

Yet another example of an IL-1 receptor antagonizing antibody, denoted 2D8 is described in WO 2005/023872.

The unpredictable and chronic nature of inflammatory diseases, as well as a high unmet medical need, warrants the development of new modes of treatment. Since tissue penetration rate is negatively associated with the size of the molecule, relatively large antibody molecules inherently have poor tissue distribution and penetration capacity.

Thus, the use of antibodies, or other large molecule drugs, is not always optimal for therapy and there is continued need for provision of agents with a high affinity for the IL-1 receptor.

Summary

It is an object of the present disclosure to provide new IL-1R-I binding agents, which could for example be used for therapeutic, prognostic and diagnostic applications.

It is an object of the present disclosure to provide a molecule allowing for efficient therapy targeting various forms of inflammatory, autoinflammatory and autoimmune diseases.

It is furthermore an object of the present disclosure to provide a molecule suitable for prognostic and diagnostic applications.

These and other objects, which are evident to the skilled person from the present disclosure, are met by different examples of the disclosure as claimed in the appended claims and as generally disclosed herein.

Thus, in the first example of the disclosure, there is provided an IL-1R-I binding polypeptide, comprising an IL-1R-I binding motif *BM*, which motif consists of an amino acid sequence selected from:

i) $EX_2X_3X_4X_5X_6X_7EIX_{10}X_{11}LPNLX_{16}RX_{18}QYX_{21}AFIX_{25}X_{26}LX_{28}D$
(SEQ ID NO:1686)

wherein, independently from each other,

X_2 is selected from A, D, E, F, H, I, L, Q, S, T and V;
 X_3 is selected from A, D, E, F, H, I, K, L, N, Q, R, S, T, V, W and Y;
 X_4 is selected from A, D, E, F, H, I, K, L, M, N, Q, R, S, T, V, W and Y;
 X_5 is selected from A, I and V;

- 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.
- 15 In one aspect, the present disclosure refers to 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)
- 20 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.

The above definition of a class of sequence related, IL-1R-I binding polypeptides is based on a statistical analysis of a number of random polypeptide variants of a parent scaffold, that were selected for their interaction with IL-1R-I in several different selection experiments. The
5 identified IL-1R-I binding motif, or "*BM*", corresponds to the target binding region of the parent scaffold, which region constitutes two alpha helices within a three-helical bundle protein domain. In the parent scaffold, the varied amino acid residues of the two *BM* helices constitute a binding surface for interaction with the constant Fc part of antibodies. In the present disclosure, the random
10 variation of binding surface residues and subsequent selection of variants have replaced the Fc interaction capacity with a capacity for interaction with IL-1R-I.

As the skilled person will realize, the function of any polypeptide, such as the IL-1R-I binding capacity of the polypeptide of the present disclosure, is
15 dependent on the tertiary structure of the polypeptide. It is therefore possible to make minor changes to the sequence of amino acids in a polypeptide without affecting the function thereof. Thus, the disclosure encompasses modified variants of the IL-1R-I binding polypeptide, which have retained IL-1R-I binding characteristics.

20 In this way, also encompassed by the present disclosure is an IL-1R-I binding polypeptide comprising an amino acid sequence with 96 % or greater

identity to a polypeptide as defined in i). Thus, certain sequence variants of the sequence defined in i) are encompassed by the above definition under the proviso that within such sequence variants X_5 is I or V. For example, it is possible that an amino acid residue belonging to a certain functional grouping of amino acid residues (e.g. hydrophobic, hydrophilic, polar etc) could be exchanged for another amino acid residue from the same functional group.

In some examples, such changes may be made in any position of the sequence of the IL-1R-I binding polypeptide as disclosed herein. In other examples, such changes may be made only in the non-variable positions, also denoted scaffold amino acid residues. In such cases, changes are not allowed in the variable positions, i.e. positions denoted with an "X" in sequence i).

The term "% identity", as used throughout the specification, may for example be calculated as follows. The query sequence is aligned to the target sequence using the CLUSTAL W algorithm (Thompson *et al*, 1994, Nucleic Acids Research, 22: 4673-4680). A comparison is made over the window corresponding to the shortest of the aligned sequences. The shortest of the aligned sequences may in some instances be the target sequence. In other instances, the query sequence may constitute the shortest of the aligned sequences. The amino acid residues at each position are compared and the percentage of positions in the query sequence that have identical correspondences in the target sequence is reported as % identity.

As used herein " X_n " and " X_m " are used to indicate amino acids in positions n and m in the sequence i) as defined above, wherein n and m are integers which indicate the position of an amino acid within said sequence as counted from the N-terminal end of said sequence. For example, X_3 and X_7 indicate the amino acid in position three and seven, respectively, from the N-terminal end of sequence i).

In examples according to the first example, there are provided polypeptides wherein X_n in sequence i) is independently selected from a group of possible residues according to Table 1. The skilled person will appreciate that X_n may be selected from any one of the listed groups of possible residues and that this selection is independent from the selection of amino acids in X_m , wherein $n \neq m$. Thus, any of the listed possible residues in position X_n in Table 1 may be independently combined with any of the listed possible residues in any other variable position in Table 1.

- The skilled person will appreciate that Table 1 is to be read as follows:
- In one example according to the first example, there is provided a polypeptide wherein amino acid residue “X_n” in sequence i) is selected from “Possible residues”. Thus, Table 1 discloses several specific and individualized
- 5 examples of the first example of the present disclosure. For example, in one example according to the first example, there is provided a polypeptide wherein X₄ in sequence i) is selected from A, D, E, I, K, Q, S and V, and in another example according to the first example, there is provided a polypeptide wherein X₄ in sequence i) is selected from A, E, I, K, Q and V.
- 10 For avoidance of doubt, the listed examples may be freely combined in yet other examples. For example, one such combined example is a polypeptide in which X₄ is selected from A, E, I, K, Q and V, while X₆ is selected from H, Q, T and Y, and X₁₁ is selected from H, R and Y.

Table 1: Examples of the first example of the present disclosure

15

Residue X _n	Possible residues
X ₂	A, E, F, H, I, L, Q, S, T, V
X ₂	A, F, H, I, L, Q, S, T, V
X ₂	A, H, I, L, Q, S, T, V
X ₂	A, H, I, L, Q, T, V
X ₂	A, H, I, L, T, V
X ₂	A, F, I, L, T, V
X ₂	A, I, L, T, V
X ₂	A, I, T, V
X ₂	A, I, L, T
X ₂	A, L, T, V
X ₂	A, I, L, V
X ₂	I, L, T, V
X ₂	A, I, T
X ₂	A, I, V
X ₂	A, T, V
X ₂	I, T, V

X ₂	I, L, T
X ₂	I, L, V
X ₂	L, T, V
X ₂	I, V
X ₂	I, L
X ₂	I, T
X ₂	I, V
X ₂	L, T
X ₂	L, V
X ₂	T, V
X ₂	A, I
X ₂	A, T
X ₂	A, V
X ₂	L
X ₂	T
X ₂	V
X ₂	I
X ₂	A
X ₃	A, D, E, F, H, I, K, L, Q, R, S, T, V, W, Y

In one example of the present disclosure there is provided an IL-1R-I binding polypeptide, wherein in i)

- X₂ is selected from A, E, F, H, I, L, Q, S, T and V;
- 5 X₃ is selected from A, D, E, F, H, I, K, L, N, Q, R, S, T, V, W and Y;
- X₄ is selected from A, D, E, F, H, I, K, L, M, N, Q, R, S, T, V, W and Y;
- X₅ is selected from A, I and V;
- X₆ is selected from F, H, Q, R, V and Y;
- X₇ is selected from A, D, E, F, G, H, I, L, M, Q, S, T, V, W and Y;
- 10 X₁₀ is selected from F and Y;
- X₁₁ is selected from A, D, E, F, G, H, I, L, M, Q, 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;
- 15 X₂₅ is selected from I and R;
- X₂₆ is selected from K and S, and
- X₂₈ is selected from F and L.

In one example of the present disclosure there is provided an IL-1R-I binding polypeptide, wherein in i)

- 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;
- 25 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;
- 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;
- 30 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.

In one example of the present disclosure there is provided an IL-1R-I binding polypeptide, wherein in i)

- X₂ is selected from A, I, L, T and V;
- X₃ is selected from E, I, V and Y;
- 5 X₄ is selected from A, D, E, F, H, I, K, L, Q, R, S, T, V, W and Y;
- X₅ is selected from A, I and V;
- X₆ is selected from Q and Y;
- X₇ is selected from F, H, I, L, M, Q, V, W and Y;
- X₁₀ is selected from F and Y;
- 10 X₁₁ is selected from A, D, E, F, G, H, K, L, 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;
- X₂₅ is selected from I and R;
- 15 X₂₆ is selected from K and S, and
- X₂₈ is selected from F and L.

In another example of the present disclosure there is provided an IL-1R-I binding polypeptide, wherein said IL-1R-I binding motif consists of an amino acid sequence selected from a sequence wherein in i)

- 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;
- 25 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;
- 30 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,

35 and an amino acid sequence which has at least 93 % identity to the sequence defined above.

In another example of the present disclosure there is provided an IL-1R-I binding polypeptide, wherein in i)

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

In a more specific example defining a sub-class of IL-1R-I binding polypeptides, sequence i) fulfills at least five 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;
- 25 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;
- VIII. X₂₅ is R;
- 30 IX. X₂₆ is selected from K and S; and
- X. X₂₈ is selected from F and L.

In some examples of an IL-1R-I binding polypeptide according to the first example, sequence i) fulfils at least six of the ten conditions I-X. More specifically, sequence i) may fulfil at least seven of the ten conditions I-X, such as at least eight of the ten conditions I-X, such as at least nine of the ten conditions I-X, such as all of the ten conditions I-X.

In some examples of an IL-1R-I binding polypeptide according to the first example, there is provided an IL-1R-I binding polypeptide, wherein $X_2X_3X_6$ is VEQ or VEY. In some examples there is provided an IL-1R-I binding polypeptide, wherein $X_2X_3X_6$ is IEQ or VEQ. In some examples X_6X_{10} is selected from the group consisting of QF, QY, YF and YY. In some examples X_6X_{10} is QF. In some examples $X_{10}X_{18}$ is selected from the group consisting of FK, FR, YK and YR. In some examples $X_{10}X_{18}$ is FK or FR. In some examples $X_{18}X_{25}X_{28}$ is KRL or RRL. In some examples X_5X_7 is AM, IM or VM. In some examples X_5X_7 is IM or VM.

In one example, X_5 is selected from I and V. As demonstrated in the appended Example 4, the unintentional alteration in position X_5 of the BM resulted in the finding of an IL-1R-I binding polypeptide (Z18557, SEQ ID NO:1205) displaying high affinity for IL-1R-I (see Table 11). The exchange of alanine in this position to valine or isoleucine allows for generation of IL-1R-I binding polypeptides with high affinity for IL-1R-I.

As described in detail in the experimental section to follow, the selection of IL-1R-I binding polypeptide variants has led to the identification of a number of individual IL-1R-I binding motif (*BM*) sequences. These sequences constitute individual examples of sequence i) according to this example. The sequences of individual IL-1R-I binding motifs correspond to amino acid positions 8-36 of the amino acid sequences listed as SEQ ID NOs 1-1632 and 1679 presented in Figure 1. Thus, in one example, of the IL-1R-I binding polypeptide according to this example, 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 and 1679, such as the group consisting of SEQ ID NO:20-1632, and 1679. In one example 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.

In another aspect, the present disclosure refers to 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 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 X_5 is I or V.

In one example sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1205 and 1250-1632.

In one example sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1206-1252 and 1679.

In another example sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of

SEQ ID NO:1253-1632. In another example sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1253-1441 or the group consisting of SEQ ID NO:1442-1632.

In one example, sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:158, 227, 268, 294, 325, 1176, 1205, 1251, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1311, 1324, 1328, 1330, 1331, 1334, 1339, 1340, 1343, 1353, 1361, 1362, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423, 1435, 1471, 1472, 1571, 1594 and 1662, such as from the group consisting of SEQ ID NO:268, 1205, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1324, 1328, 1330, 1331, 1334, 1339, 1340, 1343, 1361, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423 and 1571, such as from the group consisting of SEQ ID NO:1252, 1285, 1298, 1308, 1324, 1328, 1330, 1331, 1340, 1361, 1393, 1415, 1420 and 1421.

In one particular example 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. In one example 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, 1328, 1435 and 1679, such as the group consisting of SEQ ID NO:1252, 1328 and 1679; the group consisting of SEQ ID NO:1252, 1435, 1679; the group consisting of SEQ ID NO:1252 and 1679; or the group consisting of SEQ ID NO:1328 and 1435. In one example, sequence i) corresponds to the sequence from position 8 to position 36 in sequence selected from the group consisting of SEQ ID NO:1252, 1328 and 1435.

Figure 1 thus exemplifies polypeptide variants whose IL-1R-I binding capacity has been verified experimentally (at least by virtue of being isolated in an affinity based assay), which variants have led to the identification of a number of individual IL-1R-I binding motif (*BM*) sequences which constitute individual examples of *BM* which exhibit 93 %, where applicable, or 96 % identity with sequence i).

In some examples of the present disclosure, the *BM* as defined above “forms part of” a three-helix bundle protein domain. This is understood to mean that the sequence of the *BM* is “inserted” into or “grafted” onto the sequence of the original three-helix bundle domain, such that the *BM*

replaces a similar structural motif in the original domain. For example, without wishing to be bound by theory, the *BM* is thought to constitute two of the three helices of a three-helix bundle, and can therefore replace such a two-helix motif within any three-helix bundle. As the skilled person will realize, the replacement of two helices of the three-helix bundle domain by the two *BM* helices has to be performed so as not to affect the basic structure of the polypeptide. That is, the overall folding of the C α backbone of the polypeptide according to this example of the invention is substantially the same as that of the three-helix bundle protein domain of which it forms a part, e.g. having the same elements of secondary structure in the same order etc. Thus, a *BM* according to the present disclosure “forms part” of a three-helix bundle domain if the polypeptide according to this example has the same fold as the original domain, implying that the basic structural properties are shared, those properties e.g. resulting in similar CD spectra. The skilled person is aware of other parameters that are relevant.

In particular examples, the IL-1R-I binding motif (*BM*) thus forms part of a three-helix bundle protein domain. For example, the *BM* may essentially constitute two alpha helices with an interconnecting loop, within said three-helix bundle protein domain. In particular examples, said three-helix bundle protein domain is selected from domains of bacterial receptor proteins. Non-limiting examples of such domains are the five different three-helical domains of Protein A from *Staphylococcus aureus*, such as domain B, and derivatives thereof. In some examples, the three-helical bundle protein domain is a variant of protein Z, which is derived from domain B of staphylococcal Protein A.

In some examples where the IL-1R-I binding polypeptide as disclosed herein forms part of a three-helix bundle protein domain, the IL-1R-I binding polypeptide may comprise a binding module (*BMod*), the amino acid sequence of which is selected from:

iii) K-[*BM*]-DPSQSX_aX_bLLX_cEAKKLX_dX_eX_fQ;
(SEQ ID NO:1687)

wherein

[*BM*] is an IL-1R-I binding motif as defined herein;
X_a is selected from A and S;
X_b is selected from N and E;

X_c is selected from A, S and C;
 X_d is selected from E, N and S;
 X_e is selected from D, E and S;
 X_f is selected from A and S; and

5

- iv) an amino acid sequence which has at least 91 % identity to a sequence defined by iii).

10 In some examples, said polypeptides may beneficially exhibit high structural stability, such as resistance to chemical modifications, to changes in physical conditions and to proteolysis, during production and storage, as well as *in vivo*.

As discussed above, polypeptides comprising minor changes as compared to the above amino acid sequences, which do not largely affect the
 15 tertiary structure and the function of the polypeptides, are also within the scope of the present disclosure. Thus, in some examples, sequence iv) has at least at least 93 %, such as at least 95 %, such as at least 97 % identity to a sequence defined by iii). In particular examples, such minor changes as exemplified above may be present only in the flanking sequence, i.e. the parts
 20 of the sequence flanking the BM in iii) above. In other examples, minor changes can be present in the BM and/or in the flanking sequences.

In one example, X_a in sequence iii) is A.
 In one example, X_a in sequence iii) is S.
 In one example, X_b in sequence iii) is N.
 25 In one example, X_b in sequence iii) is E.
 In one example, X_c in sequence iii) is A.
 In one example, X_c in sequence iii) is S.
 In one example, X_c in sequence iii) is C.
 In one example, X_d in sequence iii) is E.
 30 In one example, X_d in sequence iii) is N.
 In one example, X_d in sequence iii) is S.
 In one example, X_e in sequence iii) is D.
 In one example, X_e in sequence iii) is E.
 In one example, X_e in sequence iii) is S.
 35 In one example, X_dX_e in sequence iii) is selected from EE, ES, SE and SS.

In one example, X_dX_e in sequence iii) is ES.

In one example, X_dX_e in sequence iii) is SE.

In one example, X_f in sequence iii) is A.

In one example, X_f in sequence iii) is S.

5 In one example, in sequence iii), X_a is A; X_b is N; X_c is A and X_f is A.

In one example, in sequence iii), X_a is A; X_b is N; X_c is C and X_f is A.

In one example, in sequence iii), X_a is S; X_b is E; X_c is S and X_f is S.

In one example, in sequence iii), X_a is S; X_b is E; X_c is C and X_f is S.

10 In one example, in sequence iii), X_a is A; X_b is N; X_c is A; X_dX_e is ND and X_f is A.

In one example, in sequence iii), X_a is A; X_b is N; X_c is C; X_dX_e is ND and X_f is A.

In one example, in sequence iii), X_a is S; X_b is E; X_c is S; X_dX_e is ND and X_f is S.

15 In one example, in sequence iii), X_a is S; X_b is E; X_c is C; X_dX_e is ND and X_f is S.

In one example, in sequence iii), X_a is A; X_b is N; X_c is A; X_dX_e is SE and X_f is A.

20 In one example, in sequence iii), X_a is A; X_b is N; X_c is C; X_dX_e is SE and X_f is A.

In one example, in sequence iii), X_a is S; X_b is E; X_c is S; X_dX_e is SE and X_f is S.

In one example, in sequence iii), X_a is S; X_b is E; X_c is C; X_dX_e is SE and X_f is S.

25 In one example, in sequence iii), X_a is A; X_b is N; X_c is A; X_dX_e is ES and X_f is A.

In one example, in sequence iii), X_a is A; X_b is N; X_c is C; X_dX_e is ES and X_f is A.

30 In one example, in sequence iii), X_a is S; X_b is E; X_c is S; X_dX_e is ES and X_f is S.

In one example, in sequence iii), X_a is S; X_b is E; X_c is C; X_dX_e is ES and X_f is S.

In one example, sequence iii) or iv) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1-1638 and 1667-1670.

In yet a further example, sequence iii) corresponds to the sequence
 5 from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1-1638, 1667-1668 and 1670-1679; such as the group consisting of SEQ ID NO:20-1638 and 1670-1679. In one example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1206-1638 and
 10 1670-1679, such as the group consisting of SEQ ID NO:1206-1632 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1638 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1632 and 1670-1679.

In one example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of
 15 SEQ ID NO:1205, 1250-1632 and 1670-1679.

In one example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1206-1252, 1672 and 1679.

In another example sequence iii) corresponds to the sequence from
 20 position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1253-1632, 1670-1671 and 1673-1678. In another example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1253-1441, 1670-1671 and 1674-1678 or the group consisting of SEQ ID NO:1442-1632
 25 and 1673.

In one example, sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:158, 227, 268, 294, 325, 1176, 1205, 1251, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1311, 1324, 1328, 1330, 1331, 1334, 1339, 1340,
 30 1343, 1353, 1361, 1362, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423, 1435, 1471, 1472, 1571, 1594, 1662 and 1670-1679, such as from the group consisting of SEQ ID NO:268, 1205, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1324, 1328, 1330, 1331, 1334, 1339, 1340, 1343, 1361, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423, 1571, 1670-
 35 1672, 1674, and 1676-1679, such as from the group consisting of SEQ ID

NO:1252, 1285, 1298, 1308, 1324, 1328, 1330, 1331, 1340, 1361, 1393, 1415, 1420, 1421, 1670-1672, 1674, 1676-1677 and 1679.

In one particular example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group
 5 consisting of SEQ ID NO:1252, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1670-1679. In one example sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1252, 1328, 1435, 1672, 1675-1676 and 1679 such as the group consisting of SEQ ID NO:1252, 1328 and 1679; the group
 10 consisting of SEQ ID NO:1252, 1435 and 1679; or the group consisting of SEQ ID NO:1328 and 1435. In one example, sequence i) corresponds to the sequence from position 7 to position 55 in sequence selected from the group consisting of SEQ ID NO:1252, 1328 and 1435.

In one example, sequence iii) corresponds to the sequence from
 15 position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1672, 1675-1676 and 1679, such as the group consisting of SEQ ID NO:1672 and 1675-1676.

Also, in a further example, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid sequence selected from:

- 20 v) YA-[BMod]-AP; (SEQ ID NO:1688)
 wherein [BMod] is an IL-1R-I binding module as defined herein; and
 vi) an amino acid sequence which has at least 90 % identity to a sequence defined in v).

Alternatively, there is provided an IL-1R-I binding polypeptide, which
 25 comprises an amino acid sequence selected from:

- vii) FN-[BMod]-AP; (SEQ ID NO:1689)
 wherein [BMod] is an IL-1R-I binding module as defined herein; and
 viii) an amino acid sequence which has at least 90 % identity to a sequence defined in vii).

30 In one example there is provided an IL-1R-I binding polypeptide, which comprises an amino acid selected from the group consisting of

- ix) FNK-[BM]-DPSQS ANLLX_c EAKKL NDAQA P; (SEQ ID NO:1690)
 wherein [BM] is an IL-1R-I binding motif as defined above and X_c is selected
 35 from A and C; and

x) an amino acid sequence which has at least 90 % identity to a sequence defined in ix).

In another example, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid selected from the group consisting of

5 xi) FAK-[BM]-DPSQS SELLX_c EAKKL SESQA P; (SEQ ID NO:1691)

wherein [BM] is an IL-1R-I binding motif as defined above and X_c is selected from A, S and C; and

10 xii) an amino acid sequence which has at least 90 % identity to a sequence defined in xi).

In another example, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid selected from the group consisting of

xiii) FAK-[BM]-DPSQS SELLX_c EAKKL NDSQA P; (SEQ ID NO:1692)

15 wherein [BM] is an IL-1R-I binding motif as defined above and X_c is selected from A, S and C;

xiv) an amino acid sequence which has at least 90 % identity to a sequence defined in xiii).

20 In yet another example, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid selected from the group consisting of

xv) YAK-[BM]-DPSQS SELLX_c EAKKL X_dX_eSQA P; (SEQ ID NO:1693)

25 wherein [BM] is an IL-1R-I binding motif as defined above and X_c is selected from A, S and C, X_d is selected from E, N and S, and X_e is selected from D, E and S;

xvi) and an amino acid sequence which has at least 90 % identity to a sequence defined in xv).

30 In yet another example, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid selected from the group consisting of

xvii) KYAK-[BM]-DPSQS SELLX_c EAKKL X_dX_eSQA P; (SEQ ID NO:1694)

wherein *[BM]* is an IL-1R-I binding motif as defined above and X_c is selected from A, S and C, X_d is selected from E, N and S, and X_e is selected from D, E and S;

- xviii) and an amino acid sequence which has at least 90 % identity to
5 a sequence defined in xvii).

As discussed above, polypeptides comprising minor changes as compared to the above amino acid sequences, which do not largely affect the tertiary structure and the function of the polypeptide, also fall within the scope
10 of the present disclosure. Thus, in some examples, sequence vi), viii), x), xii), xiv), xvi) or xviii) may for example be at least 90 %, such as at least 92 %, such as at least 94 %, such as at least 96 %, such as at least 98 % identical to a sequence defined by v), vii), ix), xi), xiii), xv) and xvii), respectively. In particular examples, such minor changes as exemplified above can be
15 present only in flanking sequences, i.e. the parts of the sequences flanking the *BM* in v), vii), ix), xi), xiii), xv) and xviii). In other examples, minor changes can be present in the *BM* and/or in the flanking sequences.

In some examples, the IL-1R-I binding motif may form part of a polypeptide comprising an amino acid sequence selected from:

20	ADNNFNK-[BM]-DPSQSANLLSEAKKLNESQAPK	SEQ ID NO:1695;
	ADNKFNK-[BM]-DPSQSANLLAEAKKLNDQAQPK	SEQ ID NO:1696;
	ADNKFNK-[BM]-DPSVSKEILAEAKKLNDQAQPK	SEQ ID NO:1697;
	ADAQQNNFNK-[BM]-DPSQSTNVLGAEAKKLNESQAPK	SEQ ID NO:1698;
	AQHDE-[BM]-DPSQSANVLGAEAKKLNDQAQPK	SEQ ID NO:1699;
25	VDNKFNK-[BM]-DPSQSANLLAEAKKLNDQAQPK	SEQ ID NO:1700;
	AEAKYAK-[BM]-DPSESSELLSEAKKLNKSQAPK	SEQ ID NO:1701;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNDQAQPK	SEQ ID NO:1702;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNDQAQPK	SEQ ID NO:1703;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLNDQAQPK	SEQ ID NO:1704;
30	AEAKYAK-[BM]-DPSQSSELLSEAKKLNDQAQPK	SEQ ID NO:1705;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLNDQAQPK	SEQ ID NO:1706;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLNDQAQPK	SEQ ID NO:1707;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLNDQAQPK	SEQ ID NO:1708;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1709;
35	AEAKYAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1710;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1711;

	AEAKFAK-[BM]-DPSQSSELLSEAKKLSAQAP	SEQ ID NO:1712;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLSAQAPK	SEQ ID NO:1713;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLESSQAPK	SEQ ID NO:1714;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLESSQAP	SEQ ID NO:1715;
5	AEAKYAK-[BM]-DPSQSSELLAEAKKLESAQAPK	SEQ ID NO:1716;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLSDSQAPK	SEQ ID NO:1717;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLSDSQAP	SEQ ID NO:1718;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLSDSQAPK	SEQ ID NO:1719;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLSDAQAPK	SEQ ID NO:1720;
10	VDACYAK-[BM]-DPSQSSELLSEAKKLNDSDQAPK	SEQ ID NO:1721;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNDADQAPK	SEQ ID NO:1722;
	VDACYAK-[BM]-DPSQSSELLSEAKKLSAQAPK	SEQ ID NO:1723;
	VDACYAK-[BM]-DPSQSSELLAEAKKLSAQAPK	SEQ ID NO:1724;
	VDACYAK-[BM]-DPSQSSELLSEAKKLESSQAPK	SEQ ID NO:1725;
15	VDACYAK-[BM]-DPSQSSELLAEAKKLESAQAPK	SEQ ID NO:1726;
	VDACYAK-[BM]-DPSQSSELLSEAKKLSDSQAPK	SEQ ID NO:1727;
	VDACYAK-[BM]-DPSQSSELLAEAKKLSDSQAPK	SEQ ID NO:1728;
	VDACYAK-[BM]-DPSQSSELLAEAKKLSDAQAPK	SEQ ID NO:1729;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNKAQAPK	SEQ ID NO:1730;
20	AEAKYAK-[BM]-DPSQSSELLAEAKKLNKAQAPK	SEQ ID NO:1731,
	and	
	ADACYAK-[BM]-DPSQSSELLSEAKKLNDSDQAPK	SEQ ID NO:1732,
	wherein [BM] is an IL-1R-I binding motif as defined herein.	

In one example, said IL-1R-I binding polypeptide comprises an amino acid sequence which has at least 89 % identity to any one of the sequences defined above.

In one example, the IL-1R-I binding polypeptide comprises an amino acid sequence selected from:

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

wherein [BM] is an IL-1R-I binding motif as defined herein; and

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

In one example, the IL-1R-I binding polypeptide 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 herein; and

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

In one particular example, said IL-1R-I binding polypeptide comprises
 5 an amino acid sequence selected from the group consisting of SEQ ID NO:1667-1668 and 1670-1679.

In one example, the IL-1R-I binding polypeptide comprises an amino acid sequence selected from:

xxiii) AEAKFAK-*[BM]*-DPSQSSELLSEAKKLSAQAPK (SEQ ID
 10 NO:1711) wherein *[BM]* is an IL-1R-I binding motif as defined herein; and
 xxiv) an amino acid sequence which has at least 89 % identity to the sequence defined in xxiii).

Again, polypeptides comprising minor changes as compared to the above amino acid sequences, which do not largely affect the tertiary structure
 15 and the function of the polypeptide, also fall within the scope of the present disclosure. Thus, in some examples, sequence xx), xxii) or xxiv) may for example be at least 89 %, such as at least 91 %, such as at least 93 %, such as at least 94 %, such as at least 96 %, such as at least 98 % identical to a sequence defined by xix), xxi) or xxiii) respectively. Once again, in particular
 20 examples such minor changes as exemplified above can be present only in the sequences flanking the BM as set out in xix), xxi) or xxiii). In other examples, minor changes can be present in the BM and/or in the flanking sequences.

Sequence xix)-xxiv) in such IL-1R-I binding polypeptide may be
 25 selected from the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1-1638, 1667-1668 and 1670-1679 as presented in Figure 1.

In one example of the IL-1R-I binding polypeptide according to this example, sequence xix), xxi) or xxiii) corresponds to the sequence from
 30 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:20-1638, 1667-1668 and 1670-1679. In one example sequence xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID
 35 NO:1206-1632, 1667-1668 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1632, 1667-1668 and 1670-1679.

In one example sequence xvii), 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:1205, 1250-1632 and 1670-1679.

5 In one example sequence xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1206-1252, 1672 and 1679.

In another example sequence xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1253-1632, 1670-1671 and 1673-1678. In
10 another example sequence xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1253-1441, 1670-1671 and 1674-1678 or the group consisting of 1442-1632 and 1673.

In one example sequence xix), xxi) or xxiii) corresponds to the
15 sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:158, 227, 268, 294, 325, 1176, 1205, 1251, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1311, 1324, 1328, 1330, 1331, 1334, 1339, 1340, 1343, 1353, 1361, 1362, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423, 1435, 1471, 1472, 1571, 1594, 1662 and
20 1670-1679, such as from the group consisting of SEQ ID NO:268, 1205, 1252, 1270, 1284, 1285, 1298, 1307, 1308, 1324, 1328, 1330, 1331, 1334, 1339, 1340, 1343, 1361, 1364, 1367, 1368, 1375, 1393, 1415, 1420, 1421, 1422, 1423, 1571, 1670-1672, 1674 and 1676-1679, such as from the group consisting of SEQ ID NO:1252, 1285, 1298, 1308, 1324, 1328, 1330, 1331,
25 1340, 1361, 1393, 1415, 1420, 1421, 1670-1672, 1674, 1676-1677 and 1679.

In one particular example sequence xix), xxi) or xxiii) 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. In one example sequence xix), xxi) or xxiii)
30 corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1252, 1328, 1435 1672, 1675-1676 and 1679, such as the group consisting of SEQ ID NO:1252, 1328 and 1679; the group consisting of SEQ ID NO:1252, 1435 and 1679; or the group consisting of SEQ ID NO:1328 and 1435. In one example, sequence
35 xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1252, 1328 and 1435.

In one example, sequence xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1672, 1675-1676 and 1679, such as from the group consisting of SEQ ID NO:1672, 1675 and 1676.

5

In one example, said IL-1R-I binding polypeptide has a melting temperature of above 45 °C.

Binding of a polypeptide as defined herein to IL-1R-I may interfere with signaling via IL-1R-I either *in vivo* or *in vitro*. Thus, in one example, there is provided an IL-1R-I binding polypeptide as defined herein which is capable of blocking IL-1R-I dependent signaling.

The half maximal inhibitory concentration (IC_{50}) is a measure of the effectiveness of a substance for inhibiting a specific quantifiable biological or biochemical function. This quantitative measure indicates how much of a particular substance is needed to inhibit a specific biological function by 50 % and is commonly used in the art. In one particular example, there is provided an IL-1R-I binding polypeptide as defined herein capable of blocking IL-1R-I signaling such that the half maximal inhibitory concentration (IC_{50}) of the blocking is at most 1×10^{-7} M, such as at most 5×10^{-8} M, such as at most 2×10^{-8} M, such as at most 1×10^{-8} M, such as at most 5×10^{-9} M, such as at most 2×10^{-9} M, such as at most 1×10^{-9} M, such as at most 5×10^{-10} M, such as at most 4×10^{-10} M, such as at most 3×10^{-10} M. In one example, the half maximal inhibitory concentration (IC_{50}) of the blocking is between 1×10^{-15} M and 1×10^{-7} M, such as between 1×10^{-15} M and 1×10^{-8} M, such as between 1×10^{-15} M and 1×10^{-9} M, such as between 1×10^{-15} M and 1×10^{-10} M, such as between 1×10^{-15} M and 1×10^{-11} M, such as between 1×10^{-15} M and 1×10^{-12} M.

The terms "IL-1R-I binding" and "binding affinity for IL-1R-I" as used in this specification refer to a property of a polypeptide which may be tested for example by ELISA, Biolayer Interferometry (BLI) or the use of surface plasmon resonance (SPR) technology. For example as described in the examples below, IL-1R-I binding affinity may be tested in an experiment in which samples of the polypeptide are captured on antibody-coated ELISA plates and biotinylated IL-1R-I is added followed by streptavidin-conjugated HRP. TMB substrate is added and the absorbance at 450 nm is measured using a multi-well plate reader, such as Victor³ (Perkin Elmer). The skilled person may then interpret the results obtained by such experiments to

establish at least a qualitative measure of the binding affinity of the polypeptide for IL-1R-I. If a quantitative measure is desired, for example to determine the EC_{50} value (the half maximal effective concentration) for the interaction, ELISA may also be used. The response of the polypeptide against a dilution series of biotinylated IL-1R-I is measured using ELISA as described above. The skilled person may then interpret the results obtained by such experiments, and EC_{50} values may be calculated from the results using for example GraphPad Prism 5 and non-linear regression.

IL-1R-I binding affinity may also be tested in an experiment in which IL-1R-I, or a fragment thereof, is immobilized on a sensor chip of a surface plasmon resonance (SPR) instrument, and the sample containing the polypeptide to be tested is passed over the chip. Alternatively, the polypeptide to be tested is immobilized on a sensor chip of the instrument, and a sample containing IL-1R-I, or a fragment thereof, is passed over the chip. The skilled person may then interpret the results obtained by such experiments to establish at least a qualitative measure of the binding affinity of the polypeptide for IL-1R-I. If a quantitative measure is desired, for example to determine a K_D value for the interaction, surface plasmon resonance methods may also be used. Binding values may for example be defined in a Biacore (GE Healthcare) or ProteOn XPR 36 (Bio-Rad) instrument. IL-1R-I is suitably immobilized on a sensor chip of the instrument, and samples of the polypeptide whose affinity is to be determined are prepared by serial dilution and injected in random order. K_D values may then be calculated from the results using for example the 1:1 Langmuir binding model of the BIAevaluation 4.1 software, or other suitable software, provided by the instrument manufacturer.

Thus, in one example, there is provided an IL-1R-I binding polypeptide as defined herein, which is capable of binding to IL-1R-I such that the EC_{50} value of the interaction is at most 1×10^{-7} M, such as at most 5×10^{-8} M, such as at most 1×10^{-8} M, such as at most 5×10^{-9} M, such as at most 1×10^{-9} M, such as at most 5×10^{-10} M, such as at most 4×10^{-10} M, such as at most 3×10^{-10} M, such as at most 2×10^{-10} M. In one example, the EC_{50} value of the interaction is between 1×10^{-15} M and 1×10^{-7} M, such as between 1×10^{-15} M and 1×10^{-8} M, such as between 1×10^{-15} M and 1×10^{-9} M, such as between 1×10^{-15} M and 5×10^{-10} M, such as between 1×10^{-15} M and 1×10^{-10} M, such as between 1×10^{-15} M and 5×10^{-11} M, such as between 1×10^{-15} M and 1×10^{-11} M, such as

between 1×10^{-15} M and 5×10^{-12} M, such as between 1×10^{-15} M and 1×10^{-12} M.

In one particular example, there is provided an IL-1R-I binding polypeptide which is capable of binding to IL-1R-I such that the K_D value of the interaction with IL-1R-I is at most 1×10^{-6} M, such as at most 1×10^{-7} M, such as at most 5×10^{-8} M, such as at most 4×10^{-8} M, such as at most 3×10^{-8} M, such as at most 2×10^{-8} M, such as at most 1×10^{-8} M, such as at most 7×10^{-9} M, such as at most 5×10^{-9} M, such as at most 4×10^{-9} M, such as at most 3×10^{-9} M, such as at most 2×10^{-9} M, such as at most 1×10^{-9} M, such as at most 9×10^{-10} M, such as at most 7×10^{-10} M, such as at most 5×10^{-10} M. In one example, the K_D value of the interaction with IL-1R-I is between 1×10^{-15} M and 1×10^{-6} M, between 1×10^{-15} M and 1×10^{-7} M, such as between 1×10^{-15} M and 1×10^{-8} M, such as between 1×10^{-15} M and 1×10^{-9} M, such as between 1×10^{-15} M and 1×10^{-10} M, such as between 1×10^{-15} M and 1×10^{-11} M, such as between 1×10^{-15} M and 1×10^{-12} M.

In one example, there is provided an IL-1R-I binding polypeptide as defined herein, wherein said IL-1R-I is human IL-1R-I or cynomolgus IL-1R-I, such as human IL-1R-I.

The IL-1R-I binding polypeptide as defined herein may be 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 . Thus, in one example said IL-1R-I binding polypeptide 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 .

The skilled person will understand that various modifications and/or additions can be made to an IL-1R-I binding polypeptide according to any aspect disclosed herein in order to tailor the polypeptide to a specific application without departing from the scope of the present disclosure.

For example, in one example there is provided an IL-1R-I binding polypeptide as described herein, which polypeptide has been extended by and/or comprises additional amino acids at the C terminus and/or N terminus. Such a polypeptide should be understood as a polypeptide having one or more additional amino acid residues at the very first and/or the very last position in the polypeptide chain. Thus, an IL-1R-I binding polypeptide may comprise any suitable number of additional amino acid residues, for example at least one additional amino acid residue. Each additional amino acid residue may individually or collectively be added in order to, for example, improve production, purification, stabilization *in vivo* or *in vitro*, coupling or detection of

the polypeptide. Such additional amino acid residues may comprise one or more amino acid residues added for the purpose of chemical coupling. One example of this is the addition of a cysteine residue. Additional amino acid residues may also provide a "tag" for purification or detection of the

5 polypeptide, such as a His₆ tag, a (HisGlu)₃ tag ("HEHEHE" tag), a "myc" (c-myc) tag or a "FLAG" tag for interaction with antibodies specific to the tag or for immobilized metal affinity chromatography (IMAC) in the case of a His₆-tag.

The further amino acids as discussed above may be coupled to the IL-1R-I binding polypeptide by means of chemical conjugation (using known

10 organic chemistry methods) or by any other means, such as expression of the IL-1R-I binding polypeptide as a fusion protein or joined in any other fashion, either directly or via a linker, for example an amino acid linker.

The further amino acids as discussed above may for example

15 comprise one or more polypeptide domain(s). A further polypeptide domain may provide the IL-1R-I binding polypeptide with another function, such as for example yet another binding function, an enzymatic function, a toxic function, a fluorescent signaling function or combinations thereof.

A further polypeptide domain may moreover provide another IL-1R-I

20 binding moiety with the same IL-1R-I binding function. Thus, in a further example, there is provided an IL-1R-I binding polypeptide in a multimeric form. Said multimer is understood to comprise at least two IL-1R-I binding polypeptides as disclosed herein as monomer units, the amino acid sequences of which may be the same or different. Multimeric forms of the

25 polypeptides may comprise a suitable number of domains, each having an IL-1R-I binding motif, and each forming a monomer within the multimer. These domains may have the same amino acid sequence, but alternatively, they may have different amino acid sequences. In other words, the IL-1R-I binding polypeptide of the invention may form homo- or heteromultimers, for example

30 homo- or heterodimers. In one example, there is provided an IL-1R-I binding polypeptide, wherein said monomeric units are covalently coupled together. In one example, there is provided an IL-1R-I binding polypeptide, wherein said monomeric units are non-covalently coupled together. In another example, said IL-1R-I binding polypeptide monomer units are expressed as a fusion

35 protein. In one example, there is provided an IL-1R-I binding polypeptide in dimeric form. One example of an IL-1R-I binding polypeptide which will form a disulphide bonded dimer after

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.

25 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 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
30 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 and listed above. Preferred examples of IL-1R-I binding polypeptides are disclosed in the first example.

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

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
40 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 protein or conjugate. The half-life of a first moiety (and possibly additional

moieties) is increased by fusion or conjugation to a second moiety having an *in vivo* half-life increasing activity. It will be appreciated that the corresponding fusion protein or conjugate may comprise a first IL-1R-I binding moiety as described above, a second moiety having an *in vivo* half-life increasing activity, and optionally one or more additional moieties, such as an additional IL-1R-I binding moiety. For example, said fusion protein or conjugate may comprise two IL-1R-I binding polypeptides and a second moiety which increases *in vivo* half-life compared to the fusion or conjugate comprising the two IL-1R-I binding polypeptides only. Examples of fusion proteins comprising an IL-1R-I binding polypeptide and a half-life extending moiety have been produced and experimentally tested (Example 10). In one example, said fusion protein or conjugate comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1639-1657.

Half-life extension of the resulting fusion protein or conjugate may be accomplished by a second moiety having an inherently long *in vivo* half-life. A polypeptide that increases the hydrodynamic size of the fusion protein or conjugate may for example impose an increased half-life upon the fusion protein or conjugate. Alternatively, the second moiety may consist of a natural protein having a long *in vivo* half-life, such as serum albumin or the Fc portion of an antibody.

In one example, said second moiety comprises one of the albumin binding domain of streptococcal protein G or a derivative thereof; albumin; an Fc portion of an antibody, and transferrin. In one example, said fusion protein or conjugate comprises a sequence selected from the group consisting of SEQ ID NO:1639-1658.

In one example, said second moiety is an Fc portion of an antibody, such as an IgG1 Fc (SEQ ID NO:1662) or an IgG4 Fc. An IgG4 Fc that may be used as a half-life extending moiety is the Fc part set out in Uniprot, accession number P01861, amino acid residues 99-327. In one example, said fusion protein or conjugate comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1646-1654.

In one example, said Fc portion of an antibody is a mutated Fc which relative to an unmutated form of Fc displays improved affinity to FcRn and/or reduced effector response. Thus, said Fc portion is a variant of a naturally occurring Fc in which one or more mutations have been introduced. For example, said fusion protein or conjugate comprises a polypeptide having

an amino acid sequence selected from the group consisting of SEQ ID NO:1734-1737.

In another non-limiting example, wherein said second moiety has *in vivo* half-life increasing activity, said second moiety is transferrin. In particular
 5 examples of the fusion protein or conjugate disclosed herein, there is provided a polypeptide selected from the group consisting of SEQ ID NO:1657.

In one particular example, the *in vivo* half-life increasing activity is an albumin binding activity. Non-limiting examples of moieties providing such an
 10 albumin binding activity are an albumin binding camelid Ig V_{HH} domain and an albumin binding engineered single Ig V_H domain.

In one example, said albumin binding activity is provided by the albumin binding domain of the peptostreptococcal albumin binding (PAB) protein from *Finegoldia magna*, or a derivative thereof.

15 In one example, said albumin binding activity is provided by the albumin binding domain of streptococcal protein G, or a derivative thereof. Examples of such an albumin binding domain are polypeptides having an amino acid sequence as set out in SEQ ID NO:1659-1661. Preferably, the albumin binding domain is as set out in SEQ ID NO:1661. In one example,
 20 said fusion protein or conjugate comprises a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1639-1645.

In another non-limiting example, said *in vivo* half-life increasing activity is provided by a polyethylene glycol (PEG) or a hydroxyethyl starch (HES).

For example, said fusion protein or conjugate, comprising at least one
 25 further moiety, may comprise [IL-1R-I binding polypeptide] – [half-life increasing moiety] – [moiety with affinity for selected target]. It is to be understood that the three moieties in this example may be arranged in any order from the N- to the C-terminal of the polypeptide.

Another non-limiting example is a binding activity which allow the
 30 fusion protein to display a modified tissue distribution compared to the unfused IL-1R-I binding polypeptide. In one example the binding activity is binding to the transferrin receptor. Such a binding activity could infer that the conjugate or fusion protein is transferred across the blood brain barrier and into the brain tissue (Yu *et al*, 2011, Sci Transl Med 3(84):84ra44). In a
 35 preferred example, such binding activity is provided by an antibody fragment.

Another non-limiting example of a binding activity is an activity which acts to block a biological activity.

In one example, there is provided an IL-1R-I binding polypeptide, fusion protein or conjugate wherein the binding activity acts to block a
5 biological activity.

With regard to the description above of fusion proteins or conjugates incorporating an IL-1R-I binding polypeptide according to the disclosure, it is to be noted that the designation of first, second and further moieties is made for clarity reasons to distinguish between an IL-1R-I binding polypeptide or
10 polypeptides according to the invention on the one hand, and moieties exhibiting other functions on the other hand. These designations are not intended to refer to the actual order of the different domains in the polypeptide chain of the fusion protein or conjugate. Similarly, the designations first and second monomer units are made for clarity reasons to distinguish between
15 said units. Thus, for example, said first moiety (or monomer unit) may without restriction appear at the N-terminal end, in the middle, or at the C-terminal end of the fusion protein or conjugate.

The skilled person is aware that the construction of a fusion protein often involves the use of linkers between the functional moieties to be fused,
20 and there are different kinds of linkers with different properties, such as flexible amino acid linkers, rigid amino acid linkers and cleavable amino acid linkers. Linkers have been used to for example increase stability or improve folding of fusion proteins, to increase expression, improve biological activity, enable targeting and alter pharmacokinetics of fusion proteins. Thus, in one
25 example, the polypeptide according to any example disclosed herein further comprises at least one linker, such as at least one linker selected from flexible amino acid linkers, rigid amino acid linkers and cleavable amino acid linkers.

In one example, said linker is arranged between a first moiety consisting of an IL-1R-I binding polypeptide as defined herein and a second
30 moiety consisting of a polypeptide having a desired biological activity. In another example, said linker is arranged within said first moiety. For example, one or more linker(s) may be arranged between monomeric units of the polypeptide as defined herein. In yet another example, linkers may be arranged within said first moiety and between said first moiety and said
35 second moiety.

Flexible linkers are often used in the art when the joined domains require a certain degree of movement or interaction, and may be particularly

useful in some examples. Such linkers are generally composed of small, non-polar (for example G) or polar (for example S or T) amino acids. Some flexible linkers primarily consist of stretches of G and S residues, for example (GGGGS)_p. Adjusting the copy number “p” allows for optimization of linker in
 5 order to achieve appropriate separation between the functional moieties or to maintain necessary inter-moiety interaction. Apart from G and S linkers, other flexible linkers are known in the art, such as G and S linkers containing additional amino acid residues, such as T and A, to maintain flexibility, as well as polar amino acid residues to improve solubility. In one example, said linker
 10 is a flexible linker comprising at least one amino acid residue(s) selected from the group consisting of glycine, serine and alanine. The skilled person is aware of other suitable linkers.

In one example, said linker is selected from GS, VDSS, VDGS, VEGS, ASGS, (GGGGS)₂ (SEQ ID NO:1683), AS(GGGGS)₂ (SEQ ID NO:1684) and
 15 ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685). In one particular example, said linker is AS(GGGGS)₂ (SEQ ID NO:1684) or ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685). In one example, said fusion protein or conjugate comprising a linker comprises a polypeptide having an amino acid sequence as set out in SEQ ID NO:1639-1658. In particular, an exemplary fusion protein or
 20 conjugate comprising the linker AS(GGGGS)₂ is set out in the amino acid sequence of SEQ ID NO:1646-1658, such as SEQ ID NO:1648 and 1657.

In further examples of the present disclosure, there is provided a polynucleotide encoding an IL-1R-I binding polypeptide or a fusion protein as described herein; an expression vector comprising said polynucleotide; and a
 25 host cell comprising said expression vector.

Also encompassed by this disclosure is a method of producing a polypeptide or fusion protein as described above, comprising culturing said host cell under conditions permissive of expression of said polypeptide from its expression vector, and isolating the polypeptide.

30 The IL-1R-I binding polypeptide of the present disclosure may alternatively be produced by non-biological peptide synthesis using amino acids and/or amino acid derivatives having protected reactive side-chains, the non-biological peptide synthesis comprising

- step-wise coupling of the amino acids and/or the amino acid
 35 derivatives to form a polypeptide according to the first example having protected reactive side-chains,

- 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
15 three additional active agents. Non-limiting examples of additional active agents that may prove useful in such 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
20 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 disclosed elsewhere herein.

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

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
30 agent. In one example, said IL-1R-I binding polypeptide is provided for use as a medicament.

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
35 prognostic agent.

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

As used herein, the term "IL-1R-I related disorder" refers to any disorder, disease or condition in which IL-1R-I plays a regulatory role in the signaling pathway. Thus, in one example, there is provided an IL-1R-I binding polypeptide, fusion protein or conjugate or composition as described herein,

5 for use in the treatment of an IL-1R-I related disorder, such as a disorder selected from the group consisting of inflammatory disease, auto-inflammatory syndrome, autoimmune disease, infectious disease, cardiovascular disease, ischaemic disease, cancer and diabetes. In one example, said IL-1R-I related disorder is selected from the group consisting of

10 inflammatory disease, autoinflammatory syndrome and autoimmune disease.

In one example, said IL-1R-I related disorder is selected from the group consisting of familial Mediterranean fever (FMF); cryopyrin-associated periodic syndrome (CAPS); TNF receptor-associated periodic syndrome (TRAPS); hyper-IgD syndrome (HIDS); periodic fever; aphthous stomatitis;

15 pharyngitis; adenitis (PFAPA); rheumatoid arthritis (RA), juvenile RA, juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis,; adult-onset Still's disease; Schnitzler syndrome; Muckle Wells Syndrome; macrophage activation syndrome; Behçet's disease; uveitis; acne vulgaris; pyoderma gangrenosum; gout; type 2 diabetes, new-onset diabetes; dry eye syndrome;

20 hidradenitis suppurativa; neutrophilic dermatoses, in particular cytophagic histiocytic panniculitis, Weber-Christian disease, and neutrophilic panniculitis; cardiovascular disease, myocardial infarction, stroke; liver failure, kidney failure; acute lung injury; pseudogout, calcium-pyrophosphate deposition disorder, chondrocalcinosis, deficiency of the IL-1 receptor antagonist (DIRA),

25 deficiency of the IL-36 receptor antagonist (DITRA), ADAM2 deficiency (DADA2), pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, pyoderma gangrenosum, acne and suppurative hidradenitis (PASH) syndrome, PAPA and suppurative hidradenitis (PAPASH) syndrome, autoinflammatory syndrome with lymphedema (AISLE), Phospholipase C-

30 gamma-2 mutation autoinflammatory syndrome, NALP12-associated periodic syndrome (NAPS12), mevalonate kinase deficiency (MKD), psoriatic arthritis, reactive arthritis, ankylosing spondylitis, haemochromatosis-related arthritis, periarticular calcinosis, osteoarthritis, inflammatory osteoarthritis, hand osteoarthritis, pustular psoriasis such as generalised pustular psoriasis

35 (GPP), palmoplantar pustulosis (PPP), acrodermatitis continua of Hallopeau (ACH); Blau syndrome; Sweet syndrome; various vasculitides such as giant-

cell arteritis (GCA), polymyalgia rheumatica (PMR), Takayasu arteritis, Kawasaki disease, urticarial vasculitis, and Henoch-Schönlein purpura (HSP); neutrophilic urticaria and idiopathic cold urticaria; lichen planus; polymyositis, dermatomyositis, juvenile dermatomyositis and inclusion-body myositis;

5 various stages of myeloma such as smoldering myeloma (SMM), indolent myeloma, Waldenstrom's macroglobulinemia, and multiple myeloma; tumor-induced cachexia; solid tumor growth; neonatal disorders such as bronchopulmonary dysplasia (prophylaxis), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), cerebral palsy due to perinatal cerebral

10 ischemia, and infant respiratory distress syndrome (IRDS); Whipple's disease; traumatic brain injury; refractory epilepsy; systemic inflammatory response syndrome (SIRS); cutaneous lupus; Jessner-Kanof disease; amyotrophic lateral sclerosis; systemic sclerosis (scleroderma); septic shock; acute pancreatitis; chronic recurrent multifocal osteomyelitis, non-bacterial

15 osteitis (NBO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, and Majeeed syndrome; relapsing polychondritis; idiopathic recurrent pericarditis (IRP); myocarditis; Erdheim-Chester disease; juvenile xantogranuloma; islet-cell transplantation; haemodialysis-induced systemic inflammation; graft-versus-host disease; ANCA-associated glomerulonephritis

20 and recurrent glomerulonephritis; Cogan syndrome; autoimmune inner-ear disease; chronic granulomatous disease (CGD); Castleman's disease; cardiac failure; diastolic cardiac failure; antisyntetase syndrome; acute ACL injury; acute haemorrhagic leukoencephalitis; AA amyloidosis; Di George syndrome; generalised fatigue; chronic fatigue syndrome (CFS); gulf-war

25 illness (GWI); and narcolepsy.

In another example, said IL-1R-I related disorder is cancer, such as a cancer selected from the group consisting of colon cancer, breast cancer, lung cancer, head and neck cancer, melanoma and prostate cancer.

The skilled person will appreciate that said IL-1R-I binding polypeptide,

30 fusion protein or conjugate or a composition comprising an anti-IL-1R-I binding polypeptide, fusion protein or conjugate as described herein may be administered to a subject using standard administration techniques, including oral, topical, intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, duodenal or

35 suppository administration. Thus, in one example, there is provided an IL-1R-I binding polypeptide, fusion protein or conjugate or a composition as

described herein for oral, topical, intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, duodenal or suppository administration. In one example, said administration is oral, intravenous, subcutaneous or duodenal administration and in one
5 particular example, said administration is oral administration.

As used herein, the term "subject" refers to a mammalian subject, such as a human subject.

Non-limiting examples of indications where topical administration routes could be especially relevant in IL-1R-I mediated disease include ocular
10 diseases such as dry eye disease, uveitis, scleritis, and ulcerative keratitis; dermatological diseases such as ichthyosis and generalized pustular psoriasis; pulmonary diseases such as adult respiratory distress syndrome, bronchopulmonary dysplasia, chronic obstructive pulmonary disease, asbestosis, and silicosis.

15 In some examples it may be beneficial that the polypeptide, fusion protein, conjugate or composition for use as described above, is administered repeatedly within a period of time, for example within a 24 hour period from disease onset. In one particular example wherein said IL-1R-I binding polypeptide, fusion protein, conjugate or composition is administered
20 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, to a subject in need thereof. In yet a particular example, said IL-1R-I binding polypeptide, fusion protein, conjugate or composition is administered continuously during a limited time
25 period such as during 24 hours from disease onset. Repeated or continuous administration may be preferred when distribution to the brain is required, such as in acute treatment of stroke.

In some examples wherein said fusion protein or conjugate comprises a second moiety having an *in vivo* half-life increasing activity, said fusion
30 protein or conjugate, or composition comprising such a fusion protein or conjugate, is administered once weekly to a subject in need thereof.

In a related example, there is provided a method of treatment of an IL-1R-I related disorder, comprising administering to a subject in need thereof an effective amount of an IL-1R-I binding polypeptide, fusion protein, conjugate
35 or a composition as described herein. In a more specific example of said method, the IL-1R-I binding polypeptide, fusion protein, conjugate or composition as described herein modulates IL-1R-I function *in vivo*.

In one example, said IL-1R-I related disorder is selected from the group as defined above in connection with the previous example.

In some examples of said method of treatment, it may be beneficial that the polypeptide, fusion protein, conjugate or composition as described above, is administered repeatedly within a period of time, for example within a 24 hour period from disease onset. In one particular example 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, to a subject in need thereof. In yet a particular example, said IL-1R-I binding polypeptide, fusion protein, conjugate or composition is administered continuously during a limited time period, such as within 24 hours from disease onset. Repeated or continuous administration may be preferred when distribution to the central nervous system is required, such as in acute treatment of stroke.

In other examples, of said method of treatment, said fusion protein or conjugate comprises a second moiety having an *in vivo* half-life increasing activity, or said composition comprises a fusion protein or conjugate comprising a second moiety having an *in vivo* half-life increasing activity. In such methods, said fusion protein, conjugate or composition may be administered once weekly to a subject in need thereof.

It may be beneficial to administer a therapeutically effective amount of an IL-1R-I binding polypeptide, fusion protein or conjugate or composition as described herein and at least one second drug substance, such as an immune response modulating agent as described above or an anti-cancer agent.

As used herein, the term "co-administration" encompasses both concomitant and sequential administration. Thus, in one example there is provided a method as defined above further comprising co-administration of an immune response modulating agent as described above. In another example there is provided a method as defined above further comprising co-administration of an anti-cancer agent as described above.

In another example of the present disclosure, there is provided a method of detecting IL-1R-I, comprising providing a sample suspected to contain IL-1R-I, contacting said sample with an IL-1R-I binding polypeptide, fusion protein, conjugate or a composition as described herein, and detecting the binding of the IL-1R-I binding polypeptide, fusion protein, conjugate or

composition to indicate the presence of IL-1R-I in the sample. In one example, said method further comprises an intermediate washing step for removing non-bound polypeptide, fusion protein, conjugate or composition, after contacting the sample.

5 While the disclosure has been described with reference to various exemplary aspects and examples, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or
10 molecule to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the disclosure not be limited to any particular example contemplated, but that the disclosure will include all examples falling within the scope of the appended claims.

15 Brief description of the figures

Figure 1 is a listing of the amino acid sequences of examples of IL-1R-I binding polypeptides of the present disclosure (SEQ ID NO:1-1638 and 1667-1679), albumin binding polypeptides (SEQ ID NO:1659-1661); human IgG1 Fc (SEQ ID NO:1662), human albumin (SEQ ID NO:1663) and human
20 transferrin (SEQ ID NO:1664), examples of IL-1R-1 binding fusion polypeptides comprising said polypeptides (SEQ ID NO:1639-1658 and 1734-1737) optionally including a linker, control polypeptides (GS-hIL-1 β , SEQ ID NO:1733) as well as the amino acid sequences of cynomolgus IL-1R-I-His₆ (SEQ ID NO:1665) and cynomolgus IL-1R-I-Fc (SEQ ID NO:1666) used for
25 selection, screening and/or characterization for illustration of the invention. The deduced IL-1R-I binding motifs (BM) of the IL-1R-I binding polypeptides disclosed herein extend from residue 8 to residue 36 in sequences with SEQ ID NO:1-1638 and 1667-1668 and 1670-1679. In SEQ ID NO:1669, said BM extends from residue 5 to residue 33. The amino acid sequences of the 49
30 amino acid residues long polypeptides (BMod) predicted to constitute the complete three-helix bundle within each of these Z variants extend from residue 7 to residue 55, except for the N-terminally truncated Z variant with SEQ ID NO:1669 wherein it extends from residue 4 to residue 52.

Figure 2 is a diagram showing concentration-response curves for
35 inhibition of IL-1 β induced IL-6 release in NHDF cells for six anti-IL-1R-I binding fusion proteins (PSI0536, SEQ ID NO:1648; PSI0537, SEQ ID

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:

5

- i) $EX_2X_3X_4X_5X_6X_7EIX_{10}X_{11}LPNLX_{16}RX_{18}QYX_{21}AFIX_{25}X_{26}LX_{28}D$
(SEQ ID NO:1686)

wherein, independently from each other,

10

X_2 is selected from A, I, L, T and V;

X_3 is selected from E and Y;

X_4 is selected from A, E, I, K, Q, R, T, V and Y;

X_5 is selected from I and V;

15

X_6 is selected from Q and Y;

X_7 is selected from F and M;

X_{10} is selected from F and Y;

X_{11} is selected from A, D, E, F, G, H, K, L, Q, R, S, T, V and Y;

X_{16} is selected from N and T;

20

X_{18} is selected from K and R;

X_{21} is selected from T and V;

X_{25} is selected from I and R;

X_{26} is selected from K and S, and

X_{28} 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) provided that X_5 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 the group consisting of SEQ ID NO:20-1632 and 1679,

35

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 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.

35 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)

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

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

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

10 xxi) AEAKEYAK-[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

15 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.

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 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} .

5

13. Fusion protein or conjugate comprising

- a first moiety consisting of an IL-1R-I binding polypeptide according to any preceding claim; and

10 - a second moiety consisting of a polypeptide having a desired biological activity.

14. Fusion protein or conjugate according to claim 13, 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
15 conjugate.

15. 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
20 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 13-15, 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
25 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 pharmaceutically acceptable excipient or carrier.

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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.

20. Use of an IL-1R-I binding polypeptide, fusion protein, conjugate or
5 composition according to claim 19, 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.