substitutions. The amino acid sequence can include at least 1, 2, 3, 4, or 5 substitutions, e.g., conservative substitutions.

Also provided are isolated proteins that include a methionine N-terminal to the amino acid sequence of P01, P02, P03, P04, P05, P06, or P07, or a sequence in Example 1, 5, 6, or elsewhere herein, and isolated proteins that include the amino acid sequence of P01, P02, P03, P04, P05, P06, or P07, or a sequence in Example 1, 5, 6 or elsewhere herein in which the alanine at N-terminus is absent. The foregoing sequences can include other features disclosed herein. For example, the sequence can further include a tag, such as a hexa-histidine sequence (SEQ ID NO:42), e.g., N- or C-terminal relative to the IL-1RI binding sequence. The sequence can further include a moiety that modifies the stability or pharmacokinetics of the IL-1RI binding sequence. For the sequence can further include a serum albumin and/or an Fc domain, or one or more domains thereof, e.g., one or more immunoglobulin constant domains or one or more albumin domains. The protein can have other features described herein. In some embodiments, the isolated protein consists of or consists essentially of a sequence or chimeric domain disclosed herein.

In still another aspect, the disclosure provides an isolated protein that includes a domain having a circularly permuted form of a cytokine domain described herein, e.g., a cytokine domain listed in Table 4 and/or a domain that includes SEQ ID NO:3. The protein can further include a heterologous sequence (such as an Fc domain or albumin) at the N- or C-terminus of the permuted form, optionally spaced by a linker. The protein can have other features described herein.

The disclosure also features pharmaceutical compositions that include one or more receptor binding agents described herein (such as a protein that includes a chimeric cytokine domain). The compositions can be ophthalmic pharmaceutical compositions, topical compositions, or compositions for parenteral administration.

In another aspect, the disclosure features a method of modulating an immune or inflammatory response in a subject. The method can include administering a composition that includes a receptor binding agent described herein to a subject in an amount effective to modulate the immune or inflammatory response in the subject.

In another aspect, the disclosure features a method of treating an IL-1 mediated disorder in a subject. The method includes administering a composition that includes a protein that can bind to IL-1RI, e.g., a receptor binding agent described herein, to the subject. For example, the disorder can be an autoimmune disorder, e.g., rheumatoid

$R_{merge} = \Sigma_{hkl} [\Sigma_i | I_i - \langle I \rangle | / \Sigma_i I_i]$
$R_{work} = \Sigma_{hkl} || F_{obs} | - | F_{calc} || / \Sigma_{hkl} | F_{obs} |$ where F_{obs} and F_{calc} are the observed and calculated structure factors
R_{free} was calculated from a subset of reflections (5%) not used for refinement.

The P04 crystal structure has a fold similar to that predicted by the modeling. A view of this structure is shown in FIG. 1. An overlay of the two structures is shown in FIG. 12A. The RMSD for backbone carbons was 1.41 Å and 1.09 Å for the IL-1β and IL-1Ra segments versus the same residues on the respective parent molecules. P04 has at least one unique salt bridge and two unique hydrogen bonds that involve an interaction between a residue derived from IL-1β and a counterpart derived from IL-1Ra: (i) Glu39-Lys64 of P04 (corresponding to Glu 44~~Glu39~~ from IL-1RA and Lys65~~; Lys64~~ from IL-1β) as shown in FIG. 12B, (ii) Arg9-Gln149 of P04 (corresponding to Arg 14 ~~Arg9~~ from IL-1RA and Gln149~~; Gln149~~ from IL-1β) as shown in FIG. 12C and (iii) Ser152-Lys40 of P04 (corresponding to Ser152 from IL-1β~~IL-1RA;~~ and Lys45 from IL-1RA ~~Lys50 from IL-1β~~) as shown in FIG. 12C. These unique interactions can explain P04's increased thermal stability as these interactions are absent in the IL-1β and IL-1Ra structures. The residues involved in these interactions are also present in P03 and P05, proteins that likewise have increased thermal stability.

Other embodiments are within the scope of the following claims.

CLAIMS

1. An isolated protein that comprises a chimeric interleukin-1 (IL-1) family cytokine domain wherein

at least a first segment of the domain is at least 20 amino acids in length and has at least 80% amino acid identity to a corresponding segment of a first IL-1 family cytokine, and

at least a second segment of the domain is at least 20 amino acids in length and has at least 80% amino acid identity to a corresponding segment of a second IL-1 family cytokine,

wherein the first IL-1 family cytokine is an IL-1 receptor agonist and the second IL-1 family cytokine is an IL-1 receptor antagonist and the first and second IL-1 family cytokines are selected from the group consisting of human IL-1β (SEQ ID NO: 1), human IL-1α (SEQ ID NO: 2), and human IL-1Ra (SEQ ID NO: 3), and wherein the isolated protein binds to IL-1 receptor I (IL-1RI) and agonizes or antagonizes IL-1RI receptor signaling activity.

2. The protein of claim 1 wherein the first IL-1 family cytokine is human IL-1β and the second IL-1 family cytokine is human IL-1Ra.

3. The protein of claim 1 or 2, wherein the cytokine domain is not naturally occurring, optionally wherein the cytokine domain is less than 98, 95, 90, 85, or 80% identical to human IL-1β, human IL-1α, and human IL-1Ra.

4. The protein of any one of claims 1 to 3, wherein the cytokine domain binds to IL-1 receptor I with a K_D of less than 100, 50, 20, 10, 5, or 1 nM.

5. The protein of any one of claims 1 to 4, wherein the protein inhibits signaling by IL-1β at a concentration of 0.1 ng/ml in a cellular assay with an IC50 of less than 100, 50, 20, 10 or 5 nM, optionally wherein the protein inhibits signaling with an IC50 that is less than that of IL-1Ra.

6. The protein of any one of claims 1 to 5, wherein the cytokine domain is at least 80%, at least 90%, at least 95% or 100% identical to P05 (SEQ ID NO: 21), P01 (SEQ ID NO: 17), P02 (SEQ ID NO: 18), P03 (SEQ ID NO: 19) or P04 (SEQ ID NO: 20), optionally wherein the protein comprises fewer than 15, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 non-conservative substitutions or fewer than 15, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 total substitutions.

7. The protein of any one of claims 1 to 4, comprising an amino acid sequence at least 80%, at least 90%, at least 95% or 100% identical to P06 (SEQ ID NO: 23) or P07 (SEQ ID NO: 24), optionally wherein the protein comprises fewer than 15, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 non-conservative substitutions or fewer than 15, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 total substitutions.

8. The protein of any one of claims 1 to 7, wherein at least 95, 97, 98, 99, or 100% of the positions within the cytokine domain have the property that, at each such position, the amino acid present is either identical to the first IL-1 family cytokine or to the second IL-1

family cytokine or both if the first and second IL-1 family cytokine are identical at the particular position.

9. The protein of claim 1, wherein the first segment of the cytokine domain has length at least 20 or 30 amino acids and is identical to a corresponding segment of human IL-1β.

10. The protein of claim 1, wherein the cytokine domain comprises:

(a) sequences that are identical to beta strands β2, β3, β10 and β11 of human IL-1Ra and sequences that are identical to beta strands β4, β6, β7, and β8 of human IL-1β; or

(b) one or more of β1β2, β2β3, β8β9, β10β11, and β11β12 loops that are at least 90% identical to corresponding loops from human IL-1Ra.

11. The protein of claim 1, wherein the cytokine domain comprises at least two discontinuous segments of length at least 20 amino acids that are at least 90% identical to respective corresponding segments from human IL-1β.

12. The protein of claim 10, wherein the two discontinuous segments are:

(a) identical to respective corresponding segments from human IL-1β; or

(b) are between 25-40 amino acids in length.

13. The protein of claim 11 or 12, wherein amino acids not in the two discontinuous segments are at least 90% identical to human IL-1Ra.

14. The protein of any one of claims 1 to 13, wherein the cytokine domain is 148-160 or 150-156 amino acids in length.

15. The protein of any one of claims 1 to 14, wherein the protein consists of a single polypeptide chain that is 150-160 amino acids in length.

16. The protein of claim 1, wherein at least residues 11-41 and 120-147 (according to human IL-1β numbering) are collectively at least 90% identical to corresponding residues in human IL-1Ra.

17. The protein of claim 2, wherein

(a) at least residues 1-6, 45-61 and 148-153 (according to human IL-1β numbering) are collectively at least 90% identical to corresponding residues in human IL-1β; or

(b) at least residues 1-8, 42-120, and 148-153 (according to human IL-1β numbering) are collectively at least 90% identical to corresponding residues in human IL-1β.

18. The protein of any one of claims 1 to 17, wherein the cytokine domain has greater thermostability than human IL-1β and human IL-1Ra in a physiological buffer, and optionally wherein the cytokine domain has a Tm at least 2°C greater, e.g. between 5-12°C greater, than the Tm of human IL-1β and human IL-1Ra at a concentration of about 0.5 mg/ml.

19. The protein of claim 18, wherein the cytokine domain comprises the following pairs of residues:

(i) E44 from human IL-1Ra and K65 from human IL-1β;

(ii) R14 from human IL-1Ra and Q149 from human IL-1β; and

(iii) S152 from human IL-1β and K45 from human IL-1Ra.

20. The protein of any one of claims 1 to 19, wherein the chimeric cytokine domain comprises:

(i) at least two, three, or four discontinuous segments, each of length at least at least 5, 6, 7, 10, 15, or 20 amino acids and having at least 90, 95, 96, 97, 98, 99, or 100% amino acid identity with corresponding segments of the first IL-1 family cytokine; and

(ii) amino acids at the remaining positions that are not in the discontinuous segments which are at least 90, 95, or 100% identical to corresponding residues in the second IL-1 family cytokine.

21. The protein of claim 20, wherein:

(a) the discontinuous segments comprise residues (i) 1-6 and 45-61, (ii) 1-6 and 86-95, (iii) 45-61 and 86-95, (iv) 1-6 and 148-153, (v) 45-61 and 148-153, or (vi) 86-95 and 148-153, according to the numbering of such positions in human IL-1β;

(b) the discontinuous segments comprise residues (i) 1-8, 42-120, and 141 -153, (ii) 1-10, 37-125, and 131-153, or (iii) 1-6, 45-61, 86-95, and 148-153, according to the numbering of such positions in human IL-1β; or

(c) the discontinuous segments comprise residues 1-6, 45-61, 86-95, and 148-153 according to the numbering of such positions in human IL-1β.

22. The protein of claim 20 or 21, wherein the cytokine domain is identical to the second IL-1 family cytokine at the remaining positions that are not in the discontinuous segments.

23. The protein of any one of claims 20 to 22, wherein one or more of the borders of the discontinuous segments are located at positions wherein the first and second IL-1 family cytokines have the same amino acids.

24. The protein of any one of claims 1 to 23, wherein the protein is identical to the first IL-1 family cytokine at at least 50 positions and is identical to the second IL-1 family cytokine at at least 50 positions.

25. An isolated protein comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99%, or 100% identical to P05 (SEQ ID NO: 21), P01 (SEQ ID NO: 17), P02 (SEQ ID NO: 18), P03 (SEQ ID NO: 19), P04 (SEQ ID NO: 20), P06 (SEQ ID NO: 23), or P07 (SEQ ID NO: 24).

26. The protein of claim 25, comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99%, or 100% identical to P05 (SEQ ID NO: 21).

27. The protein of claim 26, wherein the protein is P05 (SEQ ID NO: 21).

28. A pharmaceutical composition comprising a protein according to any of the preceding claims optionally wherein the pharmaceutical composition is

(a) a topical pharmaceutical composition; or

(b) an ophthalmic pharmaceutical composition

29. The pharmaceutical composition of claim 28 that is aqueous and comprises the protein at a concentration of between 0.001 - 5%.

30. The pharmaceutical composition of claim 28 for use as a medicament.

31. Use of the pharmaceutical composition of claim 28 in the manufacture of a medicament for treating a subject who has dry eye disease or disorder, allergic conjunctivitis, allergic rhinitis, or rheumatoid arthritis, wherein the composition antagonizes IL-1RI receptor signaling activity.

32. An isolated nucleic acid comprising a sequence encoding the protein of any of claims 1 to 27.

33. An isolated nucleic acid vector comprising the nucleic acid of claim 32, wherein the sequence is operably linked to a transcription control sequence.

34. A recombinant host cell comprising a recombinant nucleic acid encoding the protein of any of claims 1 to 27, optionally wherein the host cell is an *E. coli* host cell.

What is claimed is:

1. An isolated protein that comprises a chimeric interleukin-1 (IL-1) family cytokine domain wherein at least a first segment of the domain is at least 20 amino acids in length and has at least 80% amino acid identity to a corresponding segment of a first IL-1 family cytokine, and

at least a second segment of the domain is at least 20 amino acids in length and has at least 80% amino acid identity to a corresponding segment of a second IL-1 family cytokine.

2. The protein of claim 1 wherein the first and second IL-1 family cytokines are selected from the group consisting of IL-1β, IL-1α, and IL-1Ra.

3. The protein of claim 2 wherein the first IL-1 family cytokine is IL-1β and the second IL-1 family cytokine is IL-1Ra.

4. The protein of claim 2 wherein the protein binds to IL1 receptor I and inhibits IL-1 receptor I activity.

5. The protein of claim 2 wherein the first segment of the cytokine domain has length at least 20 or 30 amino acids and is identical to a corresponding segment of IL-1β.

6. The protein of claim 2 wherein the cytokine domain comprises Site A residues that are at least 80% identical to corresponding residues in IL-1Ra and Site B residues that are at least 80% identical to corresponding residues in IL-1β.

7. The protein of claim 3 wherein the cytokine domain includes (a) amino acids identical to IL-1Ra at the following positions ARG11, SER13, GLN14, GLN15, GLU25, LYS27, LEU29, HIS30, LEU31, GLN32, GLY33, GLN34, ASP35, MET36, GLN38, GLN39, ALA127, GLU128, ASN129, MET130, and GLN141 (according to the numbering of IL-1β) and

(b) amino acids identical to IL-1β at the following positions: ALA1, PRO2, VAL3, ARG4, LEU6, PHE46, GLN48, GLU51, SER52, ASN53, LYS55, ILE56, PRO57, LYS92,

LYS93, LYS94, LYS103, GLU105, ASN108, GLN149, PHE150, and SER152 (according to the numbering of IL-1β).

8. The protein of claim 2 wherein the cytokine domain comprises sequences that are identical to beta strands β2, β3, β10 and β11 of IL-1Ra and sequences that are identical to beta strands β4, β6, β7, and β8 of IL-1β.

9. The protein of claim 2 wherein one or more of the β1β2, β2β3, β8β9, β10β11, and β11β12 loops are at least 90% identical to corresponding loops from IL-1Ra.

10. The protein of claim 2 wherein the cytokine domain comprises at least two discontinuous segments of length at least 20 amino acids that are at least 90% identical to respective corresponding segments from IL-1β.

11. The protein of claim 10 wherein the two discontinuous segments are identical to respective corresponding segments from IL-1β.

12. The protein of claim 10 wherein the two discontinuous segments are between 25-40 amino acids in length.

13. The protein of claims 10, 11, or 12, wherein amino acids not in the two discontinuous segments are at least 90% identical to IL-1Ra.

14. The protein of claim 2 wherein the protein consists of a single polypeptide chain that is 150-160 amino acids in length.

15. The protein of claim 2 wherein the cytokine domain is identical to the first IL-1 family cytokine at at least 50 positions and is identical to the second IL-1 family cytokine at at least 50 positions.

16. The protein of claim 2 wherein at least residues 11-41 and 120-147 (according to IL-1β numbering) are collectively at least 90% identical to corresponding residues in IL-1Ra.

17. The protein of claim 3 wherein at least residues 1-6, 45-61 and 148-153 (according to IL-1β numbering) are collectively at least 90% identical to corresponding residues in IL-1β.

18. The protein of claim 3 wherein at least residues 1-8, 42-120, and 148-153 (according to IL-1β numbering) are collectively at least 90% identical to corresponding residues in IL-1β.

19. The protein of claim 3 wherein the cytokine domain is at least 80% identical to P01, P02, P03, P04, or P05.

20. The protein of claim 19 wherein the cytokine domain is at least 90% identical to P01, P02, P03, P04, or P05.

21. The protein of claim 20 wherein the cytokine domain is at least 95% identical to P01, P02, P03, P04, or P05.

22. The protein of claim 21 wherein the cytokine domain is identical to P01, P02, or P03.

23. The protein of claim 21 wherein the cytokine domain is identical to P04.

24. The protein of claim 21 wherein the cytokine domain is identical to P05.

25. The protein of claim 2 wherein the cytokine domain has greater thermostability than IL-1β and IL-1Ra.

26. The protein of claim 2 wherein the cytokine domain has a T_m at least 2 degrees greater than IL-1β and IL-1Ra.

27. The protein of claim 3 wherein the protein has an IC50 less than 10 ng/ml for inhibition of IL-1β (at 0.1 ng/ml) in a cellular signaling assay.

28. The protein of claim 3 wherein the protein binds to IL-1RI with a higher affinity KD, a slower dissociation rate, and/or a faster association rate than human IL-1Ra.

29. The protein of claim 3 wherein the cytokine domain comprises one or more of the following:

(a) Site A:

i. Site A residues that are at least 80% identical to corresponding residues in a first parental cytokine domain;

ii. Extended Site A residues that are at least 80% identical to corresponding residues in a first parental cytokine domain;

iii. Site A segments A1 and A2 that are at least 80% identical to corresponding segments of a first parental cytokine domain; or

iv. a Site A region that is at least 80% identical to corresponding regions of a first parental cytokine domain;

(b) Site B:

i. Site B residues that are at least 80% identical to corresponding residues in a second parental cytokine domain;

ii. Extended Site B residues that are at least 80% identical to corresponding residues in a second parental cytokine domain;

iii. Site B segments B1, B2, and B3 that are at least 80% identical to corresponding segments of a second parental cytokine domain; or

iv. a Site B region that is at least 80% identical to corresponding regions of a second parental cytokine domain.

30. An isolated IL-1 inhibitor comprising an IL-1 family cytokine domain that binds to IL-1RI and comprises

(i) a C1 segment that is at least 70% identical to corresponding residues in IL-1Ra, and

(ii) Site A or Site B residues that are at least 80% identical to corresponding residues in IL-1β, IL-1α, or IL-1Ra, and

wherein the domain is between 40% - 90% identical to IL-1Ra.

31. The IL-1 inhibitor of claim 30 wherein the C1 segment is at least 80% identical to corresponding residues in IL-1Ra.

32. The IL-1 inhibitor of claim 30 wherein the C1 segment is identical to corresponding residues in IL-1Ra.

33. The IL-1 inhibitor of claim 30 wherein the D2 segment is at least 80% identical to corresponding residues in IL-1Ra.

34. The IL-1 inhibitor of claim 30 wherein the A1 and A2 segments are collectively at least 80% identical to corresponding residues in IL-1Ra.

35. The IL-1 inhibitor of claim 30 wherein the B1, B2, and B3 segments are at least 80% identical to corresponding residues in IL-1β.

36. The IL-1 inhibitor of claim 30 that inhibits signaling by IL-1β.

37. The IL-1 inhibitor of claim 30 that binds to IL-1RI with an affinity of less than 1 nM.

38. An isolated receptor binding protein that comprises:

(a) amino acids identical to IL-1Ra at the following positions ARG11, SER13, GLN14, GLN15, GLU25, LYS27, LEU29, HIS30, LEU31, GLN32, GLY33, GLN34, ASP35, MET36, GLN38, GLN39, ALA127, GLU128, ASN129, MET130, and GLN141 (according to the numbering of IL-1β) and

(b) amino acids identical to IL-1β at the following positions: ALA1, PRO2, VAL3, ARG4, LEU6, PHE46, GLN48, GLU51, SER52, ASN53, LYS55, ILE56, PRO57, LYS92, LYS93, LYS94, LYS103, GLU105, ASN108, GLN149, PHE150, and SER152 (according to the numbering of IL-1β).

39. The protein of claim 38 that is a chimera of IL-1β and IL-1Ra.

40. The protein of claim 38 that comprises Gln48-Asn53 of IL-1β.

41. The protein of claim 38 that is at least 50% identical to a cytokine other than IL-1β.

42. The protein of claim 38 that comprises residues identical to IL-1β at positions corresponding to Ala1, Pro2, Val3, Arg4 and Leu6.

43. The protein of claim 38 that comprises at least 15 residues identical to IL-1β at positions corresponding to 45-61 of IL-1β (SEQ ID NO:1).

44. The protein of claim 38 that comprises at least 8 residues identical to IL-1β at positions corresponding to 86-95 of IL-1β (SEQ ID NO:1).

45. The protein of claim 38 that comprises at least 5 residues identical to IL-1β at positions corresponding to 148-153 of IL-1β (SEQ ID NO:1).

46. The protein of claim 38 wherein the amino acid positions corresponding to residues 11-36 and 126-130 (according to SEQ ID NO:1) are predominantly identical to IL-1Ra.

47. The protein of claim 38 wherein the amino acid positions corresponding to residues 9-41 and 121-140 (according to SEQ ID NO:1) are predominantly identical to IL-1Ra.

48. A pharmaceutical composition comprising a protein according to any of claims 1-47.

49. A topical pharmaceutical composition comprising a protein according to any of claims 1-47.

50. An ophthalmic pharmaceutical composition comprising a protein according to any of claims 1-47.

51. The pharmaceutical composition of claim 48 that is aqueous and comprises the protein at a concentration of between 0.001 – 5%.

52 Use of a composition according to claim 48 in the manufacture of a medicament to modulate an immune or inflammatory response in a subject.

53. Use of a composition according to claim 48 in the manufacture of a medicament to treat a subject who has or is at risk for a systemic autoimmune disorder.

54. Use of a composition according to claim 48 in the manufacture of a medicament to treat a subject who has or is at risk for rheumatoid arthritis.

55. Use of a composition according to claim 48 in the manufacture of a medicament to treat a subject having or is at risk for dry eye disease or allergic conjunctivitis.

56. An isolated nucleic acid comprising a sequence encoding the protein of any of claims 1 to 47.

57. An isolated nucleic acid vector comprising a sequence encoding the protein of any of claims 1 to 47, wherein the sequence is operably linked to a transcription control sequence.

58. A recombinant host cell comprising a recombinant nucleic acid encoding the protein of any of claims 1 to 47.

59. The host cell of claim 58 that is an *E. coli* host cell.

60. A method of preparing a recombinant protein, the method comprising

culturing the host cell of claim 58 under conditions that permit expression of the recombinant protein;

purifying the recombinant protein from cell lysate or cell media; and

formulating the recombinant protein for administration to a subject.

61. An isolated protein comprising a chimeric IL-1 family cytokine domain comprising at least two discontinuous segments of length at least six amino acids and having at least 80% identity to corresponding segments of a first IL-1 family cytokine and

comprising amino acids predominantly from a second IL-1 family cytokine at remaining positions.

62. The protein of claim 61, wherein the discontinuous segments comprises residues 1-6 and 45-61, 1-6 and 86-95, 45-61 and 86-95, 1-6 and 148-153, 45-61 and 148-153, or 86-95 and 148-153, according to the numbering of such positions in IL-1β.

63. The protein of claim 61 wherein the protein comprises three discontinuous segments having amino acids identical to those in corresponding segments of the first IL 1 family cytokine, and those segments include residues 1-8, 42-120, and 141-153.

64. The protein of claim 61 wherein the protein comprises four discontinuous segments having amino acids identical to those in corresponding segments of the first IL 1 family cytokine, and those segments include residues 1-6, 45-61, 86-95, and 148-153.

65. The protein of claim 61 wherein the protein comprises three discontinuous segments having amino acids identical to those in corresponding segments of the first IL 1 family cytokine, and those segments include residues 1-10, 37-125, and 131-153.

66. The protein of claim 61 wherein the protein is identical to the second IL-1 family cytokine at the remaining positions.

67. The protein of claim 61 wherein one or more of the borders of the discontinuous segments are located at positions wherein the first and second IL-1 family cytokines have the same amino acids.

68. The protein of claim 61 wherein the protein is identical to the first IL-1 family cytokine at at least 50 positions and is identical to the second IL-1 family cytokine at at least 50 positions.

69. The protein of claim 61 wherein the first and second IL-1 family cytokines are selected from the group consisting of IL-1β, IL-1α, and IL-1Ra.

70. The protein of claim 69 wherein the first IL-1 family cytokine is IL-1β and the second IL-1 family cytokine is IL-1Ra.