      768
Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
                245                 250                 255

gaa cca gga gag gag cta ctc att ccc tgt acg gtc tat ttt agt ttt      816
Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
            260                 265                 270

ctg atg gat tct cgc aat gag gtt tgg tgg acc att gat gga aaa aaa      864
Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
        275                 280                 285

cct gat gac atc act att gat gtc acc att aac gaa agt ata agt cat      912
Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
    290                 295                 300

agt aga aca gaa gat gaa aca aga act cag att ttg agc atc aag aaa      960
Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305                 310                 315                 320

gtt acc tct gag gat ctc aag cgc agc tat gtc tgt cat gct aga agt     1008
Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
                325                 330                 335
```

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gcc aaa ggc gaa gtt gcc aaa gca gcc aag gtg acg cag aaa gtg cca      1056
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            340                 345                 350

gct cca aga tac aca gtg gaa                                        1077
Ala Pro Arg Tyr Thr Val Glu
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Arg Gln Ile Gln Val Phe Glu Asp Glu Pro Ala Arg Ile Lys Cys Pro
        35                  40                  45

Leu Phe Glu His Phe Leu Lys Phe Asn Tyr Ser Thr Ala His Ser Ala
    50                  55                  60

Gly Leu Thr Leu Ile Trp Tyr Trp Thr Arg Gln Asp Arg Asp Leu Glu
65                  70                  75                  80

Glu Pro Ile Asn Phe Arg Leu Pro Glu Asn Arg Ile Ser Lys Glu Lys
                85                  90                  95

Asp Val Leu Trp Phe Arg Pro Thr Leu Leu Asn Asp Thr Gly Asn Tyr
            100                 105                 110

Thr Cys Met Leu Arg Asn Thr Thr Tyr Cys Ser Lys Val Ala Phe Pro
        115                 120                 125

Leu Glu Val Val Gln Lys Asp Ser Cys Phe Asn Ser Pro Met Lys Leu
    130                 135                 140

Pro Val His Lys Leu Tyr Ile Glu Tyr Gly Ile Gln Arg Ile Thr Cys
145                 150                 155                 160

Pro Asn Val Asp Gly Tyr Phe Pro Ser Ser Val Lys Pro Thr Ile Thr
                165                 170                 175
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Trp Tyr Met Gly Cys Tyr Lys Ile Gln Asn Phe Asn Asn Val Ile Pro
180 185 190

Glu Gly Met Asn Leu Ser Phe Leu Ile Ala Leu Ile Ser Asn Asn Gly
195 200 205

Asn Tyr Thr Cys Val Val Thr Tyr Pro Glu Asn Gly Arg Thr Phe His
210 215 220

Leu Thr Arg Thr Leu Thr Val Lys Val Val Gly Ser Pro Lys Asn Ala
225 230 235 240

Val Pro Pro Val Ile His Ser Pro Asn Asp His Val Val Tyr Glu Lys
245 250 255

Glu Pro Gly Glu Glu Leu Leu Ile Pro Cys Thr Val Tyr Phe Ser Phe
260 265 270

Leu Met Asp Ser Arg Asn Glu Val Trp Trp Thr Ile Asp Gly Lys Lys
275 280 285

Pro Asp Asp Ile Thr Ile Asp Val Thr Ile Asn Glu Ser Ile Ser His
290 295 300

Ser Arg Thr Glu Asp Glu Thr Arg Thr Gln Ile Leu Ser Ile Lys Lys
305 310 315 320

Val Thr Ser Glu Asp Leu Lys Arg Ser Tyr Val Cys His Ala Arg Ser
325 330 335

Ala Lys Gly Glu Val Ala Lys Ala Ala Lys Val Thr Gln Lys Val Pro
340 345 350

Ala Pro Arg Tyr Thr Val Glu
355

What is claimed is:

1. A method of treating a patient afflicted with a medical disorder selected from the group consisting of rheumatoid arthritis, Alzheimer's, stroke, head trauma, myocardial infarction, heart failure, periodontal disease, inflammatory bowel disease, asthma and pancreatitis, the method comprising administering to said patient a therapeutically effective amount of an IL-1 receptor and IL-1RAcP.

2. The method of Claim 1, wherein the IL-1 receptor is type II IL-1 receptor.

3. The method of Claim 2, wherein the IL-1RAcP is soluble IL-1RAcP.

4. A method of treating a patient afflicted with stroke, the method comprising administering to the patient a therapeutically effective amount of type II IL-1 receptor and IL-1RAcP.

5. The method of Claim 5 wherein the type II IL-1 receptor and the IL-1RAcP is administered intracranially.

6. A method of treating a patient afflicted with heart failure, the method comprising administering to the patient a therapeutically effective amount of type II IL-1 receptor and IL-1RAcP.

7. A method of treating a patient afflicted with a medical disorder selected from the group consisting of Alzheimer's, stroke, head trauma, myocardial infarction, heart failure, periodontal disease, inflammatory bowel disease, asthma and pancreatitis, the method comprising administering to said patient a therapeutically effective amount of IL-1RAcP.

8. The method of Claim 3, further including the step of administering one or more compounds selected from the group consisting of non-steroidal anti-inflammatory drugs; analgesics; topical steroids; systemic steroids; antagonists of inflammatory cytokines; antibodies against T cell surface proteins; anthralin; coal tar; vitamin D3 and its analogs; topical retinoids; oral retinoids; salicylic acid; methotrexate; cyclosporine; hydroxyurea; and sulfasalazine.

9. The method of Claim 2, wherein the soluble type II IL-1 receptor and IL-1RAcP is administered in combination with a TNF inhibitor.

10. The method of Claim 9 wherein the TNF inhibitor is TNFR: Fc.

11. The method of Claim 2, wherein the type II IL-1 receptor is administered in combination with a compound selected from the group consisting of antagonists of IFNγ, TGFβ, IL-6 and IL-8.

12. The method of Claim 9 wherein the soluble type II IL-1 receptor, IL-1RAcP and TNF inhibitor are administered in combination with a compound selected from the group consisting of antagonists of IFNγ, TGFβ, IL-6 and IL-8.