

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 1, wherein sequence i) fulfills at least five, such as at least six, at least seven, at least eight, at least nine or all of the ten conditions I-X:~~

~~I. — X₃ is E;~~

~~II. — X₅ is selected from I and V;~~

10 ~~III. — X₆ is selected from Q and Y;~~

~~IV. — X₇ is selected from F and M;~~

~~V. — X₁₀ is selected from F and Y;~~

~~VI. — X₁₈ is selected from K and R;~~

~~VII. — X₂₁ is T;~~

15 ~~VIII. — X₂₅ is R;~~

~~IX. — X₂₆ is selected from K and S; and~~

~~X. — X₂₈ is selected from F and L.~~

20 ~~43.~~ 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.

25 ~~54.~~ IL-1R-I binding polypeptide according to claim ~~43~~, 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.

30 ~~65.~~ 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.

35 ~~76.~~ IL-1R-I binding polypeptide according to claim ~~65~~, 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.

87. IL-1R-I binding polypeptide according to any one of the preceding
5 claims, which comprises an amino acid sequence selected from:
xix) VDAKYAK-[BM]-DPSQSSELLSEAKKLNDSQAPK (SEQ ID
NO:1721)

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

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

98. IL-1R-I binding polypeptide according to any one of claims 1-76,
which comprises an amino acid sequence selected from:
15 xxi) AEAKYAK-[BM]-DPSQSSELLSEAKKLSESQAPK (SEQ ID
NO:1709);

wherein [BM] is an IL-1R-I binding motif as defined in any one of claims 1-87; and

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

109. IL-1R-I binding polypeptide according to claims 87 or 98, 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,
25 1667-1668 and 1670-1679; such as the group consisting of SEQ ID NO:20-
1632, 1667-1668 and 1670-1679.

110. IL-1R-I binding polypeptide according to claim 109 wherein xix)
or xxi) corresponds to the sequence from position 1 to position 58 in a
30 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.

1211. IL-1R-I binding polypeptide according to claim 110, wherein
35 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.

5 ~~13~~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 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} .

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~~14~~13. Fusion protein or conjugate comprising
 - 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
 15 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.

~~15~~14. Fusion protein or conjugate according to claim ~~14~~13, wherein said second moiety is selected from the group consisting of the albumin
 20 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.

~~16~~15. Fusion protein or conjugate according to any one of claims ~~14~~13-
 25 ~~15~~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.

~~17~~16. Composition comprising an IL-1R-I binding polypeptide, fusion
 30 protein, or conjugate according to any one of claims 1-~~16~~15 and at least one pharmaceutically acceptable excipient or carrier.

~~18~~17. IL-1R-I binding polypeptide, fusion protein or conjugate
 according to any one of claims 1-~~16~~15 or a composition according to claim
 35 ~~17~~16 for use as a medicament, a diagnostic agent and/or a prognostic agent.

- | ~~19~~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
- 5 consisting of inflammatory disease, auto-inflammatory syndromes, autoimmune disease, infectious disease, cardiovascular disease, ischaemic disease, cancer and diabetes.