

Claims

1. IL-1R-I binding polypeptide, comprising an IL-1R-I binding motif *BM*,
 wherein said binding motif forms part of a three-helix bundle protein domain
 5 and consists of an amino acid sequence selected from:

i) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
 (SEQ ID NO:1686)

10 wherein, independently from each other,

X₂ is selected from A, I, L, T and V;
 X₃ is selected from E and Y;
 X₄ is selected from A, E, I, K, Q, R, T, V and Y;
 15 X₅ is selected from I and V;
 X₆ is selected from Q and Y;
 X₇ is selected from F and M;
 X₁₀ is selected from F and Y;
 X₁₁ is selected from A, D, E, F, G, H, K, L, Q, R, S, T, V and Y;
 20 X₁₆ is selected from N and T;
 X₁₈ is selected from K and R;
 X₂₁ is selected from T and V;
 X₂₅ is selected from I and R;
 X₂₆ is selected from K and S, and
 25 X₂₈ is selected from F and L,

and

ii) an amino acid sequence which has at least 93 % identity to the
 sequence defined in i) provided that X₅ is I or V.

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2. IL-1R-I binding polypeptide, comprising an IL-1R-I binding motif *BM*,
 which motif consists of an amino acid sequence selected from:

i) a sequence from position 8 to position 36 in a sequence selected
 from the group consisting of SEQ ID NO:1-1632, and 1679, such as
 35 the group consisting of SEQ ID NO:20-1632 and 1679,
 and

- ii) an amino acid sequence which has at least 96 % identity to the sequence defined in i) provided that X₅ is I or V.

5 3. IL-1R-I binding polypeptide according to claim 2, wherein sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1206-1632 and 1679, such as the group consisting of SEQ ID NO:1210-1632 and 1679.

10 4. IL-1R-I binding polypeptide according to claim 3, wherein sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1252, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1679, such as the group consisting of SEQ ID NO:1252, 1328, 1435 and 1679.

15 5. IL-1R-I binding polypeptide according to any one of the preceding claims, wherein said IL-1R-I binding motif preferably essentially forms part of two helices with an interconnecting loop, within said three-helix bundle protein domain.

20 6. IL-1R-I binding polypeptide according to claim 5, wherein said three-helix bundle protein domain is selected from bacterial receptor domains, preferably from domains of protein A from *Staphylococcus aureus* or derivatives thereof.

25 7. IL-1R-I binding polypeptide according to any one of the preceding claims, which comprises an amino acid sequence selected from:

 xix) VDAKYAK-[BM]-DPSQSSELLSEAKKLNDSQAPK (SEQ ID NO:1721)

30 wherein [BM] is an IL-1R-I binding motif as defined in any one of the preceding claims; and

 xx) an amino acid sequence which in the sequences flanking the BM has at least 89 % identity to the sequence defined in xix).

35 8. IL-1R-I binding polypeptide according to any one of claims 1-6, which comprises an amino acid sequence selected from:

xxi) AEAKEYAK-[BM]-DPSQSSELLSEAKKLSAQAPK (SEQ ID NO:1709);

wherein [BM] is an IL-1R-I binding motif as defined in any one of claims 1-7; and

5 xxii) an amino acid sequence which in the sequences flanking the BM has at least 89 % identity to the sequence defined in xxi).

9. IL-1R-I binding polypeptide according to claims 7 or 8, wherein sequence xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1-1632, 1667-1668 and 1670-1679; such as the group consisting of SEQ ID NO:20-1632, 1667-1668 and 1670-1679.

10. IL-1R-I binding polypeptide according to claim 9 wherein xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting SEQ ID NO:1206-1632, 1667-1668 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1632, 1667-1668 and 1670-1679.

20 11. IL-1R-I binding polypeptide according to claim 10, wherein sequence xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1252, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1670-1679, such as the group consisting of SEQ ID NO:1252, 1328, 1435, 1672, 1675-1676 and 1679.

12. IL-1R-I binding polypeptide according to any preceding claim, which is capable of blocking the interaction of IL-1R-I with IL-1 cytokines, such as the interaction of IL-1R-I with IL-1 α and/or IL-1 β , and/or which is 30 capable of binding to IL-1R-I such that the K_D value of the interaction is at most 1×10^{-6} M, such as at most 1×10^{-7} M, such as at most 1×10^{-8} M, such as at most 1×10^{-9} M, such as at most 9×10^{-10} .

13. Fusion protein or conjugate comprising 35 - a first moiety consisting of an IL-1R-I binding polypeptide according to any preceding claim; and

- a second moiety consisting of a polypeptide having a desired biological activity, preferably an *in vivo* half-life increasing activity such that said second moiety increases *in vivo* half-life of the fusion protein or conjugate.

5 14. Fusion protein or conjugate according to claim 13, wherein said second moiety is selected from the group consisting of the albumin binding domain of streptococcal protein G or a derivative thereof; serum albumin; an Fc portion of an antibody, such as an IgG1 Fc or an IgG4 Fc; and transferrin.

10 15. Fusion protein or conjugate according to any one of claims 13-14, comprising a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1639-1658 and 1734-1737, such as from the group consisting of SEQ ID NO:1648-1654 and 1734-1737.

15 16. Composition comprising an IL-1R-I binding polypeptide, fusion protein, or conjugate according to any one of claims 1-15 and at least one pharmaceutically acceptable excipient or carrier.

20 17. IL-1R-I binding polypeptide, fusion protein or conjugate according to any one of claims 1-15 or a composition according to claim 16 for use as a medicament, a diagnostic agent and/or a prognostic agent.

25 18. Use of an IL-1R-I binding polypeptide, fusion protein, conjugate or composition according to any one of claims 1-16 in the manufacture of a medicament for treatment, prognosis or diagnosis of an IL-1R-I related disorder, wherein said IL-1R-I related disorder is selected from the group consisting of inflammatory disease, auto-inflammatory syndromes, autoimmune disease, infectious disease, cardiovascular disease, ischaemic disease, cancer and diabetes.

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