

Claims

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

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- i) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
(SEQ ID NO:1686)

wherein, independently from each other,

10

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;

X₅ is selected from I and V;

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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;

X₁₆ is selected from N and T;

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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

X₂₈ is selected from F and L,

25

and

- ii) an amino acid sequence which has at least 93 % identity to the sequence defined in i).

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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) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
(SEQ ID NO:1686)

wherein, independently from each other,

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X₂ is selected from A, E, F, H, I, L, Q, S, T and V;

X₃ is selected from A, D, E, F, H, I, K, L, Q, R, S, T, V, W and Y;

- X₄ is selected from A, D, E, F, H, I, K, L, N, Q, R, S, T, V, W and Y;
 X₅ is selected from A, I and V;
 X₆ is selected from H, Q, R, and Y;
 X₇ is selected from A, D, E, F, G, H, I, L, M, Q, S, V, W and Y;
 5 X₁₀ is selected from F and Y;
 X₁₁ is selected from A, D, E, F, G, H, I, K, L, N, Q, R, S, T, V, W and Y;
 X₁₆ is selected from N and T;
 X₁₈ is selected from K and R;
 X₂₁ is selected from T and V;
 10 X₂₅ is selected from I and R;
 X₂₆ is selected from K and S, and
 X₂₈ is selected from F and L,
 and
- 15 ii) an amino acid sequence which has at least 96 % identity to the
 sequence defined in i) provided that X₅ is I or V.

3. IL-1R-I binding polypeptide according to claim 1 or 2, wherein
 sequence i) fulfills at least five, such as at least six, at least seven, at least
 20 eight, at least nine or all of the ten conditions I-X:

- I. X₃ is E;
 II. X₅ is selected from I and V;
 III. X₆ is selected from Q and Y;
 IV. X₇ is selected from F and M;
 25 V. X₁₀ is selected from F and Y;
 VI. X₁₈ is selected from K and R;
 VII. X₂₁ is T;
 VIII. X₂₅ is R;
 IX. X₂₆ is selected from K and S; and
 30 X. X₂₈ is selected from F and L.

4. IL-1R-I binding polypeptide according to any preceding claim,
 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:1-1632,
 35 and 1679, such as the group consisting of SEQ ID NO:20-1632 and 1679.

5. IL-1R-I binding polypeptide according to claim 4, 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.

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6. IL-1R-I binding polypeptide according to claim 5, 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.

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7. IL-1R-I binding polypeptide according to any one of the preceding claims, wherein said IL-1R-I binding motif forms part of a three-helix bundle protein domain, 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.

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8. IL-1R-I binding polypeptide according to claim 7, 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.

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

25 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

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

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

 xxi) AEAKYAK-[BM]-DPSQSSELLSEAKKLSQAPK (SEQ ID NO:1709);

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 wherein [BM] is an IL-1R-I binding motif as defined in any one of claims 1-8; and

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

11. IL-1R-I binding polypeptide according to claims 9 or 10, wherein
5 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 12. IL-1R-I binding polypeptide according to claim 11 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.

15 13. IL-1R-I binding polypeptide according to claim 12, 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
20 as the group consisting of SEQ ID NO:1252, 1328, 1435, 1672, 1675-1676 and 1679.

14. 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,
25 such as the interaction of IL-1R-I with IL-1 α and/or IL-1 β .

15. IL-1R-I binding polypeptide according to any preceding claim 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
30 as at most 1×10^{-9} M, such as at most 9×10^{-10} .

16. IL-1R-I binding polypeptide according to claim 14 or 15, wherein
said IL-1R-I is human IL-1R-I or cynomolgus IL-1R-I, such as human IL-1R-I.

35 17. IL-1R-I binding polypeptide according to any preceding claim in multimeric form, comprising at least two IL-1R-I binding polypeptide monomer units, whose amino acid sequences may be the same or different.

18. Fusion protein or conjugate comprising
- a first moiety consisting of an IL-1R-I binding polypeptide according to any preceding claim; and
 - 5 - a second moiety consisting of a polypeptide having a desired biological activity.

19. Fusion protein or conjugate according to claim 18, wherein said desired biological activity is a therapeutic activity.
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20. Fusion protein or conjugate according to claim 18, wherein said desired biological activity is a binding activity.

21. Fusion protein or conjugate according to claim 18, wherein said
- 15 desired biological activity is a binding activity modifying tissue distribution of said fusion protein or conjugate.

22. Fusion protein or conjugate according to claim 18, wherein said desired biological activity is an *in vivo* half-life increasing activity such that
- 20 said second moiety increases *in vivo* half-life of the fusion protein or conjugate.

23. Fusion protein or conjugate according to claim 18, wherein said second moiety is selected from the group consisting of the albumin binding
- 25 domain of streptococcal protein G or a derivative thereof; serum albumin; an Fc portion of an antibody, and transferrin.

24. Fusion protein or conjugate according to claim 23, wherein said second moiety is an Fc portion of an antibody, such as an IgG1 Fc or an IgG4
- 30 Fc.

25. Fusion protein or conjugate according to claim 24, wherein said Fc is a mutated Fc which relative to an unmutated form of Fc displays improved affinity to FcRn and/or reduced effector response.
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26. Fusion protein or conjugate according to any one of claims 18-25, 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.

27. A polynucleotide encoding a polypeptide or a fusion protein
5 according to any one of claims 1-26.

28. Expression vector comprising a polynucleotide according to claim
27.

29. Host cell comprising an expression vector according to claim 28.
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30. Composition comprising an IL-1R-I binding polypeptide, fusion
protein, or conjugate according to any one of claims 1-26 and at least one
pharmaceutically acceptable excipient or carrier.

31. Composition according to claim 30, further comprising at least one
15 additional active agent, such as an agent selected from an immune response
modifying agent and an anti-cancer agent.

32. Composition according to claim 30 or 31, wherein said fusion
20 protein is a fusion protein according to any one of claims 22-26.

33. IL-1R-I binding polypeptide, fusion protein or conjugate according
to any one of claims 1-26 or a composition according to any one of claims 30-
32 for use as a medicament, a diagnostic agent and/or a prognostic agent.
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34. IL-1R-I binding polypeptide, fusion protein, conjugate or
composition according to claim 33 for use as a medicament.

35. IL-1R-I binding polypeptide, fusion protein, conjugate or
30 composition for use according to any one of claims 33-34, in the treatment,
prognosis or diagnosis of an IL-1R-I related disorder.

36. IL-1R-I binding polypeptide, fusion protein, conjugate or
composition for use according to claim 35, wherein said IL-1R-I related
35 disorder is selected from the group consisting of inflammatory disease, auto-
inflammatory syndromes, autoimmune disease, infectious disease,
cardiovascular disease, ischaemic disease, cancer and diabetes.

37. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to any one of claims 33-36, wherein said IL-1R-I binding polypeptide, fusion protein, conjugate or composition is administered repeatedly within a 24 hour period from disease onset, such as at least two times within a 24 hour period from disease onset, such as at least three times within a 24 hour period from disease onset, such as continuously during 24 hours from disease onset, to a subject in need thereof.
38. Fusion protein, conjugate or composition for use according to any one of claims 33-37, wherein said fusion protein or conjugate is a fusion protein or conjugate according to any one of claims 22-26 and said composition is a composition according to claim 32.
39. Fusion protein, conjugate or composition for use according to claim 38, wherein said fusion protein, conjugate or composition is administered once weekly to a subject in need thereof.