

X₆ is selected from F, H, I, Q, R, T, V and Y;

X₇ is selected from A, D, E, F, G, H, I, L, M, Q, S, T, V, W and Y;

X₁₀ is selected from F and Y;

X₁₁ is selected from A, D, E, F, G, H, I, K, L, M, N, Q, R, S, T, V, W and Y;

X₁₆ is selected from N and T;

X₁₈ is selected from K, R and S;

X₂₁ is selected from Q, T and V;

X₂₅ is selected from I, M, R, V and Y;

X₂₆ is selected from K and S, and

X₂₈ is selected from F, I, L and M,
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.

In one aspect, the present disclosure refers to 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 and consists of an amino acid sequence selected from:

i) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
(SEQ ID NO:1686)

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;

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;

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

X₂₈ is selected from F and L,
and

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

production is the polypeptide having the sequence set out in SEQ ID NO:1658. The hinge region of IgG1 Fc (disclosed in Figure 1 as position 1-16 of SEQ ID NO:1662) may be used to accomplish dimeric forms of IL-1R-I binding polypeptides.

5 Additionally, "heterogenic" fusion polypeptides or proteins, or conjugates, in which an IL-1R-I binding polypeptide as described herein, or a multimer thereof, constitutes a first domain, or first moiety, and the second and further moieties have other functions than binding to IL-1R-I, are also contemplated and fall within the ambit of the present disclosure. The second
10 and further moiety/moieties of the fusion polypeptide or conjugate in such a protein suitably also have a desired biological activity.

 Thus, in a second example of the present disclosure, there is provided a fusion protein or a conjugate, comprising a first moiety consisting of an IL-1R -I binding polypeptide according to the first example, and a second
15 moiety consisting of a polypeptide having a desired biological activity. In another example, said fusion protein or conjugate may additionally comprise further moieties, comprising desired biological activities that can be either the same or different from the biological activity of the second moiety.

 In another aspect, the present disclosure refers to fusion protein or
20 conjugate comprising
- a first moiety consisting of an IL-1R-I binding polypeptide as disclosed herein; and
- a second moiety consisting of a polypeptide having a desired biological activity, preferably an *in vivo* half-life increasing activity such that
25 said second moiety increases *in vivo* half-life of the fusion protein or conjugate.

 Thus, in one example, said IL-1R-I binding polypeptide comprises an IL-1R-I binding motif *BM* as set out in sequence i) or ii); a binding module *BMod* as set out in sequence iii) or iv), or an amino acid sequence as set out
30 in any one of sequences v)-xxiv). In particular, said IL-1R-I binding motifs may correspond to an amino acid sequence from position 8 to 36; said binding modules may correspond to an amino acid sequence from position 7 to position 55; and said sequence xix), xxi), or xxiii) may be selected from the group consisting of sequences selected from SEQ ID NO:s shown in Figure 1
35 and listed above. Preferred examples of IL-1R-I binding polypeptides are disclosed in the first example.

 Non-limiting examples of a desired biological activity comprise a therapeutic activity, a binding activity, and an *in vivo* half-life increasing activity.

40 In one example, said desired biological activity is an *in vivo* half-life increasing activity such that said second moiety increases *in vivo* half-life of the fusion protein or conjugate.

 An *in vivo* half-life increasing activity should in this context be understood as an activity which increases the *in vivo* half-life of the fusion
45 protein or conjugate. The half-life of a first moiety (and possibly additional

- removal of the protecting groups from the reactive side-chains of the polypeptide, and

- folding of the polypeptide in aqueous solution.

5 It should be understood that the IL-1R-I binding polypeptide according to the present disclosure may be useful as a therapeutic, diagnostic or prognostic agent in its own right or as a means for targeting other therapeutic or diagnostic agents, with e.g. direct or indirect effects on IL-1R-I. A direct therapeutic effect may for example be accomplished by inhibiting IL-1R-I signaling.

10 Thus, in another example, there is provided a composition comprising an IL-1R-I binding polypeptide, fusion protein or conjugate as described herein and at least one pharmaceutically acceptable excipient or carrier. In one example, said composition further comprises at least one additional active agent, such as at least two additional active agents, such as at least three additional active agents. Non-limiting examples of additional active agents that may prove useful in such
15 combination are immune response modifying agents and anti-cancer agents as described herein. In one example, said composition comprises a fusion protein or conjugate wherein said desired biological activity is an *in vivo* half-life increasing activity such that said second moiety increases *in vivo* half-life of the fusion protein or conjugate. Examples of moieties providing such half-life increasing activities are
20 disclosed elsewhere herein.

In another aspect, the present disclosure refers to composition comprising an IL-1R-I binding polypeptide, fusion protein, or conjugate as disclosed herein and at least one pharmaceutically acceptable excipient or carrier.

25 Hence, in another example of the present disclosure, there is provided an IL-1R-I binding polypeptide, fusion protein, conjugate or composition as described herein for use as a medicament, a prognostic agent or a diagnostic agent. In one example, said IL-1R-I binding polypeptide is provided for use as a medicament.

30 In another aspect, the present disclosure refers to IL-1R-I binding polypeptide, fusion protein or conjugate as disclosed herein or a composition as disclosed herein for use as a medicament, a diagnostic agent and/or a prognostic agent.

In one example, there is provided an IL-1R-I binding polypeptide,
35 fusion protein or conjugate or composition as described herein, for use as a medicament to modulate IL-1R-I function *in vivo*. As used herein, the term "modulate" refers to changing the activity, such as rendering IL-1R-I function hypomorph, partially inhibiting or fully inhibiting IL-1R-I function.

In one example, there is provided an IL-1R-I binding polypeptide,
40 fusion protein or conjugate or composition as described herein, for use, in the treatment, prognosis or diagnosis of an IL-1R-I related disorder.

In another aspect, the present disclosure refers to use of an IL-1R-I binding polypeptide, fusion protein, conjugate or composition as disclosed herein in the manufacture of a medicament for treatment, prognosis or
45 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.

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.
 30

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 4. 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 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: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 6. 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 7. IL-1R-I binding polypeptide according to claim 6, 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.

8. 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).

9. IL-1R-I binding polypeptide according to any one of claims 1-7,
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
1-8; 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).

10. IL-1R-I binding polypeptide according to claims 8 or 9, 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.

11. IL-1R-I binding polypeptide according to claim 10 wherein xix) or
xxi) corresponds to the sequence from position 1 to position 58 in a sequence
30 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.

12. IL-1R-I binding polypeptide according to claim 11, 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.

13. IL-1R-I binding polypeptide according to any preceding claim,
5 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} .

10

14. 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. Fusion protein or conjugate according to claim 14, wherein said second moiety is selected from the group consisting of the albumin binding
20 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. Fusion protein or conjugate according to any one of claims 14-15, comprising a polypeptide having an amino acid sequence selected from the
25 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. Composition comprising an IL-1R-I binding polypeptide, fusion protein, or conjugate according to any one of claims 1-16 and at least one
30 pharmaceutically acceptable excipient or carrier.

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

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19. 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
5 disease, cancer and diabetes.