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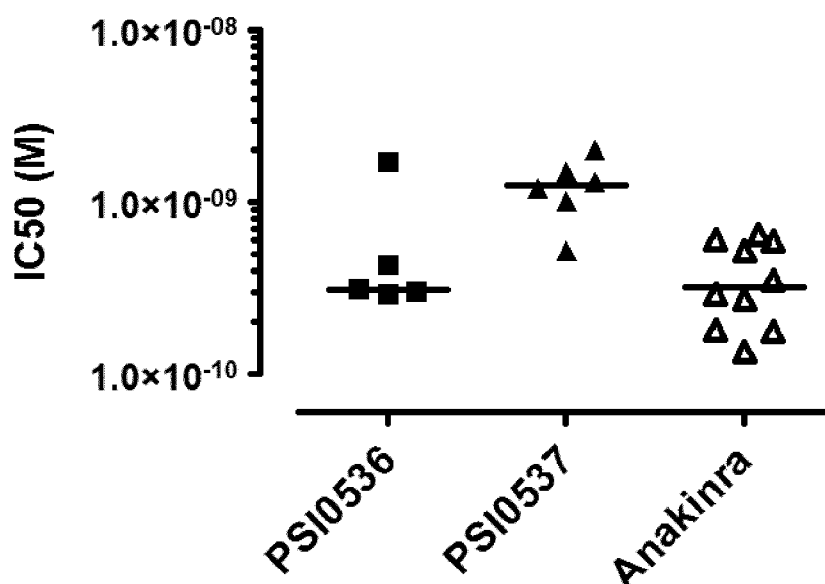
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(71) Applicant: SWEDISH ORPHAN BIOVITRUM AB
(PUBL) [SE/SE]; 112 76 Stockholm (SE).(72) Inventors: FELDWISCH, Joachim; Korallvägen 16, 135
42 Tyresö (SE). LINDBORG, Malin; Hindvägen 5, 132 48
Saltsjö-Boo (SE). NILSSON, Joakim; Mörbydalen 5, Lgh
1803, 182 52 Danderyd (SE). NORDLING, Erik; Sport-
stugevägen 14A, 182 35 Danderyd (SE). SVENSSON,
Robert; Stora Nygatan 20, Lgh 1301, 111 27 Stockholm
(SE).(74) Agent: AWA SWEDEN AB; Box 45086, 104 30 Stock-
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(54) Title: IL-1R-I BINDING POLYPEPTIDE

FIGURE 3



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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IL-1R-I BINDING POLYPEPTIDE

Field of the invention

The present disclosure relates to a class of engineered polypeptides having a binding affinity for interleukin-1 receptor type-I (in the following referred to as
5 IL-1R-I). The present disclosure also relates to the use of such an IL-1R-I binding polypeptide as a therapeutic, prognostic and/or diagnostic agent.

Background

The central role of the IL-1 system in the initiation and maintenance of
10 inflammatory response, as well as its role in innate and adaptive branches of the immune system, makes it an attractive target for pharmaceutical intervention (Dinarello, 2009, Annu Rev Immunol, 27:519-50; Sims and Smith, 2010, Nat Rev Immunol.10(2):89-102). Since the IL-1 system in many cases plays the role of initiator and master cytokine in inflammatory response, many
15 aspects of the progression of a pathological immune response can be modulated by such intervention. The biological activity of IL-1 β can be pharmacologically inhibited by antibodies that prevent, or modulate its binding to the type IL-1 receptor IL-1R-I.

The biological activity of the IL-1 system can also be modulated by
20 antagonizing the IL-1R. The recombinant form of endogenous IL-1Ra denoted anakinra (Kineret[®]) is described in e.g. US 6599873, EP 0343684 and EP 0541920. Anakinra has shown clinical efficacy in rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS; Koné-Paut and Galeotti, 2014, Expert Rev Clin Immunol,10(1):7-18), as well as in a large number of
25 other inflammatory and autoimmune conditions (Dinarello *et al*, 2011, Blood, 117(14):3720-32; Dinarello *et al*, 2012, Nat Rev Drug Discov,11(8):633-52)).

The IL-1 receptor can also be antagonized by antibodies that bind to IL-1R-I subunit and prevent ligand-mediated IL-1 receptor activation and signaling. Several such antibodies are described in WO 2004/022718, which
30 discloses IL-1R-I antagonists such as 15C4. Other examples of IL-1 receptor antagonizing antibodies binding to the IL-1R-I subunit are described in WO 2010/052505, which discloses IL-1R-I antagonists such as Antibody 9GL.

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 of the invention

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 aspects of the invention as claimed in the appended claims and as generally disclosed herein.

Thus, in the first aspect 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
 5 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;
 10 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
 15 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
 20 interaction with IL-1R-I in several different selection experiments. The
 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
 25 with the constant Fc part of antibodies. In the present disclosure, the random
 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
 30 as the IL-1R-I binding capacity of the polypeptide of the present disclosure, is
 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-
 35 1R-I binding characteristics.

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 embodiments, such changes may be made in any position of the sequence of the IL-1R-I binding polypeptide as disclosed herein. In other embodiments, 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 embodiments according to the first aspect, 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 embodiment according to the first aspect, 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

- 5 individualized embodiments of the first aspect of the present disclosure. For example, in one embodiment according to the first aspect, 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 embodiment according to the first aspect, 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 embodiments may be freely combined in yet other embodiments. For example, one such combined embodiment 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.

- 15 Table 1: Embodiments of the first aspect of the present disclosure

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

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

X ₃	E, K
X ₃	E
X ₄	A, D, E, F, H, I, K, L, N, Q, R, S, T, V, W, Y
X ₄	A, D, E, F, H, I, K, L, N, Q, R, S, T, V, Y
X ₄	A, D, E, F, H, I, K, L, Q, R, S, T, V, W, Y
X ₄	A, D, E, F, H, I, K, Q, R, S, T, V, W, Y
X ₄	A, D, E, F, H, K, L, Q, R, S, T, V, W, Y
X ₄	A, D, E, H, I, K, L, Q, R, S, T, V, W, Y
X ₄	A, D, E, H, I, K, L, N, Q, R, S, T, V, Y
X ₄	A, D, E, I, K, Q, R, S, T, V
X ₄	A, D, E, I, K, Q, T, V
X ₄	A, D, E, H, I, K, N, Q, R, S, T, V, Y
X ₄	A, D, E, H, I, K, Q, R, S, T, V, W, Y
X ₄	A, D, E, I, K, Q, R, S, T, V
X ₄	A, E, I, K, Q, R, T, V, Y
X ₄	A, D, E, H, I, K, Q, R, S, T, V
X ₄	A, D, E, H, I, K, R, S, V
X ₄	A, D, E, H, K, Q, V, W
X ₄	A, D, E, H, I, R, S, T, V
X ₄	A, D, E, I, K, Q, S, V
X ₄	A, D, E, I, Q, R, V
X ₄	A, D, E, K, Q, S, T, V
X ₄	A, D, E, I, Q, V

X ₄	A, D, E, K, Q, V
X ₄	A, E, I, K, Q, V
X ₄	A, E, H, K, Q, V
X ₄	A, D, E, I, V
X ₄	A, D, E, I, R
X ₄	D, E, R, T, V
X ₄	A, D, E, K, Q
X ₄	A, D, E, Q, V
X ₄	A, D, E, K, V
X ₄	A, E, Q, V
X ₄	A, E, I, R
X ₄	A, D, E, I
X ₄	A, D, E, Q
X ₄	A, D, E, V
X ₄	A, D, E, K
X ₄	A, E, K, V
X ₄	A, D, E
X ₄	A, E, V
X ₄	A, D
X ₄	A, E
X ₄	D, E
X ₄	E, V
X ₄	E
X ₄	D
X ₄	A
X ₄	V
X ₅	A, V
X ₅	I, V
X ₅	A, I
X ₅	A
X ₅	I
X ₅	V
X ₆	F, H, Q, R, V, Y
X ₆	H, Q, T, Y
X ₆	F, H, Q, Y

X ₆	A, H, Q, W, Y
X ₆	H, Q, Y
X ₆	Q, Y
X ₆	Y
X ₆	Q
X ₇	A, D, E, F, H, I, L, M, Q, S, V, W, Y
X ₇	A, D, E, F, H, L, M, Q, R, W, Y
X ₇	A, D, E, F, H, I, L, M, Q, W, Y
X ₇	D, E, F, H, L, M, Q, W, Y
X ₇	D, F, H, L, M, Q, W, Y
X ₇	F, H, I, L, M, Q, V, W, Y
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X ₇	F, M

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X ₇	M, Y
X ₇	F, L
X ₇	L, Y
X ₇	F, Y
X ₇	F, W
X ₇	M, W
X ₇	L
X ₇	Y
X ₇	F
X ₇	M
X ₇	W
X ₁₀	F
X ₁₀	Y
X ₁₁	A, D, E, F, G, H, I, K, L, N, Q, R, S, T, V, Y
X ₁₁	A, D, E, F, G, H, K, L, N, Q, R, S, T, V, W, Y
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X ₁₁	A, D, E, F, G, H, K, N, Q, R, S, T, V, Y
X ₁₁	A, D, E, F, G, H, K, N, Q, R, S, V, Y

X ₁₁	A, D, E, F, G, H, K, Q, R, S, V, W, Y
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X ₁₁	A, E, G, H, K, N, Q, R, S, Y
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X ₁₁	H, R

X ₁₁	H, Y
X ₁₁	R, Y
X ₁₁	A, E
X ₁₁	A,
X ₁₁	G
X ₁₁	R
X ₁₁	Y
X ₁₁	H
X ₁₁	E
X ₁₆	N
X ₁₆	T
X ₁₈	K, R
X ₁₈	R
X ₁₈	K
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X ₂₁	V
X ₂₅	I, M, R
X ₂₅	I, R
X ₂₅	R
X ₂₅	I
X ₂₆	K
X ₂₆	S
X ₂₈	F, I, L
X ₂₈	F, L
X ₂₈	F
X ₂₈	L

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

In one embodiment, 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 embodiments of sequence i) according to this aspect. 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 embodiment, of the IL-1R-I binding polypeptide according to this aspect, 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 SEQ ID NO:20-1632, and 1679. In one embodiment 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 one embodiment 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 embodiment 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 embodiment 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 embodiment 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.

5 In one embodiment, 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,
10 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,
15 1331, 1340, 1361, 1393, 1415, 1420 and 1421.

In one particular embodiment 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 embodiment sequence i) corresponds to
20 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
25 embodiment, 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
30 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 embodiments of *BM* which exhibit 93 %, where applicable, or 96 % identity with sequence i).

In some embodiments of the present disclosure, the *BM* as defined
35 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 embodiment 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 embodiment 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 embodiments, 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 embodiments, 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 embodiments, the three-helical bundle protein domain is a variant of protein Z, which is derived from domain B of staphylococcal Protein A.

In some embodiments 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:

30

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

wherein

35 [*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).

In some embodiments, said polypeptides may beneficially exhibit high
 10 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 embodiments, 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 embodiments, such minor
 changes as exemplified above may be present only in the flanking sequence,
 20 i.e. the parts of the sequence flanking the BM in iii) above. In other
 embodiments, minor changes can be present in the BM and/or in the flanking
 sequences.

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

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

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

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

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

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

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

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

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

In one embodiment, 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.

15 In one embodiment, 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 embodiment, 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.

20 In one embodiment, 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 embodiment, 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.

In one embodiment, 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.

25 In one embodiment, 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 embodiment, 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.

30 In one embodiment, 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 embodiment, 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.

In one embodiment, 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.

35 In one embodiment, 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 embodiment, 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 embodiment, sequence iii) corresponds to the
5 sequence 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
10 embodiment 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 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 embodiment 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:1205, 1250-1632 and 1670-1679.

In one embodiment 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.

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

In one embodiment, sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of
30 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 1670-1679, such as
35 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, 1340, 1361, 1393, 1415, 1420, 1421, 1670-1672, 1674, 1676-1677 and 1679.

In one particular embodiment 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, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1670-1679. In one embodiment 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 consisting of SEQ ID NO:1252, 1435 and 1679; or the group consisting of SEQ ID NO:1328 and 1435. In one embodiment, 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 embodiment, sequence iii) corresponds to the sequence from 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 embodiment, there is provided an IL-1R-I binding polypeptide, which comprises an amino acid sequence selected from:

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 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).

In one embodiment 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 from A and C; and

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

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

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

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

In another embodiment, 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)

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).

In yet another embodiment, 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)

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).

In yet another embodiment, 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 embodiments, 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 embodiments, 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 embodiments, minor changes can be present in the *BM* and/or in the flanking sequences.

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

ADNNFNK- <i>[BM]</i> -DPSQSANLLSEAKKLNESQAPK	SEQ ID NO:1695;
ADNKFNK- <i>[BM]</i> -DPSQSANLLAEAKKLNDQAAPK	SEQ ID NO:1696;
ADNKFNK- <i>[BM]</i> -DPSVSKEILAEAKKLNDQAAPK	SEQ ID NO:1697;
ADAQQNNFNK- <i>[BM]</i> -DPSQSTNVLGEAKKLNESQAPK	SEQ ID NO:1698;
25 AQHDE- <i>[BM]</i> -DPSQSANVLGEAQKLNDQAPK	SEQ ID NO:1699;
VDNKFNK- <i>[BM]</i> -DPSQSANLLAEAKKLNDQAAPK	SEQ ID NO:1700;
AEAKYAK- <i>[BM]</i> -DPSESSELLSEAKKLNKSQAPK	SEQ ID NO:1701;
VDAKYAK- <i>[BM]</i> -DPSQSSELLAEAKKLNDQAAPK	SEQ ID NO:1702;
VDAKYAK- <i>[BM]</i> -DPSQSSELLAEAKKLNDQAPK	SEQ ID NO:1703;
30 AEAKYAK- <i>[BM]</i> -DPSQSSELLSEAKKLNDQAPK	SEQ ID NO:1704;
AEAKYAK- <i>[BM]</i> -DPSQSSELLSEAKKLNDQAP	SEQ ID NO:1705;
AEAKFAK- <i>[BM]</i> -DPSQSSELLSEAKKLNDQAPK	SEQ ID NO:1706;
AEAKFAK- <i>[BM]</i> -DPSQSSELLSEAKKLNDQAP	SEQ ID NO:1707;
AEAKYAK- <i>[BM]</i> -DPSQSSELLAEAKKLNDQAAPK	SEQ ID NO:1708;
35 AEAKYAK- <i>[BM]</i> -DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1709;
AEAKYAK- <i>[BM]</i> -DPSQSSELLSEAKKLSESQAP	SEQ ID NO:1710;
AEAKFAK- <i>[BM]</i> -DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1711;

	AEAKFAK-[BM]-DPSQSSELLSEAKKLSESQAP	SEQ ID NO:1712;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLSEAQAPK	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	VDAKYAK-[BM]-DPSQSSELLSEAKKLNDSDQAPK	SEQ ID NO:1721;
	VDAKYAK-[BM]-DPSQSSELLAEAKKLNDAAQAPK	SEQ ID NO:1722;
	VDAKYAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1723;
	VDAKYAK-[BM]-DPSQSSELLAEAKKLSEAQAPK	SEQ ID NO:1724;
	VDAKYAK-[BM]-DPSQSSELLSEAKKLESSQAPK	SEQ ID NO:1725;
15	VDAKYAK-[BM]-DPSQSSELLAEAKKLESAQAPK	SEQ ID NO:1726;
	VDAKYAK-[BM]-DPSQSSELLSEAKKLSDSQAPK	SEQ ID NO:1727;
	VDAKYAK-[BM]-DPSQSSELLAEAKKLSDSQAPK	SEQ ID NO:1728;
	VDAKYAK-[BM]-DPSQSSELLAEAKKLSDAQAPK	SEQ ID NO:1729;
	VDAKYAK-[BM]-DPSQSSELLAEAKKLNKAQAPK	SEQ ID NO:1730;
20	AEAKYAK-[BM]-DPSQSSELLAEAKKLNKAQAPK	SEQ ID NO:1731,
	and	
	ADAKYAK-[BM]-DPSQSSELLSEAKKLNDSDQAPK	SEQ ID NO:1732,
	wherein [BM] is an IL-1R-I binding motif as defined herein.	

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

xxi) AEAKEYAK-[BM]-DPSQSSELLSEAKKLSESQAPK (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 embodiment, said IL-1R-I binding polypeptide
5 comprises an amino acid sequence selected from the group consisting of
SEQ ID NO:1667-1668 and 1670-1679.

In one embodiment, 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 embodiments, 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 embodiments 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
embodiments, minor changes can be present in the BM and/or in the flanking
sequences.

25 Sequence xix)-xxiv) in such IL-1R-I binding polypeptide may be
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 embodiment of the IL-1R-I binding polypeptide according to this
30 aspect, 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: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 embodiment sequence
xix), xxi) or xxiii) corresponds to the sequence from position 1 to position 58 in
35 a sequence selected from the group consisting of 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.

In one embodiment 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.

In one embodiment sequence xix), xxi) or xxiii) corresponds to the
 5 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 embodiment 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 embodiment 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 embodiment 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 embodiment 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 embodiment sequence xix),
 30 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, 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
 35 embodiment, 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, 1328 and 1435.

In one embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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
 5 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-
 10 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
 15 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
 20 (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
 25 BIAevaluation 4.1 software, or other suitable software, provided by the instrument manufacturer.

Thus, in one embodiment, 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 $5 \times$
 30 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 embodiment, 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 $1 \times$
 35 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment 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 embodiment 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-
10 1R-I binding polypeptide by means of chemical conjugation (using known 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 embodiment, 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 embodiment, there is provided an IL-1R-I binding polypeptide, wherein said monomeric units are covalently coupled together. In one embodiment, there is provided an IL-1R-I binding polypeptide, wherein said monomeric units are non-covalently coupled together. In another embodiment, said IL-1R-I binding polypeptide monomer
35 units are expressed as a fusion protein. In one embodiment, 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 aspect 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 aspect, and a second
15 moiety consisting of a polypeptide having a desired biological activity. In another embodiment, 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.

Thus, in one embodiment, said IL-1R-I binding polypeptide comprises
20 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 modules may correspond to an amino acid sequence from position 7 to
25 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 embodiments of IL-1R-I binding polypeptides are disclosed in the first aspect.

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

In one embodiment, 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.

35 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 embodiment, 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 embodiment, 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 embodiment, said fusion protein or conjugate comprises a sequence selected from the group consisting of SEQ ID NO:1639-1658.

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

In one embodiment, 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 embodiment, 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
20 embodiment, 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).

25 For example, said fusion protein or conjugate, comprising at least one 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.

30 Another non-limiting example is a binding activity which allow the fusion protein to display a modified tissue distribution compared to the unfused IL-1R-I binding polypeptide. In one embodiment 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
35 into the brain tissue (Yu *et al*, 2011, Sci Transl Med 3(84):84ra44). In a preferred embodiment, 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 embodiment, 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 embodiment, the polypeptide according to any aspect 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiments. 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 embodiment, said
10 linker 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 embodiment, said linker is selected from GS, VDSS, VDGS, VEGS, ASGS, (GGGGS)₂ (SEQ ID NO:1683), AS(GGGGS)₂ (SEQ ID
15 NO:1684) and ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685). In one particular embodiment, said linker is AS(GGGGS)₂ (SEQ ID NO:1684) or ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685). In one embodiment, 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
20 exemplary fusion protein or 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 aspects of the present disclosure, there is provided a polynucleotide encoding an IL-1R-I binding polypeptide or a fusion protein as
25 described herein; an expression vector comprising said polynucleotide; and a 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
30 its expression vector, and isolating the polypeptide.

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

35 - step-wise coupling of the amino acids and/or the amino acid derivatives to form a polypeptide according to the first aspect 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
10 signaling.

 Thus, in another aspect, 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 embodiment, said composition further comprises at least one additional active
15 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 combination are immune response modifying agents and anti-cancer agents as described herein. In one embodiment, said composition comprises a fusion protein or conjugate wherein said desired
20 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 disclosed elsewhere herein.

 Hence, in another aspect of the present disclosure, there is provided
25 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 embodiment, said IL-1R-I binding polypeptide is provided for use as a medicament.

 In one embodiment, there is provided an IL-1R-I binding polypeptide,
30 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 embodiment, there is provided an IL-1R-I binding polypeptide,
35 fusion protein or conjugate or composition as described herein, for use, in the 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 embodiment, there is provided an IL-1R-I binding polypeptide, fusion protein or conjugate or composition as described
5 herein, 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 embodiment, said IL-1R-I related disorder is selected from the group
10 consisting of inflammatory disease, autoinflammatory syndrome and autoimmune disease.

In one embodiment, 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
15 (TRAPS); hyper-IgD syndrome (HIDS); periodic fever; aphthous stomatitis; 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
25 disorder, chondrocalcinosis, deficiency of the IL-1 receptor antagonist (DIRA), 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,
30 autoinflammatory syndrome with lymphedema (AISLE), Phospholipase C-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
35 osteoarthritis, pustular psoriasis such as generalised pustular psoriasis (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 Majeed 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 embodiment, 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.

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

35 transdermal, intramuscular, intranasal, buccal, sublingual, duodenal or suppository administration. Thus, in one embodiment, 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 embodiment, said administration is oral, intravenous, subcutaneous or duodenal administration
5 and in one particular embodiment, 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 embodiments 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 embodiment 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 embodiment, 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 embodiments wherein said fusion protein or conjugate comprises a second moiety having an *in vivo* half-life increasing activity, said
30 fusion 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 aspect, 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 embodiment 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 embodiment, said IL-1R-I related disorder is selected from the group as defined above in connection with the previous aspect.

In some embodiments of said method of treatment, it may be beneficial that the polypeptide, fusion protein, conjugate or composition as described
5 above, is administered repeatedly within a period of time, for example within a 24 hour period from disease onset. In one particular embodiment 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
10 three times within a 24 hour period from disease onset, to a subject in need thereof. In yet a particular embodiment, 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
15 nervous system is required, such as in acute treatment of stroke.

In other embodiments, 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
20 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
25 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 embodiment there is provided a method as defined above further comprising co-administration of
30 an immune response modulating agent as described above. In another embodiment there is provided a method as defined above further comprising co-administration of an anti-cancer agent as described above.

In another aspect of the present disclosure, there is provided a method of detecting IL-1R-I, comprising providing a sample suspected to contain IL-
35 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 embodiment, 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 invention has been described with reference to various exemplary aspects and embodiments, 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 molecule to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the invention not be limited to any particular embodiment contemplated, but that the invention will include all embodiments 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 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 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 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.

35

Figure 2 is a diagram showing concentration-response curves for 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

NO:1649; PSI0534, SEQ ID NO:1646; PSI0535, SEQ ID NO:1647; PSI0538, SEQ ID NO:1650; PSI0539, SEQ ID NO:1651). Anakinra (dotted line) was included as a reference.

Figure 3 is a diagram showing concentration of IL-1R-I binding Z variants at 50 % inhibition (IC_{50}) of IL-1 β induced IL-6 release in human whole blood from five to ten individual donors. The median IC_{50} was 0.31, 1.25 and 0.30 nM for PSI0536 (SEQ ID NO:1648), PSI537 (SEQ ID NO:1649) and anakinra, respectively.

10 Examples

Summary

The following Examples disclose the development of novel Z variant molecules targeted to interleukin 1 receptor I (IL-1R-I) based on phage display technology. The IL-1R-I binding polypeptides described herein were sequenced, and their amino acid sequences are listed in Figure 1 with the sequence identifiers SEQ ID NO:1-1632. Additional IL-1R-I binding polypeptides disclosed herein are listed in Figure 1 with sequence identifiers SEQ ID NO:1633-1638 and 1667-1679. The Examples further describe the characterization of IL-1R-I binding polypeptides and *in vitro* functionality of said polypeptides. As used herein, the term "IL-1R-I binding Z variants" refers to 58 amino acid long IL-1R-I binding polypeptides comprising an IL-1R-I binding motif as disclosed herein.

25 Example 1

Selection and screening of IL-1R-I binding Z variants

In this Example, human and cynomolgus IL-1R-I (hIL-1R-I and cIL-1R-I, respectively) were used as target proteins in phage display selections using a phage library of Z variants. The DNA of selected clones was sequenced, the Z variants were produced in *E. coli* as periplasmic fractions and assayed against IL-1R-I in ELISA (enzyme-linked immunosorbent assay).

Materials and methods

35 Biotinylation of target protein: Human IL-1R-I-Fc (hIL-1RI-Fc Creative BioMart cat. no. IL1RI-771H) and human IL-1R-I (hIL-1RI, RnD Systems cat. no. 269-1R/CF) were biotinylated according to the manufacturer's

recommendations at room temperature (RT) for 30 min using No-Weigh EZ-Link Sulfo-NHS-LC-Biotin (Thermo Scientific, cat. no. 21327) at a 10 x molar excess. Prior to the biotinylation, a buffer exchange to phosphate buffered saline (PBS, 10 mM phosphate, 137 mM NaCl, 2.68 mM KCl, pH 7.4) was performed for hIL-1R-I-Fc using a dialysis cassette (Slide-a-lyzer 3.5 K, 3500 MWCO, Thermo Scientific, cat. no. 66333), according to the manufacturer's instructions, and hIL-1R-I was dissolved in 100 mM phosphate buffer pH 6.5. After the biotinylation, a buffer exchange to PBS was performed for both proteins, as described above.

10 Expression of his-tagged target protein: Expression of cynomolgus IL-1R-I-His₆ (cIL-1R-I-His₆, SEQ ID NO:1665) was performed using the FreeStyle 293-F expression system (Thermo Fisher Scientific), essentially according to the manufacturer's protocol. Supernatants were harvested by centrifugation 5 days after transfection of expression vectors and stored at -
15 70°C. The frozen supernatant from the FreeStyle 293-F cultures were thawed and filtrated (0.22 µm). The supernatant, containing the cIL-1R-I-His₆ was purified using affinity chromatography with an IMAC column. The purified protein was buffer exchanged to PBS. The purity of the protein was analyzed by SDS-PAGE stained with Coomassie Blue and the molecular weight was
20 analyzed using mass spectrometry (HPLC/MS or MALDI-TOF/MS).

Phage display selection of IL-1R-I binding Z variants: A library of random variants of protein Z displayed on bacteriophage in fusion to a wild type albumin binding domain (abbreviated ABD001, SEQ ID NO:1660) was used to select IL-1R-I binding Z variants. The library, which is denoted
25 Zlib006Naive.II, has a size of 1.5×10^{10} library members (Z variants). The construction in the phage library vector pAY02592 and the phage stock production was previously described in WO 2016/113246.

 Selections against hIL-1R-I-Fc, biotinylated hIL-1R-I-Fc (b-hIL-1R-I-Fc), biotinylated hIL-1R-I (b-hIL-1R-I) and cIL-1R-I-His₆ (SEQ ID NO:1665)
30 were performed in four selection cycles. In the first cycle, four selection tracks were run in parallel; 1-1 to 1-4. The selection tracks 1-1 and 1-4 were divided into two parts in cycle two, resulting in a total of six parallel tracks in round 2, 3 and 4; 2-1 to 2-9, 3-1 to 3-9 and 4-1 to 4-9, respectively, as presented in Table 2. The number of phage particles used for selections was more than
35 2000 times the number of eluted phage particles in the previous cycle, but a lower amount was used in selection tracks 4-1 to 4-5. Phage stock preparation, selection procedure and amplification of phage between

selection cycles were performed essentially as described in WO 2009/077175 with the following exceptions 1-8. Exception 1: PBS supplemented with 10 % fetal calf serum (FCS, Gibco, cat. no. 10108-165), 1.5 μ M human serum albumin (HSA, Novozymes, cat. no. 230-005) and 0.1 % Tween20 (Acros Organics, cat. no. 233362500) was used as selection buffer. Exception 2: pre-selection was performed in cycles 1-4 at >60 min at RT or overnight at 4 °C by incubation of phage stock with Dynabeads® M-280 Streptavidin (SA beads, Life technologies/Invitrogen, cat. no. 11206D), SA beads pre-coated with biotinylated human IgG1-Fc (b-hFc, Jackson Immuno Research cat. no. 009-060-008) (Fc/SA beads), SA beads pre-coated with b-hFc and (Z00000)₂-Cys-biotin, prepared essentially as described in WO 2009/077175 (Fc/Z00000/SA beads), protein A beads (Life technologies/Novex, cat. no. 10002D) pre-coated with b-hFc (Fc/protein A beads) or Dynabeads® His-Tag Isolation and Pulldown (IM beads, Life Technologies/Novex, cat. no. 10104D), respectively, as presented in Table 2. b-hFc was incubated with the beads (5, 8.5 or 10 μ g b-hFc per mg Z00000/SA beads, protein A beads or SA beads, respectively) for >1 h at RT, then the beads were washed with 2 x PBST (PBS supplemented with 0.1 % Tween20) before use in pre-selection. Exception 3: all tubes and beads used in the selections were pre-blocked with PBS supplemented with 3 % BSA (bovine serum albumin, Sigma cat. no. A3059) and 0.1 % Tween20. Exception 4: selections were performed in solution at RT and the time for selection was 140 min in the first cycle and 120 min in the following cycles. Exception 5: target-phage complexes were captured on beads using the following amount of target protein and beads: 3.2 μ g hIL-1R-I-Fc per mg Z00000/SA beads, 4 μ g hIL-1R-I-Fc per mg protein A beads, 2 μ g b-hIL-1R-I-Fc or 2 μ g b-hIL-1R-I per mg SA beads and 4.5 μ g cIL-1R-I-His₆ per mg IM beads, respectively. The bead type used for each selection track is the same as presented for pre-selection in Table 2. Exception 6: *E. coli* strain ER2738 cells (Lucigen, Middleton, WI, USA) grown in medium supplemented with 10 μ g/ml tetracycline were used for phage infection. Exception 7: a 5 x excess of M13K07 helper phage compared to bacteria was allowed to infect log phase bacteria. Exception 8: amplification of phage particles after round 2 and 3 was performed essentially as described in WO 2016/113246; Example 5, but using Tryptic Soy Broth + Yeast Extract (TSB-YE) medium supplemented with 100 μ M IPTG, 25 μ g/ml kanamycin, 100 μ g/ml ampicillin and 2 % glucose in the overnight culture.

An overview of the selection strategy, describing an increased stringency in the selection cycles obtained by using a lowered target concentration and an increased number of washes, is shown in Table 2.

5 *Table 2: Overview of the phage display selection from a naive library.*

Cycle	Selection track	Phage stock from library or selection track	Preselection beads	Target	Target concentration (nM)	Number of washes
1	1-1	Zlib006Naive.II	Fc/Z00000/SA	hIL-1R-I-Fc	100	2
1	1-2	Zlib006Naive.II	Fc/protein A	hIL-1R-I-Fc	100	2
1	1-3	Zlib006Naive.II	Fc/SA	b-hIL-1R-I-Fc	100	2
1	1-4	Zlib006Naive.II	SA	b-hIL-1R-I	100	2
2	2-1	1-1	Fc/Z00000/SA	hIL-1R-I-Fc	67	4
2	2-2	1-1	Fc/Z00000/SA	hIL-1R-I-Fc	33	4
2	2-3	1-2	Fc/protein A	hIL-1R-I-Fc	67	4
2	2-5	1-3	Fc/SA	b-hIL-1R-I-Fc	67	4
2	2-7	1-4	SA	b-hIL-1R-I	67	4
2	2-9	1-4	IM	cIL-1R-I-His ₆	67	4
3	3-1	2-1	Fc/Z00000/SA	hIL-1R-I-Fc	44	6
3	3-2	2-2	Fc/Z00000/SA	hIL-1R-I-Fc	11	6
3	3-3	2-3	Fc/protein A	hIL-1R-I-Fc	44	6
3	3-5	2-5	Fc/SA	b-hIL-1R-I-Fc	44	6
3	3-7	2-7	SA	b-hIL-1R-I	44	6
3	3-9	2-9	SA	b-hIL-1R-I	44	6
4	4-1	3-1	Fc/Z00000/SA	hIL-1R-I-Fc	30	8
4	4-2	3-2	Fc/Z00000/SA	hIL-1R-I-Fc	3.7	8
4	4-3	3-3	Fc/protein A	hIL-1R-I-Fc	30	8
4	4-5	3-5	Fc/SA	b-hIL-1R-I-Fc	30	8
4	4-7	3-7	SA	b-hIL-1R-I	30	8
4	4-9	3-9	IM	cIL-1R-I-His ₆	30	8

Washes were performed for 1 min using PBST 0.1 %, and elution was carried out as in the protocol for bead bound phage/target complexes eluted at pH 2 described in WO 2009/077175.

- 10 Production of Z variants for ELISA: The Z variants were produced essentially as described in WO 2016/113246 with the exception that the final volume of pellet dissolving from the 1 ml culture was 1000 µl PBST 0.05 % (PBS supplemented with 0.05 % Tween20).

- 15 The final supernatant of the periplasmic extract contained the Z variants as fusions to ABD (Z-ABD; ABD001, SEQ ID NO:1660), expressed as AQHDEALE-[Z#####]-VDYV-[ABD]-YVPG (Grönwall et al. (2007) J

Biotechnol, 128:162-183). Z##### refers to individual 58 amino acid residue Z variants.

ELISA screening of Z variants: The binding of Z variants to human IL-1R-I was analyzed in ELISA, essentially as described in WO 2016/113246, using 1 nM hIL-1R-I-Fc as target, and using a goat anti-human IgG-HRP (Southern Biotech, cat. no. 2040-05) diluted 1:10,000 for detection. As blank control, PBST 0.05 % was added instead of the Z-ABD periplasmic sample and as negative control, a periplasmic extract with ABD001 (SEQ ID NO:1660) was added instead of the Z-ABD periplasmic sample. Control plates were assayed in a similar setup using 100 nM b-hFc instead of target protein and streptavidin conjugated HRP (Thermo Scientific, cat. no. N100) diluted 1:30,000 for detection.

Sequencing: In parallel with the ELISA screening, the clones were picked for sequencing. PCR fragments, amplified from single colonies, were sequenced and analyzed essentially as described in WO 2009/077175.

EC₅₀ analysis of Z variants: A selection of IL-1R-I binding Z variants was subjected to an analysis of response against a dilution series of hIL-1R-I-Fc using ELISA as described above. The target protein hIL-1R-I-Fc was diluted stepwise 1:10 from 100 to 0.01 nM. As a background control, the Z variants were assayed with no target protein added. Obtained data was analyzed using GraphPad Prism 5 and non-linear regression, and the EC₅₀ values (the half maximal effective concentration) were calculated.

Results

Phage display selection of IL-1R-I binding Z variants: Individual clones were obtained after four cycles of phage display selections against human and cynomolgus IL-1R-I.

ELISA screening of Z variants: The clones obtained after four cycles of selection were produced individually in 96-well plates and were screened for hIL-1R-I-Fc binding activity in ELISA using 1 nM target protein. In parallel, an ELISA to exclude Fc binding was run. Clones positive to hIL-1R-I were identified and none of the IL-1R-I positive clones were positive to Fc solely. No response was obtained for the ABD negative control. 45 identified Z variants displayed an ELISA screening result that was more than 0,71 AU (8.5 x the control background).

Sequencing: In parallel with ELISA screening, sequencing was performed for clones obtained after four cycles of selection. Each variant was

given a unique identification number #####, and individual variants are referred to as Z#####. The amino acid sequences of a subset of the identified 58 amino acid residues long Z variants are listed in Figure 1 and in the sequence listing as SEQ ID NO:1-19. The deduced IL-1R-I binding motifs extend from residue 8 to residue 36 in each sequence. The amino acid sequences of the 49 amino acid residues long polypeptides predicted to constitute the complete three-helix bundle within each of these Z variants extend from residue 7 to residue 55.

EC₅₀ analysis of Z variants: A subset of said Z variants (SEQ ID NO:1-19) was subjected to an ELISA target titration using hIL-1R-I-Fc. Obtained results were used for calculation of EC₅₀ values (Table 3).

Table 3: Calculated EC₅₀ values from ELISA titration analysis.

Z variant	SEQ ID NO	EC ₅₀ (M)	Z variant	SEQ ID NO	EC ₅₀ (M)
Z12884	13	6.4x10 ⁻¹⁰	Z12922	3	2.9x10 ⁻⁹
Z12891	19	2.2x10 ⁻⁹	Z12929	17	1.7x10 ⁻⁸
Z12895	12	2.3x10 ⁻¹⁰	Z12933	2	1.5x10 ⁻⁹
Z12905	7	7.3x10 ⁻⁹	Z12941	4	4.6x10 ⁻¹⁰
Z12910	11	2.3x10 ⁻¹⁰	Z12961	16	2.9x10 ⁻¹⁰
Z12911	18	3.2x10 ⁻¹⁰	Z12964	1	3.9x10 ⁻¹⁰
Z12912	10	3.9x10 ⁻¹⁰	Z12967	9	1.7x10 ⁻¹⁰
Z12915	5	4.3x10 ⁻⁹	Z12974	8	2.1x10 ⁻¹⁰
Z12917	15	3.3x10 ⁻¹⁰	Z12975	6	2.6x10 ⁻¹⁰
Z12920	14	6.6x10 ⁻⁹			

15

Example 2

Production and characterization of primary IL-1R-I binding Z variants

This Example describes the general procedure for subcloning and production of His-tagged Z variants originating from the primary phage selection, characterization of their target binding, target blocking and melting points.

20

Materials and methods

Subcloning of Z variants with a His₆ tag: The DNA of respective Z variant was amplified from the phage library vector pAY02592. A subcloning strategy for construction of monomeric Z variant molecules with N-terminal His₆ tag was applied using standard molecular biology techniques. The Z

25

gene fragments were subcloned into an expression vector resulting in the encoded sequence MGSSHHHHHHLQ-[Z#####]-VD.

Cultivation: *E. coli* T7E2 cells (GeneBridges) were transformed with plasmids containing the gene fragment of each respective IL-1R-I binding Z variant. The resulting recombinant strains were cultivated in media supplemented with 50 µg/ml kanamycin, either at 30 °C in 50 ml scale using the EnPresso protocol (BioSilta), or at 37 °C in 930 ml TSB-YE medium. In order to induce protein expression, IPTG was added to a final concentration of 0.2 mM at OD600 ≈ 10 (EnPresso) or 2 (TSB+YE). After induction, the cultivations were incubated for 16 h (EnPresso) or 5 h (TSB+YE). The cells were harvested by centrifugation.

Purification of IL-1R-I binding Z variants with a His₆ tag: Approximately 1-2 g of each cell pellet was resuspended in binding buffer (20 mM sodium phosphate, 0.5 M NaCl, 20 mM imidazole, pH 7.4) supplemented with Benzonase® (Merck). After cell disruption, cell debris was removed by centrifugation and each supernatant was applied on a 1 ml His GraviTrap IMAC column (GE Healthcare). Contaminants were removed by washing with wash buffer (20 mM sodium phosphate, 0.5 M NaCl, 60 mM imidazole, pH 7.4) and the Z variants were subsequently eluted with elution buffer (20 mM sodium phosphate, 0.5 M NaCl, 500 mM imidazole, pH 7.4). After the IMAC purification, the buffer was exchanged to PBS (2.68 mM KCl, 137 mM NaCl, 1.47 mM KH₂PO₄, 8.1 mM Na₂HPO₄, pH 7.4) using PD-10 desalting columns (GE Healthcare). All Z variants were subjected to a second purification step. Each Z variant was loaded on a 1 ml Resource 15RPC column (GE Healthcare), previously equilibrated with RPC solvent A (0.1 % TFA, 10 % ACN, 90 % water). After column wash with RPC solvent A, bound proteins were eluted with a linear gradient 0-50 % RPC solvent B (0.1 % TFA, 80 % ACN, 20 % water) for 20 ml. The buffer was then exchanged to PBS (2.68 mM KCl, 137 mM NaCl, 1.47 mM KH₂PO₄, 8.1 mM Na₂HPO₄, pH 7.4) using PD-10 desalting columns (GE Healthcare).

Protein concentrations were determined by measuring the absorbance at 280 nm, using a NanoDrop® ND-1000 spectrophotometer (Saveen Werner AB) and the extinction coefficient of the respective protein. Samples with a concentration less than approximately 1 mg/ml were concentrated using Amicon Ultra - 4, Ultracel - 3K (MerckMillipore). The purity was analyzed by SDS-PAGE stained with Coomassie Blue and the identity of each purified Z variant was confirmed using LC/MS analysis.

Biacore affinity analysis: Affinities (K_D) for human and cynomolgus IL-1R-I were determined for His₆-tagged Z variants using a Biacore 2000 instrument (GE Healthcare). hIL-1R-I or cIL-1R-I-His₆ was immobilized on the carboxylated dextran layer in different flow cells of a CM5 chip (GE Healthcare, cat. no. BR100012). The immobilization was performed using amine coupling chemistry according to the manufacturer's protocol. Acetate pH 4.5 (GE Healthcare, cat. no. BR100350) was used for ligand dilution and HBS-EP (GE Healthcare, cat. no. BR100188) was used as running buffer. One flow cell surface on the chip was activated and deactivated for use as blank during analyte injections. In the kinetic experiment, HBS-EP was used as running buffer, the flow rate was 50 μ l/min and the temperature was 25 °C. The analytes, i.e. the Z variants, were each diluted in HBS-EP buffer to final concentrations of 40 nM and 10 nM, and were injected over the target chip surfaces for 2 min, followed by dissociation in running buffer for 8 min. Kinetic constants were calculated from the obtained sensorgrams using a 1:1 binding model, in the BiaEvaluation software 4.1 (GE Healthcare).

In vitro IL-1 β neutralization assay: The TF-1 cell line proliferates in response to many different cytokines including IL-1 β . This cell line was used to assess the ability of primary IL-1R1 binders to inhibit IL-1 β actions. TF-1 cells were maintained in RPMI1640 with L-glutamine (Lonza) supplemented with 10 % FCS (Gibco), Penicillin-Streptomycin (Lonza) and 2 ng/ml rhGM-CSF (R&D Systems). Prior to use, cells were washed twice in RPMI1640 without rhGM-CSF. Cells were then counted and dispensed into 96 well flat bottomed plates at a density of 3×10^4 cells per well. In separate plates, serial dilutions of the inhibitory binders; His₆-tagged IL-1R-I binding Z variants, with a concentration range of 400-0.1 nM, or the IL-1R-I binding protein Kineret (anakinra, Sobi), with a concentration range of 0.3-0.0003 nM, were incubated in the presence of 0.6 nM IL-1 β (PeproTech). The pre-mixed complexes of the Z variant polypeptides and IL-1 β were transferred to wells containing TF-1 cells. The cells were stimulated for 72 h at 37 °C in a humidified 5 % CO₂ atmosphere. During the last four hours of incubation, 19 μ l of 2 x diluted CCK-8 (Fluka, Sigma Aldrich), was added per well to determine the proliferative responses. The absorbance was measured at 450 nm using a microplate reader (Victor3, Perkin Elmer). The data on cell growth was assessed by non-linear regression to a four-parameter dose-response curve, and the half maximal inhibitory concentration (IC₅₀) was determined using GraphPadPrism program.

Circular dichroism (CD) spectroscopy analysis: Purified His₆-tagged Z variants were diluted to 0.5 mg/ml in PBS. For each diluted Z variant, a CD spectrum at 250-195 nm was obtained at 20 °C. In addition, a variable temperature measurement (VTM) was performed to determine the melting temperature (T_m). In the VTM, the absorbance was measured at 221 nm while the temperature was raised from 20 to 90 °C, with a temperature slope of 5 °C/min. A new CD spectrum was obtained at 20 °C after the heating procedure in order to study the refolding ability of the Z variants. The CD measurements were performed on a Jasco J-810 spectropolarimeter (Jasco Scandinavia AB) using a cell with an optical path length of 1 mm.

Results

Production of His₆-tagged Z variants: The IL-1R-I binding Z variants with a His₆ tag were expressed as soluble gene products in *E. coli*. The amount of purified protein from approximately 1-2 g bacterial pellet was determined spectrophotometrically by measuring the absorbance at 280 nm and ranged from approximately 3 to 25 mg for the different IL-1R-I binding Z variants before RPC purification. SDS-PAGE analysis of each final protein preparation showed that these predominantly contained the IL-1R-I binding Z variant. The correct identity and molecular weight of each Z variant were confirmed by HPLC-MS analysis.

Biacore affinity analysis: The interactions of His₆-tagged IL-1R-I binding Z variants with human and cynomolgus IL-1R-I were analyzed in a Biacore instrument by injecting two concentrations of each Z variant over surfaces containing immobilized IL-1R-I. The calculated affinities (K_D) for human IL-1R-I are presented in Table 4. The strongest binder to human IL-1R-I (Z12967, SEQ ID NO:9) bound to human IL-1R-I with an affinity of 1.2 x 10⁻⁹ M and to cynomolgus IL-1R-I with an affinity of 3.5 x 10⁻⁸ M.

Table 4. Affinities for His₆-Z polypeptides binding to IL-1R-I.

Z variant	SEQ ID NO	Human IL-1R-I K _D (M)
Z12884	13	1.8x10 ⁻⁸
Z12895	12	5.5x10 ⁻⁹
Z12911	18	7.1x10 ⁻⁹
Z12917	15	8.0x10 ⁻⁹
Z12922	3	9.8x10 ⁻⁹
Z12967	9	1.2x10 ⁻⁹
Z12974	8	1.5x10 ⁻⁸
Z12975	6	8.9x10 ⁻⁸

In vitro IL-1 β neutralization assay: The IL-1 β inhibition ability of His₆-tagged IL-1R-I-binding Z variants was analyzed in a TF-1 cell assay. The resulting IC₅₀ values are presented in Table 5.

Table 5: IC₅₀ values for His₆-Z polypeptides from a TF-1 cell assay.

Z variant	SEQ ID NO	IC ₅₀ (nM)
Z12884	13	27
Z12895	12	7.1
Z12911	18	30
Z12917	15	11
Z12922	3	66
Z12967	9	1.1
Z12974	8	60
Z12975	6	35
Kineret	-	0.05

CD analysis: The CD spectra determined for the IL-1R-I binding Z variants with a His₆ tag showed that each had an α -helical structure at 20 °C. This result was also verified in the variable temperature measurements, wherein the melting temperatures were determined (Table 6). Reversible folding was seen for all the IL-1R-I binding Z variants when overlaying spectra measured before and after heating to 90 °C.

Table 6: Melting temperatures (T_m).

Z variant	SEQ ID NO	T_m (°C)	Z variant	SEQ ID NO	T_m (°C)
Z12911	18	64	Z12975	6	51
Z12967	9	58	Z12884	13	49
Z12922	3	47	Z12917	15	56
Z12974	8	49	Z12895	12	55

Example 3

Design and construction of a first matured library of IL-1R-I binding Z variants

5

In this Example, a matured library was constructed. The library was used for selection of further IL-1R-I binding Z variants. Selections from matured libraries are usually expected to result in binders with increased affinity (Orlova *et al.*, (2006) Cancer Res 66(8):4339-48).

10

Materials and methods

Library design: The library was primarily based on human IL-1R-I binding Z variants from the primary selection described in Example 1 and 2. Sequences of a subset of the Z variants derived from the primary selection are listed in Figure 1 and in the sequence listing as SEQ ID NO:1-19. In the new library, denoted Zlib006IL-1RI.I, ten variable positions in the Z molecule scaffold were biased towards certain amino acid residues, and three positions were kept constant. Two oligonucleotides, generated by the TRIM technology, which enables incorporation of randomized sets of trinucleotide building blocks, were ordered from Ella Biotech (Martinsried, Germany). The oligonucleotides represented helix 1 and helix 2 of the Z molecule, respectively, and contained an annealing region of 18 overlapping nucleotides. The assembled double stranded DNA sequence was: 5'-AA ATA AAT CTC GAG GTA GAT GCC AAA TAC GCC AAA GAA NNN NNN NNN GCG NNN NNN GAG ATC NNN NNN CTG CCT AAC CTC ACC NNN NNN CAA NNN NNN GCC TTC ATC NNN AAA TTA NNN GAT GAC CCA AGC CAG AGC TCA TTA TTT A-3' (SEQ ID NO:1680; designed codons are denoted NNN). The sequence encodes a partially randomized helix 1 and 2 of the Z variant amino acid sequence flanked by the restriction sites XhoI and SacI. The design for each amino acid residue of the new library, including ten variable amino acid positions (9, 10, 11, 13, 14, 17, 18, 25, 32 and 35) and three constant amino acid positions (24, 27 and 28) in the Z molecule

scaffold, are displayed in Table 7. The resulting theoretical library size was 9.7×10^8 variants. An even theoretical distribution of the different amino acids was applied within each amino acid position, except from position 9, 13, 17, 18, 32 and 35, where a higher portion of selected amino acids was applied.

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Table 7: Design of first maturation library Zlib006IL-1RI.I.

Amino acid position in the Z variant molecule	Amino acid randomization (percentage when uneven distribution)	No. of different amino acids
9	A(30 %),E,F,H,I,K,L,Q,R,S,T,V,W,Y	14
10	A,D,E,F,H,I,K,L,Q,R,S,T,V,W,Y	15
11	A,D,E,F,H,I,K,L,N,Q,R,S,T,V,W,Y	16
13	A,F,H,I,L,Q(20 %),S,T,V,W,Y(20 %)	11
14	A,D,E,F,H,I,K,L,M,Q,R,S,T,V,W,Y	16
17	F,W(20 %),Y	3
18	A(11 %),D,E,F,G,H,I,K,L,N,Q,R,S,T,V,W,Y	17
24	R	1
25	H,K,R,S	4
27	Y	1
28	T	1
32	A,I,L,R(70 %)	4
35	F(80 %),L(20 %)	2

Library construction: The two oligonucleotides were assembled, amplified, cloned into vector pAY02592, and transformed into *E. coli* ER2738, essentially as described for matured libraries in WO 2015/189430. Clones from the Zlib006IL-1RI.I library were sequenced (as described in WO 2009/077175) in order to verify the content and to evaluate the outcome of the constructed library vis-à-vis the library design.

Preparation of phage stock: A phage stock containing the phagemid library was prepared in shake flasks in two batches. Cells from a glycerol stock containing the phagemid library were inoculated in 2 and 3 l, respectively, of TSB-YE medium, supplemented with 2 % glucose, 10 µg/ml tetracycline and 100 µg/ml ampicillin. The cultivations were grown at 37 °C until OD₆₀₀ reached log-phase 0.5-0.9. The cultivations were infected using a 4-10 x molar excess of M13K07 helper phage and were incubated for 30 minutes at 37 °C. Batch 1 cultivations were pelleted by centrifugation, dissolved in TSB-YE medium, supplemented with 100 µg/ml ampicillin, 25 µg/ml kanamycin and 0.1 mM IPTG and grown at 30 °C overnight. To batch 2

cultivation, 0.1 mM IPTG was added, followed by an incubation of 1 h at 37 °C. After addition of 25 µg/ml kanamycin, the cultures were grown at 30 °C overnight. For both batches, the overnight grown cells were pelleted by centrifugation at 4,000 g and the phage particles remaining in the medium were thereafter precipitated twice in PEG/NaCl, filtered and dissolved in PBS and glycerol as described in Grönwall *et al.*, *supra*. Phage stocks were stored at -80 °C until use in selection.

Results

Library construction: The new library Zlib006IL-1RI.I was designed based on a set of IL-1R-I binding Z variants with verified binding properties (Example 1 and 2). The theoretical size of the designed library was 9.7×10^8 Z variants. The actual size of the library, determined by titration after transformation to *E. coli* ER2738 cells, was 5.6×10^9 transformants. The library quality was tested by sequencing 192 transformants and by comparing their actual sequences with the theoretical design. The contents of the actual library compared to the designed library were shown to be satisfactory. A first matured library of potential binders to IL-1R-I was thus successfully constructed.

Example 4

Selection and screening of Z variants from the first matured library

In this Example, human and cynomolgus IL-1R-I were used as target proteins in phage display selections using a matured phage library of Z variants. The DNA of selected clones was sequenced, the Z variants were produced in *E. coli* periplasmic fractions and assayed against IL-1R-I in ELISA and Biacore.

Materials and methods

Expression of target protein: Expression of Fc fused cynomolgus IL-1R-I (cIL-1R-I-Fc, SEQ ID NO:1666) was performed using the Expi293 expression system (Thermo Fisher Scientific), essentially according to the manufacturer's protocol. Supernatants were harvested by centrifugation 7 days after transfection of expression vectors and stored at -70 °C. The frozen supernatant from the Expi293 culture were thawed and filtrated (0.22 µm). The supernatant containing the cIL-1R-I-Fc was purified using affinity chromatography with a MabSelect SuRe column. The purified protein was

buffer exchanged to PBS. The purity of the protein was analyzed by SDS-PAGE stained with Coomassie Blue and the molecular weight was analyzed using mass spectrometry (HPLC/MS or MALDI-TOF/MS).

Phage display selection of IL-1R-I binding Z variants: The biotinylated human target proteins b-hIL-1R-I-Fc and b-hIL-1R-I, and the cynomolgus target proteins cIL-1R-I-Fc (SEQ ID NO:1666) and b-cIL-1R-I-Fc (cIL-1R-I-Fc biotinylated as hIL-1R-I-Fc in Example 1), were used in phage selections using the new library of Z variant molecules described in Example 3. An overview of the selection strategy, describing the parallel selection tracks and an overall increased stringency in the selection cycles obtained by using a lowered target concentration and an increased number of washes, is shown in Table 8. The selections were performed in four to five cycles essentially as described in Example 1, with the following exceptions 1-6. Exception 1: pre-selection was performed for >60 min at RT by incubation of phage stocks with Fc/SA beads (selection tracks 1-1, 1-2, 1-4, 1-6, 1-8, 2-14 and 2-16), SA beads (selection tracks 1-3, 1-7, 1-9, 2-15 and 2-17) or Fc/protein A beads (selection track 1-5), respectively. Exception 2: the time for selection was 30-100 min as presented for each track in Table 8. Exception 3: target-phage complexes were captured on beads using the following amount of target protein and beads: 8 µg b-hIL-1R-I-Fc, 1 µg b-hIL-1R-I or 4 µg cIL-1R-I-Fc per mg SA beads, respectively, and 5 µg cIL-1R-I-Fc per mg protein A beads. In selection round 5, 2 mg SPHERO neutravidin beads (SpheroTech cat. no. NVM-20-5) were used for target-phage complex capture. Exception 4: in the second final wash step of tracks 2-14, 2-15, 2-17, 3-14, 3-15 and 3-17, respectively, hIL-1R-I was added to the wash buffer in 100 times higher concentration than the target concentration of the respective track and the wash was run for 15-20 min. Exception 5: the phage/target/bead complexes of selection tracks 4-1 to 4-13 were divided into two after the bead wash procedure. Half of the samples was submitted to elution and the other half, denoted 4-1x to 4-13x, was submitted to an extra 66 h, wash step before elution. Exception 6: two selection rounds four tracks, 4-4x and 4-6x, were submitted to a fifth selection round, resulting in tracks 5-1 and 5-2, as presented in Table 8. *E. coli* XL-1 Blue cells (Agilent Technologies, cat. no. 200268), grown in medium supplemented with 10 µg/ml tetracycline, were used for phage infection and a 10 x excess of M13K07 helper phage compared to bacteria was allowed to infect log phase bacteria. Amplification

of phage particles after round 1 to 3 was performed essentially as described for round 2 and 3 in Example 1.

Table 8: Overview of selections from the first matured library.

Cycle	Selection track	Phage stock from library or selection track	Target	Target concentration (nM)	Selection time (min)	Number of washes
1	1-1	Zlib006IL-1RI.I	b-hIL-1R-I-Fc	50	70	4
1	1-2	Zlib006IL-1RI.I	b-hIL-1R-I-Fc	10	70	4
1	1-3	Zlib006IL-1RI.I	b-hIL-1R-I	50	70	4
1	1-4	Zlib006IL-1RI.I	b-clL-1R-I-Fc	100	70	2
1	1-5	Zlib006IL-1RI.I	cIL-1R-I-Fc	100	70	2
1	1-6	Zlib006IL-1RI.I	b-hIL-1R-I-Fc	10	45	5
1	1-7	Zlib006IL-1RI.I	b-hIL-1R-I	10	45	5
1	1-8	Zlib006IL-1RI.I	b-hIL-1R-I-Fc	10	45	5
1	1-9	Zlib006IL-1RI.I	b-hIL-1R-I	10	45	5
2	2-1	1-1	b-hIL-1R-I-Fc	20	60	6
2	2-2	1-1	b-hIL-1R-I-Fc	5	60	6
2	2-3	1-2	b-hIL-1R-I-Fc	4	60	8
2	2-4	1-2	b-hIL-1R-I-Fc	4	60	12
2	2-5	1-3	b-hIL-1R-I	20	60	6
2	2-6	1-3	b-hIL-1R-I	10	60	6
2	2-7	1-3	b-hIL-1R-I	10	60	10
2	2-8	1-4	b-clL-1R-I-Fc	50	60	4
2	2-9	1-5	cIL-1R-I-Fc	50	60	4
2	2-10	1-1	b-clL-1R-I-Fc	100	60	2
2	2-11	1-1	b-clL-1R-I-Fc	50	60	6
2	2-12	1-1	cIL-1R-I-Fc	100	60	2
2	2-13	1-1	cIL-1R-I-Fc	50	60	6
2	2-14	1-8	b-hIL-1R-I-Fc	2	30	10*
2	2-15	1-9	b-hIL-1R-I	2	30	10*
2	2-16	1-9	b-clL-1R-I-Fc	25	30	3
2	2-17	1-6/1-7 pool	b-hIL-1R-I	2	30	10*
3	3-1	2-1	b-hIL-1R-I-Fc	5	60	8
3	3-2	2-2	b-hIL-1R-I-Fc	0.5	60	8
3	3-3	2-3	b-hIL-1R-I-Fc	1	60	12

3	3-4	2-4	b-hIL-1R-I-Fc	1	60	24
3	3-5	2-5	b-hIL-1R-I	5	60	8
3	3-6	2-6	b-hIL-1R-I	1	60	8
3	3-7	2-7	b-hIL-1R-I	2	60	20
3	3-8	2-8	b-cIL-1R-I-Fc	25	60	6
3	3-9	2-9	cIL-1R-I-Fc	25	60	6
3	3-10	2-10	b-hIL-1R-I-Fc	25	60	6
3	3-11	2-11	b-hIL-1R-I-Fc	5	60	8
3	3-12	2-12	b-hIL-1R-I-Fc	25	60	6
3	3-13	2-13	b-hIL-1R-I-Fc	5	60	8
3	3-14	2-14	b-hIL-1R-I-Fc	0.5	40	16*
3	3-15	2-15	b-hIL-1R-I	0.5	40	16*
3	3-16	2-16	b-hIL-1R-I	2	40	9
3	3-17	2-17	b-hIL-1R-I	0.4	40	16*
4	4-1	3-1	b-hIL-1R-I-Fc	1	40	10**
4	4-2	3-2	b-hIL-1R-I-Fc	0.05	40	10**
4	4-3	3-3	b-hIL-1R-I-Fc	0.2	40	16**
4	4-4	3-4	b-hIL-1R-I-Fc	0.2	40	36**
4	4-5	3-5	b-hIL-1R-I	1	40	10**
4	4-6	3-6	b-hIL-1R-I	0.1	40	10**
4	4-7	3-7	b-hIL-1R-I	0.4	40	30**
4	4-8	3-8	b-cIL-1R-I-Fc	12.5	40	8**
4	4-9	3-9	cIL-1R-I-Fc	50	40	8**
4	4-10	3-10	b-cIL-1R-I-Fc	50	40	6**
4	4-11	3-11	b-cIL-1R-I-Fc	10	40	12**
4	4-12	3-12	cIL-1R-I-Fc	50	40	6**
4	4-13	3-13	cIL-1R-I-Fc	10	40	12**
4	4-14	3-14	b-hIL-1R-I-Fc	0.1	40	20
4	4-15	3-15	b-hIL-1R-I	0.1	40	20
4	4-16	3-16	b-cIL-1R-I-Fc	5	40	16
4	4-17	3-17	b-hIL-1R-I	0.2	40	16
5	5-1	4-4x	b-hIL-1R-I-Fc	50	100	3
5	5-2	4-6x	b-hIL-1R-I	50	100	3

*Addition of hIL-1R-I in the second final wash step.

**Selection track divided into two after washes. One part submitted to an extra wash, over the weekend, before elution.

In the first selection cycle, nine selection tracks were run; 1-1 to 1-9. In
5 cycle two, some tracks were divided into two, three or six tracks and two
tracks were pooled into one track, resulting in a total of 17 parallel tracks in
cycle 2, 3 and 4; 2-1 to 2-17, 3-1 to 3-17 and 4-1 to 4-17, respectively. In
cycle 5, two tracks were run; 5-1 and 5-2. In selection tracks 1-1 to 1-5, batch
1 of Zlib006IL-1RI.I was used, and in 1-6 to 1-9, batch 2 was used,
10 respectively. All selection tracks are presented in Table 8. The number of
phage particles used for selections was typically more than 2,000 times the
number of eluted phage particles in the previous cycle.

Sequencing: Individual clones from cycle 4 or 5 of the different
selection tracks were picked for sequencing. Amplification and sequence
15 analysis of gene fragments were performed essentially as described in
Example 1.

Production of Z variants for ELISA and Biacore screening: Z variants
were produced essentially as described in Example 1 with the exception that
the culture volume was 1.2 ml and that the periplasmic extracts were clarified
20 by filtration using 1.2 µm 96 well filter plates (MerckMillipore cat. no.
MSANLY50) after the freeze-thawing procedure. Z variants screened in
Biacore were diluted five times in HBS-EP buffer.

ELISA screening of Z variants: The binding of Z variants to human was
analyzed in ELISA, essentially as described in Example 1, using 0.3 nM hIL-
25 1R-I-Fc as target protein. As blank control, PBST 0.05 % was added instead
of the Z-ABD periplasmic extract.

EC₅₀ analysis of Z variants: A selection of IL-1R-I binding Z variants
was subjected to an analysis of response against a dilution series of hIL-1R-I-
Fc using ELISA as described above. The target protein hIL-1R-I-Fc was
30 diluted stepwise 1:10 from 100 to 0.01 nM. As a background control, the Z
variants were assayed with no target protein added. Obtained data was
analyzed using GraphPad Prism 5 and non-linear regression, and the EC₅₀
values (the half maximal effective concentration) were calculated. A
periplasmic extract with Z12967 (SEQ ID NO:9) was analyzed in parallel for
35 signal comparison.

Biacore screening of Z variants: The binding of Z variants to human IL-
1R-I was analyzed in a kinetic screening using a Biacore T200 instrument. A

polyclonal goat anti-ABD antibody (goat anti-ABD) was immobilized on CM5 chip surfaces basically as described for other proteins in Example 2. For the kinetic screening, analytes were injected in two steps. First, a Z-ABD (ABD001, SEQ ID NO:1660) periplasmic extract was injected over the surface at 5 μ l/min for 1 min. As a second step, 100 nM hIL-1R-I was injected at 30 μ l/min for 2 min, followed by 2 min of dissociation in running buffer HBS-EP. Glycine-HCl pH 2.0 (cat. no. BR100355, GE Healthcare) was used for regeneration of the antibody surfaces between the cycles. The temperature of the assay was 25 °C. Before performing the kinetic analyses, the signal from 100 nM hIL-1R-I injected over a reference surface containing goat anti-ABD but no Z-ABD sample was subtracted from the sensorgram of Z-ABD binding to hIL-1R-I. Rough screening affinities (K_D) were calculated from the reference subtracted 100 nM hIL-1R-I response using a 1:1 binding model of the BiaEvaluation software 4.1 (GE Healthcare). A periplasmic extract of Z12967 was included in the screening analysis for comparison. Periplasmic extracts of four Z variants were also submitted to a single cycle kinetics (SCK) assay, using the same setup as above, but injecting five hIL-1R-I concentrations and evaluating the data with a 1:1 model for single cycle kinetics.

20

Results

Phage display selection of IL-1R-I binding Z variants: Individual clones were obtained after four or five cycles of phage display selections against human and cynomolgus IL-1R-I.

25 Sequencing: Sequencing was performed for clones obtained after four or five cycles of selection. Each variant was given a unique identification number #####, and individual variants are referred to as Z#####. The amino acid sequences of the 58 amino acid residues long Z variants are listed in Figure 1 and in the sequence listing as SEQ ID NO:20-1209. The deduced IL-1R-I binding motifs extend from residue 8 to residue 36 in each sequence. 30 The amino acid sequences of the 49 amino acid residues long polypeptides predicted to constitute the complete three-helix bundle within each of these Z variants extend from residue 7 to residue 55. It was observed that in one sequenced Z variant (Z18557, SEQ ID NO:1205) a valine residue was 35 present in position 12.

ELISA screening of Z variants: Clones obtained after four or five cycles of selection were produced individually in 96-well plates and were screened

for human IL-1R-I binding activity in ELISA. 98 % of the assayed Z variants gave a positive signal of 2 x the blank control or higher against 0.3 nM hIL-1R-I-Fc.

- EC₅₀ analysis of Z variants: A subset of 115 Z variants displaying results over 0.99 AU (16.5 x the blank control) was subjected to ELISA target titration using hIL-1R-I-Fc. Obtained results were used for calculation of EC₅₀ values (Table 9). The result for Z12967 (SEQ ID NO:9) was 2.4×10^{-10} M.

Table 9: Calculated EC₅₀ values from ELISA titration analysis.

Z variant	SEQ ID NO	EC ₅₀ (M)	Z variant	SEQ ID NO	EC ₅₀ (M)	Z variant	SEQ ID NO	EC ₅₀ (M)
Z15811	21	2.5×10^{-10}	Z16054	258	2.4×10^{-10}	Z16246	441	3.9×10^{-10}
Z15813	23	3.5×10^{-10}	Z16058	262	2.3×10^{-10}	Z16255	449	1.7×10^{-10}
Z15824	34	2.3×10^{-10}	Z16070	273	2.3×10^{-10}	Z16263	457	2.6×10^{-10}
Z15840	49	2.5×10^{-10}	Z16072	275	2.2×10^{-10}	Z16264	458	3.0×10^{-10}
Z15862	71	2.1×10^{-10}	Z16084	287	2.2×10^{-10}	Z16277	470	2.6×10^{-10}
Z15876	1206	4.2×10^{-10}	Z16089	291	2.4×10^{-10}	Z16301	494	2.2×10^{-10}
Z15886	94	2.6×10^{-10}	Z16092	293	2.4×10^{-10}	Z16302	495	2.8×10^{-10}
Z15897	105	2.5×10^{-10}	Z16093	294	2.1×10^{-10}	Z16305	498	2.2×10^{-10}
Z15923	131	2.4×10^{-10}	Z16097	298	2.0×10^{-10}	Z16312	504	2.4×10^{-10}
Z15927	135	2.2×10^{-10}	Z16102	302	2.8×10^{-10}	Z16319	511	3.0×10^{-10}
Z15929	137	2.4×10^{-10}	Z16106	306	2.3×10^{-10}	Z16321	513	2.7×10^{-10}
Z15932	1207	2.3×10^{-10}	Z16116	316	2.1×10^{-10}	Z16329	519	4.5×10^{-10}
Z15949	154	2.5×10^{-10}	Z16117	317	2.1×10^{-10}	Z16341	531	1.7×10^{-10}
Z15953	158	2.1×10^{-10}	Z16121	321	2.3×10^{-10}	Z16363	550	2.0×10^{-10}
Z15960	165	2.3×10^{-10}	Z16122	322	2.9×10^{-10}	Z16377	562	2.1×10^{-10}
Z15961	166	2.1×10^{-10}	Z16127	325	2.1×10^{-10}	Z16378	563	2.0×10^{-10}
Z15975	1209	2.4×10^{-10}	Z16135	333	2.5×10^{-10}	Z16388	573	2.9×10^{-10}
Z15978	182	4.8×10^{-10}	Z16141	339	2.8×10^{-10}	Z16405	590	3.6×10^{-10}
Z15987	191	2.3×10^{-10}	Z16143	341	2.1×10^{-10}	Z16678	853	2.4×10^{-10}
Z15996	200	2.5×10^{-10}	Z16155	351	2.9×10^{-10}	Z16681	856	2.3×10^{-10}
Z15997	201	2.5×10^{-10}	Z16156	352	2.4×10^{-10}	Z16688	863	2.7×10^{-10}
Z15999	203	2.4×10^{-10}	Z16161	357	2.5×10^{-10}	Z16749	921	2.7×10^{-10}
Z16000	204	2.4×10^{-10}	Z16162	358	2.7×10^{-10}	Z16771	943	2.4×10^{-10}
Z16003	207	2.8×10^{-10}	Z16163	359	1.7×10^{-10}	Z17244	1147	4.2×10^{-10}
Z16004	208	2.5×10^{-10}	Z16164	360	6.8×10^{-10}	Z17255	1158	2.5×10^{-10}
Z16007	211	2.2×10^{-10}	Z16165	361	2.2×10^{-10}	Z17257	1160	4.8×10^{-10}
Z16008	212	2.3×10^{-10}	Z16168	364	2.8×10^{-10}	Z17269	1171	2.7×10^{-10}
Z16011	215	2.2×10^{-10}	Z16169	365	1.8×10^{-10}	Z17270	1172	3.0×10^{-10}
Z16023	227	2.1×10^{-10}	Z16173	369	3.6×10^{-10}			

Z16034	238	2.3×10^{-10}	Z16178	374	2.4×10^{-10}	Z17274	1176	2.1×10^{-10}
Z16041	245	2.4×10^{-10}	Z16206	402	4.5×10^{-10}	Z17278	1180	2.7×10^{-10}
Z16042	246	2.4×10^{-10}	Z16207	403	2.2×10^{-10}	Z17279	1181	2.8×10^{-10}
Z16043	247	2.3×10^{-10}	Z16219	415	2.4×10^{-10}	Z17280	1182	2.2×10^{-10}
Z16046	250	2.7×10^{-10}	Z16234	429	5.4×10^{-10}	Z17288	1190	4.2×10^{-10}
Z16048	252	2.5×10^{-10}	Z16236	431	2.4×10^{-10}	Z17292	1194	2.0×10^{-10}
Z16049	253	2.4×10^{-10}	Z16241	436	4.9×10^{-10}	Z17296	1198	3.2×10^{-10}
Z16050	254	2.3×10^{-10}	Z16243	438	2.2×10^{-10}	Z17297	1199	2.4×10^{-10}
Z16051	255	2.5×10^{-10}	Z16245	440	2.2×10^{-10}	Z18557	1205	1.9×10^{-10}
Z16053	257	2.5×10^{-10}						

On average, the Z variants originating from this library (first matured library) displayed an improvement in EC_{50} values by a factor 10 compared with the average EC_{50} for the Z variants originating from the primary selection.

- 5 Biacore screening of Z variants: A selection of IL-1R-I binding Z variants was submitted to a Biacore kinetic screening. A single concentration of hIL-1R-I was injected over each Z-ABD captured from periplasmic extracts on a sensor chip surface containing an anti-ABD antibody. The calculated screening affinities are presented in Table 10. Z16062 (SEQ ID NO:266) got
- 10 the best K_D value (7.6×10^{-9} M) of the assayed binders. The K_D of Z12967 was 2.5×10^{-8} M. The four binders assayed in a SCK experiment got K_D values that deviated from their respective screening kinetics affinities by 0-14 %.

Table 10: Calculated K_D values from Biacore kinetic screening.

Z variant	SEQ ID NO	K_D (M)	Z variant	SEQ ID NO	K_D (M)	Z variant	SEQ ID NO	K_D (M)
Z15824	34	9.2×10^{-9}	Z16019	223	1.5×10^{-8}	Z16042	246	9.7×10^{-9}
Z15840	49	1.1×10^{-8}	Z16020	224	2.0×10^{-8}	Z16043	247	8.3×10^{-9}
Z15864	73	1.6×10^{-8}	Z16021	225	9.6×10^{-9}	Z16044	248	1.7×10^{-8}
Z15873	82	2.3×10^{-8}	Z16022	226	1.5×10^{-8}	Z16045	249	2.0×10^{-8}
Z15876	1206	8.3×10^{-9}	Z16023	227	9.2×10^{-9}	Z16046	250	1.8×10^{-8}
Z15882	90	9.0×10^{-9}	Z16024	228	1.4×10^{-8}	Z16047	251	1.9×10^{-8}
Z15889	97	1.5×10^{-8}	Z16025	229	1.9×10^{-8}	Z16048	252	1.1×10^{-8}
Z15897	105	1.2×10^{-8}	Z16026	230	1.6×10^{-8}	Z16049	253	1.4×10^{-8}
Z15908	116	1.7×10^{-8}	Z16027	231	1.4×10^{-8}	Z16050	254	1.3×10^{-8}
Z15947	152	1.1×10^{-8}	Z16028	232	1.9×10^{-8}	Z16051	255	1.5×10^{-8}
Z15953	158	1.1×10^{-8}	Z16029	233	2.1×10^{-8}	Z16052	256	1.2×10^{-8}
Z15972	177	1.2×10^{-8}	Z16030	234	1.7×10^{-8}	Z16053	257	1.1×10^{-8}
Z15986	190	9.5×10^{-9}	Z16031	235	2.0×10^{-8}	Z16054	258	2.9×10^{-8}

Z16009	213	2.0×10^{-8}	Z16032	236	2.6×10^{-8}	Z16055	259	1.2×10^{-8}
Z16010	214	1.2×10^{-8}	Z16033	237	1.9×10^{-8}	Z16056	260	1.3×10^{-8}
Z16011	215	1.1×10^{-8}	Z16034	238	9.1×10^{-9}	Z16057	261	3.3×10^{-8}
Z16012	216	1.2×10^{-8}	Z16035	239	1.7×10^{-8}	Z16058	262	1.4×10^{-8}
Z16013	217	1.8×10^{-8}	Z16036	240	1.1×10^{-8}	Z16059	263	1.6×10^{-8}
Z16014	218	1.1×10^{-8}	Z16037	241	1.4×10^{-8}	Z16060	264	1.9×10^{-8}
Z16015	219	1.5×10^{-8}	Z16038	242	8.9×10^{-9}	Z16061	265	1.2×10^{-8}
Z16016	220	1.2×10^{-8}	Z16039	243	1.4×10^{-8}	Z16062	266	7.6×10^{-9}
Z16017	221	1.8×10^{-8}	Z16040	244	2.0×10^{-8}	Z16063	267	1.2×10^{-8}
Z16018	220	1.6×10^{-8}	Z16041	245	1.0×10^{-8}	Z16065	268	7.8×10^{-9}

Example 5

Production and characterization of IL-1R-I binding Z variants from the first matured library

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This Example describes the general procedure for subcloning and production of His₆-tagged and ABD-fused Z variants (originating from the first maturation library phage selection), characterization of their IL-1R-I binding, blocking and melting points.

10

Materials and methods

Subcloning of Z variants with a His₆ tag: The DNA of the respective Z variant was amplified from the phage library vector pAY02592 and was subcloned with an N-terminal His₆ tag using standard molecular biology techniques essentially as described in Example 2.

Subcloning of Z variants in fusion with ABD: The N terminal sequence of respective Z variant was mutated, in position 1 and 2 to amino acid residues A and E respectively, using standard molecular biology techniques. The resulting new Z variants were subcloned into an expression vector containing an ABD variant, giving the encoding sequence [Z#####]-ASGS-ABD, where the ABD variant was PP013 (SEQ ID NO:1661). Z##### refers to individual, 58 amino acid residue long Z variants.

Cultivation: *E. coli* T7E2 cells (GeneBridges) were transformed with plasmids containing the gene fragment of each respective IL-1R-I binding Z variant. The resulting recombinant strains were cultivated in media supplemented with 50 µg/ml kanamycin at 30 °C in 50 ml scale using the EnPresso protocol (BioSilta). In order to induce protein expression, IPTG was

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added to a final concentration of 0.2 mM at OD600 $\approx$ 10. After induction, the cultivations were incubated for 16 h. The cells were harvested by centrifugation.

Purification of IL-1R-I binding Z variants with a His₆ tag: Purification was performed essentially as described in Example 2, but without the buffer exchange between the IMAC and RPC purification steps for the majority of the samples. During RPC purification, the RPC solvent A was changed to 0.1 % TFA in 100 % water and the linear gradient was 0-60 % RPC solvent B for 18 ml.

Purification of IL-1R-I binding Z variants with ABD fusion:
Approximately 2 g of each cell pellet was re-suspended in TST-buffer (25 mM Tris-HCl, 1 mM EDTA, 200 mM NaCl, 0.05 % Tween20, pH 8.0) supplemented with Benzonase® (Merck). After cell disruption and clarification by centrifugation, each supernatant was applied on a gravity flow column with 1 ml agarose immobilized with an anti-ABD ligand (produced in-house). After washing with TST-buffer and 5 mM NH₄Ac pH 5.5 buffer, the ABD fused Z variants were eluted with 0.1 M HAc. The buffer of the eluate was exchanged to PBS (2.68 mM KCl, 137 mM NaCl, 1.47 mM KH₂PO₄, 8.1 mM Na₂HPO₄, pH 7.4) using PD-10 desalting columns (GE Healthcare).

Protein concentrations were determined by measuring the absorbance at 280 nm, using a NanoDrop® ND-1000 spectrophotometer (Saveen Werner AB) and the extinction coefficient of the respective protein. The purity was analyzed by SDS-PAGE stained with Coomassie Blue and the identity of each purified Z variant was confirmed using LC/MS analysis.

Biacore kinetic analysis: The kinetic constants (k_{on} and k_{off}) and affinities (K_D) for human and cynomolgus IL-1R-I were determined for His₆-tagged Z variants using a Biacore 2000 instrument (GE Healthcare). The experiment was run essentially as described in Example 2, using 100, 10 and 1 nM of the Z variants. The analyte injection time was 3 min followed by 15 min dissociation and 2 x 5 s glycine pH 3.0 (GE Healthcare, cat. no. BR100357), supplemented with 0.5 M NaCl, was used for regeneration of the surfaces between the cycles. Kinetic constants were calculated from the obtained sensorgrams of two or three concentrations of the respective Z variant, using a 1:1 binding model in the BiaEvaluation software 4.1 (GE Healthcare). His₆-tagged Z12967 was included in the assay for comparison.

In vitro IL-1 β neutralization assay: His₆-tagged IL-1R-I specific Z variants were tested for their inhibitory capacity in the TF-1 cell assay. The

assay was run as described in Example 2. The data on cell growth was assessed by non-linear regression to a four-parameter dose-response curve, and IC₅₀ values were determined using GraphPadPrism program. His₆-tagged Z12967 was included for comparison.

- 5 Circular dichroism (CD) spectroscopy analysis: CD was analyzed for His₆-tagged Z variants, as described in Example 2.

Results

- 10 Subcloning with His₆ tag: Z variants were subcloned into constructs with an N-terminal His₆.

- 15 Production of His₆-tagged Z variants: The IL-1R-I binding Z variants with a His₆ tag were expressed as soluble gene products in *E. coli*. The amount of purified protein was determined spectrophotometrically by measuring the absorbance at 280 nm and ranged from approximately 1 to 7 mg protein per g pellet. SDS-PAGE analysis of each final protein preparation showed that these predominantly contained the IL-1R-I binding Z variant. The correct identity and molecular weight of each Z variant were confirmed by HPLC-MS analysis.

- 20 Biacore kinetic analysis: The interactions of His₆-tagged IL-1R-I binding Z variants with human and cynomolgus IL-1R-I were analyzed in a Biacore instrument by injecting various concentrations of the Z variants over a surface containing immobilized IL-1R-I. A summary of the calculated kinetic parameters (K_D , k_{on} and k_{off}) for the human IL-1R-I binding is given in Table 11. The strongest binder to human IL-1R-I, Z18557 (SEQ ID NO:1205), got a K_D of 1.5×10^{-10} against human IL-1R-I and 7.6×10^{-9} M against cynomolgus IL-1R-I. The K_D of Z12967 to human IL-1R-I was 5.1×10^{-10} M.

Table 11. Kinetic parameters and affinities for His₆-Z polypeptides binding to human IL-1R-I.

Z variant	SEQ ID NO	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
Z15862	71	2.8×10^6	1.9×10^{-3}	6.7×10^{-10}
Z15876	1206	2.1×10^6	1.3×10^{-3}	6.2×10^{-10}
Z15927	135	2.4×10^6	1.2×10^{-3}	5.1×10^{-10}
Z15953	158	6.0×10^6	1.5×10^{-3}	2.4×10^{-10}
Z15961	166	4.3×10^6	2.0×10^{-3}	4.6×10^{-10}
Z16007	211	2.3×10^6	2.1×10^{-3}	9.2×10^{-10}
Z16023	227	5.3×10^6	1.5×10^{-3}	2.9×10^{-10}
Z16043	247	2.5×10^6	1.1×10^{-3}	4.4×10^{-10}

Z16062	266	2.6×10^6	1.1×10^{-3}	4.4×10^{-10}
Z16065	268	6.9×10^6	1.3×10^{-3}	1.9×10^{-10}
Z16072	275	4.6×10^6	2.2×10^{-3}	4.7×10^{-10}
Z16093	294	5.6×10^6	1.4×10^{-3}	2.5×10^{-10}
Z16097	298	3.1×10^6	1.5×10^{-3}	4.8×10^{-10}
Z16116	316	2.6×10^6	2.3×10^{-3}	8.8×10^{-10}
Z16117	317	4.0×10^6	2.7×10^{-3}	6.9×10^{-10}
Z16127	325	6.7×10^6	1.9×10^{-3}	2.9×10^{-10}
Z16143	341	3.1×10^6	1.6×10^{-3}	5.3×10^{-10}
Z16163	359	3.5×10^6	2.0×10^{-3}	5.5×10^{-10}
Z16165	361	2.1×10^6	3.6×10^{-3}	1.7×10^{-9}
Z16169	365	2.6×10^6	1.0×10^{-3}	3.9×10^{-10}
Z16219	415	2.5×10^6	5.6×10^{-3}	2.2×10^{-9}
Z16245	440	2.7×10^6	3.1×10^{-3}	1.2×10^{-9}
Z16255	449	3.0×10^6	3.1×10^{-3}	1.0×10^{-9}
Z16301	494	3.1×10^6	2.1×10^{-3}	6.6×10^{-10}
Z16341	531	3.0×10^6	1.6×10^{-3}	5.2×10^{-10}
Z16363	550	3.2×10^6	1.8×10^{-3}	5.7×10^{-10}
Z16377	562	2.1×10^6	1.1×10^{-3}	5.4×10^{-10}
Z16378	563	6.6×10^6	3.6×10^{-3}	5.5×10^{-10}
Z16681	856	3.6×10^6	5.0×10^{-3}	1.4×10^{-9}
Z17274	1176	1.1×10^7	2.4×10^{-3}	2.2×10^{-10}
Z17280	1182	2.4×10^6	5.3×10^{-3}	2.2×10^{-9}
Z17292	1194	1.3×10^7	5.0×10^{-3}	3.8×10^{-10}
Z18557	1205	4.4×10^6	6.7×10^{-4}	1.5×10^{-10}

In vitro IL-1 β neutralization assay: The IL-1 β inhibition ability of His₆-tagged IL-1R-I-binding Z variants was analyzed in a TF-1 cell assay. The resulting IC₅₀ values are presented in Table 12. Z18557 (SEQ ID NO:1205) displayed the best inhibition capacity with an IC₅₀ value below 0.5 nM. The IC₅₀ of Z12967 was 5.2 nM.

Table 12: IC₅₀ values for His₆-Z polypeptides from a TF-1 cell assay.

Z variant	SEQ ID NO	IC ₅₀ (nM)	Z variant	SEQ ID NO	IC ₅₀ (nM)
Z15862	71	6.6	Z16163	359	1.8
Z15876	1206	2.4	Z16165	361	11.5
Z15927	135	2.5	Z16169	365	0.76
Z15953	158	3.7	Z16219	415	24.2
Z15961	166	2.9	Z16245	440	8.2
Z16007	211	5.9	Z16255	449	8.5

Z16023	227	3.8	Z16301	494	4.5
Z16043	247	2.5	Z16341	531	3.9
Z16062	266	1.8	Z16363	550	8.1
Z16065	268	1.7	Z16377	562	3.1
Z16072	275	4.3	Z16378	586	32.7
Z16093	294	3.3	Z16681	856	20.1
Z16097	298	3.4	Z17274	1176	4.6
Z16116	316	4.1	Z17280	1182	5.4
Z16117	317	8.5	Z17292	1194	13.2
Z16127	325	4.1	Z18557	1205	<0.5
Z16143	341	4.8			

- CD analysis: The CD spectra determined for the IL-1R-I binding Z variants with a His₆ tag showed that each had an α -helical structure at 20 °C. This result was also verified in the variable temperature measurements, wherein melting temperatures were determined (Table 13). Reversible folding was seen for all the IL-1R-I binding Z variants when overlaying spectra measured before and after heating to 90 °C.

Table 13: Melting temperatures (T_m).

Z variant	SEQ ID NO	T _m (°C)	Z variant	SEQ ID NO	T _m (°C)
Z15876	1206	55	Z16117	317	63
Z15927	135	56	Z16127	325	59
Z15953	158	56	Z16163	359	57
Z15961	166	59	Z16169	365	48
Z16023	227	60	Z16245	440	63
Z16043	247	54	Z16341	531	59
Z16062	266	54	Z16377	562	52
Z16065	268	59	Z16681	856	68
Z16093	294	52	Z17280	1182	62
Z16097	298	56	Z18557	1205	60
Z16116	316	59			

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Example 6

Design and construction of two second matured libraries of IL-1R-I binding Z variants

- 15 In this Example, two second matured libraries were constructed. The libraries were used for selections of additional IL-1R-I binding Z variants.

Materials and methods

Library design: The libraries were primarily based on sequences of human IL-1R-I binding Z variants described in Example 4 and 5. In the new libraries, denoted Zlib006IL-1RI.II and Zlib006IL-1RI.III, 10 variable positions in the Z molecule scaffold were biased towards certain amino acid residues and three positions were kept constant, respectively, according to a strategy mainly based on Z variants (SEQ ID NO:19-1209) from the selection from the first matured library. In addition, in both libraries, a new amino acid position was included for variation; position 12 of the 58 aa Z variant sequence, resulting in 11 variable positions, in total. Position 12 of Z18557 (SEQ ID NO:1205), characterized in Example 5, was valine. The library design allowed for the amino acids A, V and I in position 12.

For Zlib006IL-1RI.II, a DNA linker was generated using split-pool synthesis containing the following sequence ordered from DNA 2.0 (Menlo Park, CA, USA): 5'-AA ATA AAT CTC GAG GTA GAT GCC AAA TAC GCC AAA GAA NNN NNN NNN NNN NNN NNN GAG ATC NNN NNN CTG CCT AAC CTC ACC NNN NNN CAA NNN NNN GCC TTC ATC NNN AAA TTA NNN GAT GAC CCA AGC CAG AGC TCA TTA TTT A-3' (SEQ ID NO:1681, designed codons are denoted NNN). The design for each amino acid residue of the new library, including eleven variable amino acid positions (9, 10, 11, 12, 13, 14, 17, 18, 25, 28 and 35) and three constant amino acid positions (24, 27 and 32) in the Z molecule scaffold, are displayed in Table 14. The resulting theoretical library size was 2.2×10^7 variants. An even theoretical distribution of the different amino acids was applied within each amino acid position, except from position 10, 11, 12, 13, 17, 28 and 35, where a higher portion of selected amino acids was applied.

For Zlib006IL-1RI.III, the library was constructed similarly as Zlib006IL-1RI.I, described in Example 3, using the TRIM technology. The DNA sequence, 5'-AA ATA AAT CTC GAG GTA GAT GCC AAA TAC GCC AAA GAA NNN NNN NNN NNN NNN NNN GAG ATC NNN NNN CTG CCT AAC CTC ACC NNN NNN CAA NNN NNN GCC TTC ATC NNN AAA TTA NNN GAT GAC CCA AGC CAG AGC TCA TTA TTT A-3 (SEQ ID NO:1682, designed codons are denoted NNN) was ordered from Ella Biotech (Martinsried, Germany). The design for each amino acid residue of the new library, including eleven variable amino acid positions (9, 10, 11, 12, 13, 14, 17, 18, 25, 32 and 35) and three constant amino acid positions (24, 27 and 28) in the Z molecule scaffold, are displayed in Table 15. The resulting

theoretical library size was 1.0×10^8 variants. An even theoretical distribution of the different amino acids was applied within each amino acid position, except from position 10, 11, 12, 32 and 35, where a higher portion of selected amino acids was applied.

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Table 14: Zlib006IL-1RI.II library design, second maturation.

Amino acid position in the Z variant molecule	Amino acid randomization (percentage when uneven distribution)	No. of different amino acids
9	A,E,I,L,T,V	6
10	E(50 %),I,L,R,V,Y	6
11	A,E(27 %),I,K,Q,R,T,V,Y	9
12	A(50 %),I,V	3
13	A,I,L,Q(50 %),V,Y	6
14	F,M,Q,W,Y	5
17	F(70 %),Y(30 %)	2
18	A,D,E,F,G,H,I,K,L,Q,R,S,T,V,W,Y	16
24	R	1
25	K,R	2
27	Y	1
28	I,T(71.4 %),V	3
32	R	1
35	F(25 %),I(12.5 %),L(50 %),Y(12.5 %)	4

Table 15: Zlib006IL-1RI.III library design, second maturation.

Amino acid position in the Z variant molecule	Amino acid randomization (percentage when uneven distribution)	No. of different amino acids
9	A,E,I,L,T,V	6
10	E(60 %),I,V	3
11	A,D,E(15 %),F,H,I,K,L,Q,R,S,T,V,W,Y	15
12	A(50 %),I(20 %), V(30 %)	3
13	A,E,F,H,I,K,L,Q,R,S,T,V,W,Y	14
14	A,E,F,H,I,K,L,Q,R,S,T,V,W,Y	14
17	F,I,L,W,Y	5
18	A,D,E,F,G,H,I,K,L,Q,R,S,T,V,W,Y	16
24	R	1
25	K,R	2
27	Y	1
28	T	1
32	I(10 %),R(90 %)	2
35	F(30 %),L(70 %)	2

Library construction and phage stock preparation: Zlib006IL-1RI.II and Zlib006IL-1RI.III were constructed as described in WO 2016/113246 (Example 4) and in Example 3, respectively. For both libraries, *E. coli* XL-1 Blue was used for library transformation. Clones from the libraries of Z variants were sequenced (as described in Example 3) in order to verify the content and to evaluate the outcome of the constructed library vis-à-vis the library design.

Phage stocks containing the phagemid libraries were prepared in shake flasks. Cells from glycerol stocks containing the phagemid library were inoculated in 0.5 or 1 l, respectively, of TSB-YE medium, essentially as described for Zlib006IL-1RI.I batch 2 in Example 3. The cultivations were infected using a 10-20 x molar excess of M13K07 helper phage at an OD₆₀₀ of 0.8-0.9. Phage stocks were prepared as described in Example 3.

Results

Library construction: The new libraries were designed based on a set of IL-1R-I binding Z variants, selected from Zlib006IL-1RI.I, with verified binding properties (Examples 4 and 5). The theoretical sizes of Zlib006IL-1RI.II and Zlib006IL-1RI.III were 2.2×10^7 and 1.0×10^8 Z variants, respectively. The actual sizes of the libraries, determined by titration after transformation to *E. coli* XL-1 Blue cells, were 1.2×10^9 and 7.0×10^9 transformants, respectively.

The library qualities were tested by sequencing of 192 and 96 transformants from Zlib006IL-1RI.II and Zlib006IL-1RI.III, respectively, and by comparing their actual sequences with the theoretical design. The contents of the actual library compared to the designed library were shown to be satisfactory. Two matured libraries of potential binders to IL-1R-I were thus successfully constructed.

Example 7

Selection of Z variants from the second matured libraries

In this Example, human and cynomolgus IL-1R-I were used as target proteins in phage display selections using two second matured phage libraries of Z variants.

Materials and methods

Phage display selection of IL-1R-I binding Z variants: The biotinylated human target proteins b-hIL-1R-I-Fc and b-hIL-1R-I, and the cynomolgus target protein b-cIL-1R-I-Fc, were used in phage selections using the new libraries of Z variant molecules described in Example 6. An overview of the selection strategy, describing the parallel selection tracks and an overall increased stringency in the selection cycles obtained by using a lowered target concentration and an increased number of washes, is shown in Table 16.

10

Table 16: Overview of selections from the two second matured libraries.

Cycle	Selection track	Phage stock from library or selection track	Target	Target concentration (nM)	Selection time (min)	Number of washes
1	1-1	Zlib006IL-1RI.II	b-hIL-1R-I-Fc	10	45	5
1	1-2	Zlib006IL-1RI.II	b-hIL-1R-I	10	45	5
1	1-3	Zlib006IL-1RI.II	b-cIL-1R-I-Fc	25	45	3
1	1-4	Zlib006IL-1RI.III	b-hIL-1R-I-Fc	20	45	5
1	1-5	Zlib006IL-1RI.III	b-hIL-1R-I	20	45	5
1	1-6	Zlib006IL-1RI.III	b-cIL-1R-I-Fc	50	45	3
1	1-7	Zlib006IL-1RI.II	b-hIL-1R-I-Fc	10	45	5
1	1-8	Zlib006IL-1RI.II	b-hIL-1R-I	10	45	5
1	1-9	Zlib006IL-1RI.II	b-cIL-1R-I-Fc	25	45	3
1	1-10	Zlib006IL-1RI.III	b-hIL-1R-I-Fc	20	45	5
1	1-11	Zlib006IL-1RI.III	b-hIL-1R-I	20	45	5
1	1-12	Zlib006IL-1RI.III	b-cIL-1R-I-Fc	50	45	3
2	2-1	1-1	b-hIL-1R-I-Fc	1	30	10*
2	2-2	1-2	b-hIL-1R-I	2	30	10
2	2-3	1-2	b-hIL-1R-I	1	30	10
2	2-4	1-2	b-hIL-1R-I	1	30	10*
2	2-5	1-3	b-hIL-1R-I	10	30	8
2	2-6	1-4	b-hIL-1R-I-Fc	4	30	8
2	2-7	1-5	b-hIL-1R-I	4	30	8
2	2-8	1-5	b-hIL-1R-I	2	30	10
2	2-9	1-5	b-hIL-1R-I	2	30	10*
2	2-10	1-6	b-hIL-1R-I	20	30	6
2	2-11	1-7/1-8/1-9 pool	b-hIL-1R-I	1	30	10*

2	2-12	1-10/1-11/1-12 pool	b-hIL-1R-I	2	30	10*
3	3-1	2-1	b-hIL-1R-I-Fc	0.4	40	16*
3	3-2	2-2	b-hIL-1R-I	0.4	40	15
3	3-3	2-3	b-hIL-1R-I	0.1	40	20
3	3-4	2-4	b-hIL-1R-I	0.1	40	16*
3	3-5	2-5	b-cIL-1R-I-Fc	5	40	12
3	3-6	2-6	b-hIL-1R-I-Fc	0.8	40	12
3	3-7	2-7	b-hIL-1R-I	0.8	40	12
3	3-8	2-8	b-hIL-1R-I	0.2	40	20
3	3-9	2-9	b-hIL-1R-I	0.2	40	16*
3	3-10	2-10	b-cIL-1R-I-Fc	10	40	9
3	3-11	2-11	b-hIL-1R-I	0.4	40	16*
3	3-12	2-12	b-hIL-1R-I	0.4	40	16*
4	4-1	3-1	b-hIL-1R-I-Fc	0.125	40	20**
4	4-2	3-2	b-hIL-1R-I	0.125	40	20
4	4-3	3-3	b-hIL-1R-I	0.05	40	30
4	4-4	3-4	b-hIL-1R-I	0.05	40	20**
4	4-5	3-5	b-hIL-1R-I	1	40	16
4	4-6	3-6	b-hIL-1R-I-Fc	0.16	40	16**
4	4-7	3-7	b-hIL-1R-I	0.16	40	16
4	4-8	3-8	b-hIL-1R-I	0.1	40	30
4	4-9	3-9	b-hIL-1R-I	0.1	40	20**
4	4-10	3-10	b-hIL-1R-I	2	40	16
4	4-11	3-11	b-hIL-1R-I	0.2	40	16
4	4-12	3-12	b-hIL-1R-I	0.2	40	16

*Addition of hIL-1R-I in the second final wash step.

**Selection track divided into two before second final wash step. One part submitted to an over-night wash in the presence of hIL-1R-I and one part submitted to a 1 h wash in PBST.

5

The selections were performed in four cycles essentially as described in Example 4, with the following exceptions 1-3. Exception 1: pre-selection was performed in selection round 1 and 2 for >60 min at RT by incubation of phage stocks with SA beads (b-hIL-1R-I tracks) or Fc/SA beads (b-IL-1RI-Fc tracks). Exception 2: in the second final wash step of tracks 2-1, 2-4, 2-9, 2-11, 2-12, 3-1, 3-4, 3-9, 3-11 and 3-12, respectively, hIL-1R-I was added to the wash buffer in 100 times higher concentration than the target concentration of the respective track and the wash was run for 15-20 min. Exception 3: In the fourth selection round, the tracks 4-1, 4-4 and 4-6 were divided into two before the second final wash step. For one part, hIL-1R-I was added to the wash buffer in 100 times higher concentration than the target concentration of

the respective track and the second final wash was run overnight. For the other part, a 1 h wash in PBST was applied for the second final wash.

In the first selection cycle, twelve selection tracks were run; 1-1 to 1-12. In cycle two, two tracks were divided into three, and six tracks were pooled into two tracks, resulting in a total of 12 parallel tracks in cycle 2, 3 and 4; 2-1 to 2-12, 3-1 to 3-12 and 4-1 to 4-12, respectively. All selection tracks are presented in Table 16. The number of phage particles used for selections was typically more than 2000 times the number of eluted phage particles in the previous cycle.

Results

Phage display selection of IL-1R-I binding Z variants: Individual clones were obtained after four cycles of phage display selections against human and cynomolgus IL-1R-I.

Example 8

Screening of Z variants from the first and second matured libraries

In this Example, DNA of selected clones from Example 4 and Example 7 was sequenced, the Z variants were produced in *E. coli* periplasmic fractions and assayed against IL-1R-I in ELISA and Biacore.

Materials and methods

Sequencing of potential binders: Individual clones from cycle 4 of selections using the three matured libraries Zlib006IL-1RI.I, Zlib006IL-1RI.II and Zlib006IL-1RI.III were picked for sequencing. Amplification and sequence analysis of gene fragments were performed essentially as described in Example 1.

Production of Z variants for ELISA and Biacore screening: Z variants were produced essentially as described in Example 4 with the exception that the periplasmic extracts were prepared by heat-treatment (82 °C, 20 min) followed by clarification by filtration. Z variants screened in Biacore were diluted five times in HBS-EP buffer.

ELISA screening of Z variants: The binding of Z variants to human IL-1R-I was analyzed in ELISA, essentially as described in Example 1, using 0.2 nM hIL-1R-I-Fc as target protein. As negative control, a periplasmic extract of ABD001 was used.

EC₅₀ analysis of Z variants: A selection of IL-1R-I binding was subjected to an analysis of response against a dilution series of hIL-1R-I-Fc using ELISA as described above. The target protein hIL-1R-I-Fc was diluted stepwise 1:10 from 20 to 0.002 nM. As a background control, the Z variants
5 were assayed with no target protein added. Obtained data was analyzed using GraphPad Prism 5 and non-linear regression, and the EC₅₀ values (the half maximal effective concentration) were calculated. Periplasmic extracts with Z12967, Z16065 and Z16218 (corresponding to SEQ ID:9, 268 and 414, respectively) were analyzed in parallel for signal comparison. As negative
10 control, a periplasmic extract of ABD001 was used.

Biacore screening of Z variants: The binding of Z variants to human IL-1R-I was analyzed in a kinetic screening, using a Biacore 2000 instrument, essentially as described in Example 4, but with the exception that Z-ABD (ABD001, SEQ ID NO:1660) periplasmic extracts were injected during 2 min.
15 Periplasmic extracts of Z12967, Z16065 and Z16218 were included in the screening analysis in duplicates for comparison. A periplasmic extract with ABD (ABD001, SEQ ID NO:1660) was included as negative control.

Results

Sequencing: Sequencing was performed for clones obtained after four
20 cycles of selection. Each variant was given a unique identification number #####, and individual variants are referred to as Z#####. The amino acid sequences of the 58 amino acid residues long Z variants are listed in Figure 1 and in the sequence listing as SEQ ID NO: 1210-1632. The deduced IL-1R-I
25 binding motifs extend from residue 8 to residue 36 in each sequence. The amino acid sequences of the 49 amino acid residues long polypeptides predicted to constitute the complete three-helix bundle within each of these Z variants extend from residue 7 to residue 55.

ELISA screening of Z variants: Clones obtained after four cycles of
30 selection were produced individually in 96-well plates and were screened for human IL-1R-I binding activity in ELISA. 99.5 % of the assayed Z variants gave a positive signal of 2 x the blank control or higher against 0.2 nM hIL-1R-I-Fc.

EC₅₀ analysis of Z variants: A subset of 102 Z variants displaying
35 results over 0.74 AU (8.2 x the blank control) was subjected to ELISA target titration using hIL-1R-I-Fc. Obtained results were used for calculation of EC₅₀

values (Table 17). The results for Z12967, Z16065 and Z16218 were 2.6×10^{-10} , 2.1×10^{-10} and 2.2×10^{-10} M, respectively.

Table 17: Calculated EC_{50} values from ELISA titration analysis.

Z variant	SEQ ID NO	EC_{50} (M)	Z variant	SEQ ID NO	EC_{50} (M)	Z variant	SEQ ID NO	EC_{50} (M)
Z15840	49	2.3×10^{-10}	Z18811	1405	2.8×10^{-10}	Z18920	1270	2.4×10^{-10}
Z15862	71	2.5×10^{-10}	Z18813	1375	2.0×10^{-10}	Z18966	1272	2.5×10^{-10}
Z15876	1206	1.9×10^{-10}	Z18814	1368	2.7×10^{-10}	Z18967	1388	3.1×10^{-10}
Z15934	1208	1.7×10^{-10}	Z18819	1276	2.9×10^{-10}	Z18968	1472	2.0×10^{-10}
Z15945	150	2.3×10^{-10}	Z18820	1417	3.3×10^{-10}	Z18971	1559	3.5×10^{-10}
Z15975	1209	1.9×10^{-10}	Z18824	1264	2.8×10^{-10}	Z18982	1553	2.5×10^{-10}
Z16062	266	2.1×10^{-10}	Z18825	1275	3.5×10^{-10}	Z19012	1588	2.4×10^{-10}
Z16183	379	2.3×10^{-10}	Z18826	1356	2.4×10^{-10}	Z19053	1526	2.4×10^{-10}
Z16208	404	2.2×10^{-10}	Z18827	1318	2.4×10^{-10}	Z19054	1528	2.5×10^{-10}
Z16603	782	2.2×10^{-10}	Z18831	1308	2.9×10^{-10}	Z19056	1586	2.2×10^{-10}
Z16606	785	2.3×10^{-10}	Z18832	1340	1.5×10^{-10}	Z19057	1558	2.2×10^{-10}
Z18754	1252	3.5×10^{-10}	Z18834	1361	2.5×10^{-10}	Z19059	1240	3.5×10^{-10}
Z18757	1321	3.0×10^{-10}	Z18836	1430	2.3×10^{-10}	Z19060	1228	2.2×10^{-10}
Z18758	1281	2.4×10^{-10}	Z18838	1337	2.4×10^{-10}	Z19072	1554	1.6×10^{-10}
Z18759	1314	2.4×10^{-10}	Z18843	1309	2.8×10^{-10}	Z19075	1618	1.5×10^{-10}
Z18760	1435	1.7×10^{-10}	Z18846	1331	1.9×10^{-10}	Z19078	1248	2.2×10^{-10}
Z18763	1431	2.6×10^{-10}	Z18866	1324	3.1×10^{-10}	Z19085	1564	2.1×10^{-10}
Z18766	1274	3.3×10^{-10}	Z18874	1421	2.2×10^{-10}	Z19090	1540	2.0×10^{-10}
Z18769	1339	2.9×10^{-10}	Z18875	1420	2.9×10^{-10}	Z19115	1489	2.3×10^{-10}
Z18770	1284	2.8×10^{-10}	Z18877	1301	3.5×10^{-10}	Z19117	1631	2.1×10^{-10}
Z18771	1341	2.5×10^{-10}	Z18878	1302	3.7×10^{-10}	Z19118	1579	2.3×10^{-10}
Z18774	1389	2.6×10^{-10}	Z18879	1390	3.4×10^{-10}	Z19123	1241	2.6×10^{-10}
Z18776	1418	2.2×10^{-10}	Z18881	1355	2.8×10^{-10}	Z19151	1594	2.3×10^{-10}
Z18777	1326	2.6×10^{-10}	Z18882	1311	3.1×10^{-10}	Z19158	1571	1.5×10^{-10}
Z18785	1323	2.5×10^{-10}	Z18884	1403	2.3×10^{-10}	Z19159	1364	2.1×10^{-10}
Z18786	1320	2.4×10^{-10}	Z18886	1432	2.9×10^{-10}	Z19171	1593	2.3×10^{-10}
Z18790	1439	2.6×10^{-10}	Z18887	1386	2.1×10^{-10}	Z19172	1551	1.6×10^{-10}
Z18799	1423	2.3×10^{-10}	Z18888	1422	2.3×10^{-10}	Z19180	1393	2.0×10^{-10}
Z18803	1327	2.5×10^{-10}	Z18889	1344	2.4×10^{-10}	Z19181	1549	1.8×10^{-10}
Z18804	1329	2.7×10^{-10}	Z18890	1352	2.5×10^{-10}	Z19182	1628	1.7×10^{-10}
Z18805	1437	2.7×10^{-10}	Z18904	1587	3.8×10^{-10}	Z19183	1235	2.2×10^{-10}
Z18806	1271	2.7×10^{-10}	Z18908	1591	2.4×10^{-10}	Z19302	1419	2.6×10^{-10}
Z18808	1342	4.0×10^{-10}	Z18912	1251	1.4×10^{-10}	Z19304	1273	2.7×10^{-10}
Z18810	1278	2.9×10^{-10}	Z18917	1509	2.2×10^{-10}	Z19305	1261	2.6×10^{-10}

Biacore screening of Z variants: A subset of 188 IL-1R-I binding Z variants was submitted to a Biacore kinetic screening. A single concentration of hIL-1R-I was injected over each Z-ABD captured from periplasmic extracts on a sensor chip surface containing an anti-ABD antibody. The calculated screening affinities are presented in Table 18. The K_D values of Z12967, Z16065 and Z16218 were 2.7×10^{-8} , 7.5×10^{-9} and 1.3×10^{-8} M (average of duplicates), respectively.

Z18814, which has an amino acid sequence that only differs from Z16065 in position X_5 of the binding motif BM, has three times higher affinity than Z16065. Z16065 has the highest binding affinity (K_D) among the IL-1R-I binding Z variants (Table 11) with an alanine residue in position X_5 . Z18814 has an isoleucine residue in position X_5 . Several Z variants with valine or isoleucine in position X_5 were found to have high affinity to IL-1R-I.

Table 18: Calculated K_D values from Biacore kinetic screening.

Z variant	SEQ ID NO	Biacore screening K_D (M)	Z variant	SEQ ID NO	Biacore screening K_D (M)	Z variant	SEQ ID NO	Biacore screening K_D (M)
Z15840	49	6.9×10^{-9}	Z18830	1295	2.9×10^{-9}	Z18938	1370	4.5×10^{-9}
Z15862	71	1.3×10^{-8}	Z18831	1308	3.0×10^{-9}	Z18941	1409	3.3×10^{-9}
Z15876	1206	5.7×10^{-9}	Z18832	1340	1.6×10^{-9}	Z18942	1483	1.5×10^{-8}
Z15932	1207	5.5×10^{-9}	Z18833	1297	3.8×10^{-9}	Z18948	1414	4.3×10^{-9}
Z15934	1208	9.4×10^{-9}	Z18834	1361	2.4×10^{-9}	Z18952	1290	3.0×10^{-9}
Z15945	150	9.6×10^{-9}	Z18836	1430	2.9×10^{-9}	Z18956	1625	1.4×10^{-8}
Z15975	1209	8.9×10^{-9}	Z18838	1337	3.3×10^{-9}	Z18958	1283	2.8×10^{-9}
Z16062	266	6.4×10^{-9}	Z18839	1440	3.1×10^{-9}	Z18959	1357	2.9×10^{-9}
Z16183	379	6.5×10^{-9}	Z18841	1359	2.5×10^{-9}	Z18966	1272	2.9×10^{-9}
Z16191	387	6.3×10^{-9}	Z18843	1309	3.1×10^{-9}	Z18967	1388	3.2×10^{-9}
Z16208	404	1.1×10^{-8}	Z18844	1349	4.0×10^{-9}	Z18968	1472	2.4×10^{-9}
Z16397	582	1.3×10^{-8}	Z18846	1331	2.1×10^{-9}	Z18971	1559	5.5×10^{-9}
Z16440	624	1.3×10^{-8}	Z18847	1363	3.0×10^{-9}	Z18982	1553	5.2×10^{-9}
Z16603	782	9.1×10^{-9}	Z18848	1304	3.0×10^{-9}	Z18989	1592	4.5×10^{-9}
Z16606	785	9.6×10^{-9}	Z18849	1299	3.0×10^{-9}	Z19012	1588	4.5×10^{-9}
Z16737	910	1.2×10^{-8}	Z18850	1367	2.6×10^{-9}	Z19031	1600	3.1×10^{-9}
Z18754	1252	2.5×10^{-9}	Z18851	1291	3.6×10^{-9}	Z19043	1505	3.4×10^{-9}
Z18756	1366	2.9×10^{-9}	Z18853	1298	2.3×10^{-9}	Z19053	1526	8.7×10^{-9}
Z18757	1321	3.0×10^{-9}	Z18856	1330	2.9×10^{-9}	Z19054	1528	7.0×10^{-9}
Z18758	1281	4.8×10^{-9}	Z18860	1265	6.2×10^{-9}	Z19056	1586	6.9×10^{-9}
Z18759	1314	3.4×10^{-9}	Z18861	1369	3.3×10^{-9}	Z19057	1558	4.2×10^{-9}
Z18760	1435	3.0×10^{-9}	Z18863	1362	2.4×10^{-9}	Z19059	1240	9.2×10^{-9}
Z18762	1415	2.1×10^{-9}	Z18866	1324	2.7×10^{-9}	Z19060	1228	1.0×10^{-8}

Z18763	1431	5.2×10^{-9}	Z18868	1391	2.7×10^{-9}	Z19072	1554	5.2×10^{-9}
Z18766	1274	3.1×10^{-9}	Z18870	1428	3.0×10^{-9}	Z19075	1618	4.8×10^{-9}
Z18767	12353	5.1×10^{-9}	Z18871	1332	3.5×10^{-9}	Z19078	1248	9.5×10^{-9}
Z18769	1339	2.7×10^{-9}	Z18872	1410	2.6×10^{-9}	Z19079	1236	1.4×10^{-8}
Z18770	1284	2.6×10^{-9}	Z18873	1306	3.1×10^{-9}	Z19085	1564	4.9×10^{-9}
Z18771	1341	3.0×10^{-9}	Z18874	1421	2.3×10^{-9}	Z19090	1540	3.0×10^{-9}
Z18774	1389	3.0×10^{-9}	Z18875	1420	2.7×10^{-9}	Z19094	1231	1.8×10^{-8}
Z18776	1418	2.8×10^{-9}	Z18876	1286	3.7×10^{-9}	Z19099	1548	3.8×10^{-9}
Z18777	1326	3.8×10^{-9}	Z18877	1301	2.7×10^{-9}	Z19107	1566	6.7×10^{-9}
Z18782	1333	2.7×10^{-9}	Z18878	1302	3.8×10^{-9}	Z19115	1489	6.1×10^{-9}
Z18783	1257	3.4×10^{-9}	Z18879	1390	6.2×10^{-9}	Z19117	1631	4.2×10^{-9}
Z18784	1433	3.7×10^{-9}	Z18881	1355	3.2×10^{-9}	Z19118	1579	8.4×10^{-9}
Z18785	1323	2.7×10^{-9}	Z18882	1311	2.6×10^{-9}	Z19123	1241	1.1×10^{-8}
Z18786	1320	4.8×10^{-9}	Z18884	1403	2.7×10^{-9}	Z19127	1213	9.8×10^{-9}
Z18790	1439	3.0×10^{-9}	Z18885	1294	3.9×10^{-9}	Z19135	1247	1.6×10^{-8}
Z18794	1424	3.7×10^{-9}	Z18886	1432	3.9×10^{-9}	Z19141	1506	1.7×10^{-8}
Z18796	1352	3.6×10^{-9}	Z18887	1386	2.9×10^{-9}	Z19143	1471	1.4×10^{-9}
Z18798	1268	3.2×10^{-9}	Z18888	1422	2.6×10^{-9}	Z19144	1374	3.1×10^{-9}
Z18799	1423	2.6×10^{-9}	Z18889	1344	3.4×10^{-9}	Z19146	1434	2.9×10^{-9}
Z18800	1328	1.9×10^{-9}	Z18890	1352	3.1×10^{-9}	Z19147	1307	2.4×10^{-9}
Z18803	1327	3.1×10^{-9}	Z18893	1353	2.1×10^{-9}	Z19151	1594	2.7×10^{-9}
Z18804	1329	3.3×10^{-9}	Z18894	1312	2.5×10^{-9}	Z19153	1310	3.1×10^{-9}
Z18805	1437	3.7×10^{-9}	Z18895	1411	2.6×10^{-9}	Z19158	1571	1.5×10^{-9}
Z18806	1271	4.1×10^{-9}	Z18896	1436	3.5×10^{-9}	Z19159	1364	1.9×10^{-9}
Z18807	1400	3.8×10^{-9}	Z18898	1285	2.5×10^{-9}	Z19160	1379	3.8×10^{-9}
Z18808	1342	4.2×10^{-9}	Z18904	1587	3.4×10^{-9}	Z19166	1305	3.5×10^{-9}
Z18810	1278	3.1×10^{-9}	Z18908	1591	3.6×10^{-9}	Z19168	1500	4.6×10^{-9}
Z18811	1405	4.5×10^{-9}	Z18909	1303	2.7×10^{-9}	Z19169	1402	2.7×10^{-9}
Z18813	1375	2.0×10^{-9}	Z18910	1416	3.1×10^{-9}	Z19170	1334	2.0×10^{-9}
Z18814	1368	2.4×10^{-9}	Z18911	1441	2.8×10^{-9}	Z19171	1593	3.0×10^{-9}
Z18817	1343	3.5×10^{-9}	Z18912	1251	3.6×10^{-9}	Z19172	1551	4.5×10^{-9}
Z18819	1276	3.0×10^{-9}	Z18916	1536	4.1×10^{-9}	Z19180	1393	7.9×10^{-10}
Z18820	1417	3.3×10^{-9}	Z18917	1509	7.1×10^{-9}	Z19181	1549	9.7×10^{-9}
Z18821	1269	3.5×10^{-9}	Z18919	1350	2.8×10^{-9}	Z19182	1628	2.8×10^{-9}
Z18823	1282	2.4×10^{-9}	Z18920	1270	3.2×10^{-9}	Z19183	1235	1.2×10^{-8}
Z18824	1264	3.3×10^{-9}	Z18922	1533	4.9×10^{-9}	Z19302	1419	3.2×10^{-9}
Z18825	1275	4.9×10^{-9}	Z18923	1482	9.0×10^{-9}	Z19303	1262	4.0×10^{-9}
Z18826	1356	3.5×10^{-9}	Z18925	1479	1.1×10^{-8}	Z19304	1273	4.5×10^{-9}
Z18827	1318	4.3×10^{-9}	Z18927	1372	3.4×10^{-9}	Z19305	1261	3.8×10^{-9}
Z18828	1296	2.6×10^{-9}						

Example 9

Production and characterization of Z variants from the first and second matured libraries

5 This Example describes the general procedure for subcloning and production of His₆-tagged Z variants originating from the first and second maturation library phage selections, characterization of their target binding, target blocking and melting points.

10 *Materials and methods*

Subcloning of Z variants with a His₆ tag: A subset of Z variants screened in Example 8 was chosen for subcloning. The DNA of the respective Z variant was amplified from the phage library vector pAY02592 and was subcloned with an N-terminal His₆ tag using standard molecular biology techniques essentially as described in Example 2.

15 Cultivation: *E. coli* T7E2 cells (GeneBridges) were transformed with plasmids containing the gene fragment of each respective IL-1R-I binding Z variant. The resulting recombinant strains were cultivated in media supplemented with 50 µg/ml kanamycin at 30 °C in 50 ml scale using the EnPresso protocol (BioSilta). In order to induce protein expression, IPTG was added to a final concentration of 0.2 mM at OD₆₀₀ ≈ 10. After induction, the cultivations were incubated for 16 h. The cells were harvested by centrifugation.

Purification of IL-1R-I binding Z variants with a His₆ tag: Approximately 25 2/3 of the IL-1R-I binding Z variants were purified as described in Example 2 but without the buffer exchange between the IMAC and RPC purification steps. The linear gradient during RPC purification was also changed to 0-60 % RPC solvent B for 18 ml. The remaining 1/3 of the IL-1R-I binding Z variants were only IMAC purified before the final buffer exchange to PBS. Purification was essentially performed as described in the first part of 30 Example 2. Approximately 1-2 g of each cell pellet was used.

Biacore kinetic analysis: The kinetic constants (k_{on} and k_{off}) and affinities (K_D) for human and cynomolgus IL-1R-I were determined for His₆-tagged Z variants using a Biacore 2000 instrument (GE Healthcare). The experiment was run essentially as described in Example 5, using 48, 12, 3 35 and 0.75 nM of the Z variants. The analyte injection time was 3 min followed by 6 min dissociation and 2 x 5 s glycine pH 3.0, supplemented with 0.5 M

NaCl, was used for regeneration of the surfaces between the cycles. Kinetic constants were calculated from the obtained sensorgrams of three or four concentrations of the respective Z variant, using a 1:1 binding model in the BiaEvaluation software 4.1 (GE Healthcare). His₆-tagged Z12967 (SEQ ID NO:9), Z16065 (SEQ ID NO:268), Z16163 (SEQ ID NO:359) and Z18557 (SEQ ID NO:1205) were included in the assay for comparison.

In vitro IL-1 β neutralization assay: His₆-tagged IL-1R-I specific Z variants were tested for their inhibitory capacity in the TF-1 cell assay. The assay was run as described in Example 2. The data on cell growth was assessed by non-linear regression to a four-parameter dose-response curve, and IC₅₀ values were determined using GraphPadPrism program. His₆-tagged Z12967, Z16065, Z16163 and Z18557 were included for comparison.

Circular dichroism (CD) spectroscopy analysis: CD was analyzed for His₆-tagged Z variants, as described in Example 2.

Results

Production of His₆-tagged Z variants: The IL-1R-I binding Z variants with a His₆ tag were expressed as soluble gene products in *E. coli*. The amount of purified protein was determined spectrophotometrically by measuring the absorbance at 280 nm and ranged from approximately 0.4 to 7 mg protein per g pellet for IL-1R-I binding Z variants which were both IMAC and RPC purified. The amount of purified protein ranged from approximately 4 to 15 mg protein per g pellet for IL-1R-I binding Z variants which were only IMAC purified. SDS-PAGE analysis of each final protein preparation showed that these predominantly contained the IL-1R-I binding Z variant. The correct identity and molecular weight of each Z variant were confirmed by HPLC-MS analysis.

Biacore kinetic analysis: The interactions of His₆-tagged IL-1R-I binding Z variants with human and cynomolgus IL-1R-I were analyzed in a Biacore instrument by injecting various concentrations of the Z variants over a surface containing immobilized IL-1R-I. A summary of the calculated kinetic parameters (K_D , k_{on} and k_{off}) for the human IL-1R-I binding is given in Table 19. The K_D values of Z12967, Z16065, Z16163 and Z18557 were 8.2×10^{-10} , 5.1×10^{-10} , 7.6×10^{-10} and 1.4×10^{-10} M, respectively. The K_D values of cynomolgus IL-1R-I binding were 2.0×10^{-9} , 6.7×10^{-9} and 3.3×10^{-9} M for Z18754, Z18760 and Z18800, respectively.

Table 19. Kinetic parameters and affinities for His₆-Z polypeptides binding to human IL-1R-I.

Z variant	SEQ ID NO	k _{on} (1/Ms)	k _{off} (1/s)	K _D (M)
Z15876	1206	5.2x10 ⁶	4.1x10 ⁻³	8.0x10 ⁻¹⁰
Z15932	1207	1.8x10 ⁷	1.1x10 ⁻²	6.4x10 ⁻¹⁰
Z15934	1208	1.4x10 ⁷	1.1x10 ⁻²	7.5x10 ⁻¹⁰
Z15975	1209	4.1x10 ⁷	2.9x10 ⁻²	7.1x10 ⁻¹⁰
Z18754	1252	7.0x10 ⁷	6.0x10 ⁻³	8.6x10 ⁻¹¹
Z18760	1435	1.3x10 ⁷	2.7x10 ⁻³	2.1x10 ⁻¹⁰
Z18762	1415	4.2x10 ⁷	5.2x10 ⁻³	1.3x10 ⁻¹⁰
Z18769	1339	1.9x10 ⁷	3.1x10 ⁻³	1.6x10 ⁻¹⁰
Z18770	1284	3.0x10 ⁷	5.0x10 ⁻³	1.7x10 ⁻¹⁰
Z18799	1423	2.6x10 ⁷	4.5x10 ⁻³	1.8x10 ⁻¹⁰
Z18800	1328	1.8x10 ⁷	2.5x10 ⁻³	1.4x10 ⁻¹⁰
Z18813	1375	2.0x10 ⁷	3.9x10 ⁻³	2.0x10 ⁻¹⁰
Z18814	1368	3.0x10 ⁷	4.4x10 ⁻³	1.5x10 ⁻¹⁰
Z18817	1343	2.8x10 ⁷	4.8x10 ⁻³	1.7x10 ⁻¹⁰
Z18823	1283	4.7x10 ⁶	1.8x10 ⁻³	3.8x10 ⁻¹⁰
Z18831	1308	4.0x10 ⁷	5.3x10 ⁻³	1.3x10 ⁻¹⁰
Z18832	1340	5.9x10 ⁷	7.0x10 ⁻³	1.2x10 ⁻¹⁰
Z18834	1361	5.8x10 ⁷	8.0x10 ⁻³	1.4x10 ⁻¹⁰
Z18846	1331	4.7x10 ⁷	5.1x10 ⁻³	1.1x10 ⁻¹⁰
Z18850	1367	1.3x10 ⁷	2.3x10 ⁻³	1.7x10 ⁻¹⁰
Z18853	1298	2.2x10 ⁷	3.0x10 ⁻³	1.4x10 ⁻¹⁰
Z18856	1330	4.6x10 ⁷	5.7x10 ⁻³	1.2x10 ⁻¹⁰
Z18863	1362	2.2x10 ⁷	4.8x10 ⁻³	2.2x10 ⁻¹⁰
Z18866	1324	3.6x10 ⁷	4.2x10 ⁻³	1.2x10 ⁻¹⁰
Z18874	1421	4.9x10 ⁷	5.2x10 ⁻³	1.1x10 ⁻¹⁰
Z18875	1420	2.4x10 ⁷	2.8x10 ⁻³	1.2x10 ⁻¹⁰
Z18882	1311	1.2x10 ⁷	3.0x10 ⁻³	2.5x10 ⁻¹⁰
Z18888	1422	1.8x10 ⁷	2.9x10 ⁻³	1.6x10 ⁻¹⁰
Z18893	1353	8.6x10 ⁶	2.4x10 ⁻³	2.7x10 ⁻¹⁰
Z18898	1285	6.7x10 ⁷	4.4x10 ⁻³	6.6x10 ⁻¹¹
Z18912	1251	9.2x10 ⁷	1.9x10 ⁻²	2.1x10 ⁻¹⁰
Z18920	1270	3.6x10 ⁷	5.5x10 ⁻³	1.5x10 ⁻¹⁰
Z18968	1472	3.0x10 ⁷	8.4x10 ⁻³	2.8x10 ⁻¹⁰
Z19072	1554	4.3x10 ⁷	1.8x10 ⁻²	4.1x10 ⁻¹⁰
Z19075	1618	1.4x10 ⁷	6.4x10 ⁻³	4.5x10 ⁻¹⁰
Z19143	1471	1.7x10 ⁷	3.9x10 ⁻³	2.2x10 ⁻¹⁰
Z19147	1307	2.8x10 ⁷	4.3x10 ⁻³	1.5x10 ⁻¹⁰
Z19151	1594	2.8x10 ⁷	7.0x10 ⁻³	2.5x10 ⁻¹⁰
Z19158	1571	2.7x10 ⁷	4.4x10 ⁻³	1.6x10 ⁻¹⁰

Z19159	1364	2.7×10^7	5.0×10^{-3}	1.9×10^{-10}
Z19170	1334	2.1×10^7	4.3×10^{-3}	2.0×10^{-10}
Z19172	1551	4.9×10^7	2.3×10^{-2}	4.6×10^{-10}
Z19180	1393	2.2×10^7	3.1×10^{-3}	1.4×10^{-10}
Z19181	1549	2.0×10^7	1.6×10^{-2}	8.2×10^{-10}
Z19182	1628	2.1×10^7	5.5×10^{-3}	2.6×10^{-10}

In vitro IL-1 β neutralization assay: The IL-1 β inhibition ability of His₆-tagged IL-1R-I-binding Z variants was analyzed in a TF-1 cell assay. The resulting IC₅₀ values are presented in Table 20. The IC₅₀ values of Z12967, Z16065, Z16163 and Z18557 were 7.4, 3.3, 3.3 and 0.6 nM, respectively.

Table 20: IC₅₀ values for His₆-Z polypeptides from a TF-1 cell assay.

Z variant	SEQ ID NO	IC ₅₀ (nM)
Z15934	1208	6.4
Z15975	1209	3.3
Z18754	1252	0.6
Z18760	1435	0.9
Z18813	1375	1.2
Z18814	1368	0.4
Z18831	1308	0.4
Z18832	1340	0.5
Z18834	1361	0.5
Z18846	1331	0.2
Z18874	1421	0.3
Z18912	1251	1
Z18968	1472	1.4
Z19072	1554	2.4
Z19159	1364	1.2
Z19172	1551	2
Z19181	1549	4.6
Z19182	1628	1.5

CD analysis: The CD spectra determined for the IL-1R-I binding Z variants with a His₆ tag showed that each had an α -helical structure at 20 °C. This result was also verified in the variable temperature measurements, wherein melting temperatures were determined (Table 21). Reversible folding was seen for all the IL-1R-I binding Z variants when overlaying spectra measured before and after heating to 90 °C.

The thermo-stability and the α -helical content of the IL-1R-I binding Z variants having a valine or isoleucine residue in position X₅ of the BM (Z18912, Z18920, Z18968, Z19072, Z19075, Z19143, Z19147, Z19151, Z19158, Z19159, Z19170, Z19172, Z19180, Z19181 and Z19182) were not substantially different from the Z variants having an alanine residue in position X₅.

Table 21: Melting temperatures (T_m).

Z variant	SEQ ID NO	T _m (°C)	Z variant	SEQ ID NO	T _m (°C)
Z15876	1206	55	Z18866	1324	61
Z15932	1207	60	Z18874	1421	61
Z15934	1208	62	Z18875	1420	61
Z15975	1209	59	Z18882	1311	53
Z18754	1252	63	Z18888	1422	61
Z18760	435	57	Z18893	1353	60
Z18762	1415	62	Z18898	1285	59
Z18769	1339	59	Z18912	1251	53
Z18770	1284	59	Z18920	1270	56
Z18799	1423	60	Z18968	1472	62
Z18800	1328	67	Z19072	1554	63
Z18813	1375	61	Z19075	1618	56
Z18814	1368	61	Z19143	1471	56
Z18817	1343	60	Z19147	1307	57
Z18823	1283	52	Z19151	1594	59
Z18831	1308	58	Z19158	1571	55
Z18832	1340	58	Z19159	1364	54
Z18834	1361	58	Z19170	1334	52
Z18846	1331	60	Z19172	1551	59
Z18850	1367	62	Z19180	1393	58
Z18853	1298	59	Z19181	1549	61
Z18856	1330	61	Z19182	1628	62
Z18863	1362	57			

10

Example 10

Production and characterization of IL-1R-I binding fusion proteins

This Example describes the common steps for DNA construction and production of different IL-1R-I binding proteins variants fused to different *in vivo* half-life extending fusion partners.

15

Materials and methods

DNA construction: DNA encoding a set of IL-1R-I binding Z variants (see below) fused to human IgG1 Fc (SEQ ID NO:1662), an albumin binding polypeptide variant (PP013; SEQ ID NO:1661), human albumin (SEQ ID NO:1663) or human transferrin (SEQ ID NO:1664), optionally via different linkers (Table 22), were codon optimized for expression in *E. coli* or for expression in Chinese hamster ovary (CHO) cells and synthesized by the Invitrogen GeneArt Gene Synthesis service at Thermo Fisher Scientific. The genes were cloned in expression vectors for subsequent expression in *E. coli* or in CHO cells.

The fusion proteins were based on the binding motifs of the IL-1R-I binding Z variants a) Z12967 (SEQ ID NO:9), b) Z12895 (SEQ ID NO:12), c) Z18831 (SEQ ID NO:1308), d) Z18846 (SEQ ID NO:1331), e) Z18754 (SEQ ID NO:1252), f) Z19151 (SEQ ID NO:1594), g) Z18874 (SEQ ID NO:1421), h) Z18760 (SEQ ID NO:1435), i) Z18800 (SEQ ID NO:1328), j) Z18898 (SEQ ID NO:1285) and k) Z19147 (SEQ ID NO:1307) and the different fusions partners described above. The IL-1R-I binding Z variants a)-k) contained different scaffold mutations, (positions 1, 2, 23, 52 and/or 53) or a deletion combined with mutations (deletion at positions 1-3; Δ V1D2A3, mutations in positions 52 and 53), see Table 22 below. The mutated Z variants are listed in Figure 1 as SEQ ID NO:1667-1668 and 1670-1679. These obtained fusion polypeptides were PSI0405 (SEQ ID NO:1639), PSI0407 (SEQ ID NO:1640), PSI0411 (SEQ ID NO:1641), PSI0412 (SEQ ID NO:1642), PSI0415 (SEQ ID NO:1643), PSI0416 (SEQ ID NO:1644), PSI0417 (SEQ ID NO:1645), PSI0534 (SEQ ID NO:1646), PSI0535 (SEQ ID NO:1647), PSI0536 (SEQ ID NO:1648), PSI0537 (SEQ ID NO:1649), PSI0538 (SEQ ID NO:1650), PSI0539 (SEQ ID NO:1651), PSI0574 (SEQ ID NO:1652), PSI0575 (SEQ ID NO:1653), PSI0576 (SEQ ID NO:1654), PSI0580 (SEQ ID NO:1655), PSI0581 (SEQ ID NO:1656), PSI0582 (SEQ ID NO:1657), see Table 22.

Table 22: Fusion proteins and expression systems

SEQ ID NO	Fusion proteins	Construct	Expression system
1639	PSI0405	Z12967[V1A;D2E;N52S;D53E]-VEGS-ABD	<i>E. coli</i>
1640	PSI0407	Z12895[V1A;D2E;N52S;D53E]-VEGS-ABD	<i>E. coli</i>
1641	PSI0411	AS-ABD-GS-Z12967[V1A;D2E;N52S;D53E]	<i>E. coli</i>
1642	PSI0412	AS-ABD-(G ₄ S) ₂ -Z12967[V1A;D2E;N52S;D53E]	<i>E. coli</i>
1643	PSI0415	AS-ABD-Z12967[V1A;D2E;N52S;D53E]	<i>E. coli</i>
1644	PSI0416	AS-ABD-Z12967[ΔV1D2A3;N52S;D53E]	<i>E. coli</i>
1645	PSI0417	AS-ABD-((KEAAA) ₃ KE ₄ LA) ₂ -Z12967[V1A;D2E;N52S;D53E]	<i>E. coli</i>
1646	PSI0534	Z18831[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1647	PSI0535	Z18846[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1648	PSI0536	Z18754[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1649	PSI0537	Z19151[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1650	PSI0538	Z18874[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1651	PSI0539	Z18760[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1652	PSI0574	Z18800[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1653	PSI0575	Z18898[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1654	PSI0576	Z19147[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -IgG1 Fc	<i>E. coli</i>
1655	PSI0580	Z18754[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -Albumin	CHO
1656	PSI0581	Z18754[V1A;D2E;T23N;N52S;D53E]-AS(G ₄ S) ₂ -Albumin	CHO
1657	PSI0582	Z18754[V1A;D2E;N52S;D53E]-AS(G ₄ S) ₂ -Transferrin	CHO
1658	PSI0589	PSI0536[amino acids 1-86], dimeric	

Cultivation and purification of fusion proteins: *E. coli* cells were transformed with expression vectors containing the gene fragments corresponding to the IL-1R-I binding fusion proteins, see Table 22, and then cultivated in bioreactors using fed-batch techniques or in shake flasks, followed by protein expression and harvest of cells by centrifugation. Cell pellets were stored at -20 °C. Expression of IL-1R-I binding Z variants, see Table 22, were also performed using the ExpiCHO expression system (Thermo Fisher Scientific), essentially according to the manufacturer's

protocol. Supernatants were harvested by centrifugation 12 days after transfection of expression vectors and stored at -70 °C.

Frozen *E. coli* cell pellets were resuspended and then disrupted by sonication and the cell debris subsequently removed by centrifugation followed by filtration (0.22 µm). The frozen supernatants from the ExpiCHO cultures were thawed and filtrated (0.22 µm). Each supernatant, containing the IL-1R-I binding Z variants was purified using conventional chromatography methods, such as affinity chromatography, ion exchange chromatography, hydrophobic interaction chromatography and size exclusion chromatography. Z variants for use in animal studies were also subjected to an endotoxin removal purification using Detoxi-Gel Endotoxin Removing Columns (Pierce, cat.no. 20344). Purified Z variants were buffer exchanged to PBS and, unless otherwise stated, PBS was also the formulation buffer used in subsequent experiments. The purity of the IL-1R-I binding Z variants was analyzed by SDS-PAGE stained with Coomassie Blue and the molecular weight of each purified Z variant was analyzed using mass spectrometry (HPLC/MS or MALDI-TOF/MS).

The IL-1R-I binding fusion protein PSI0589 (SEQ ID NO:1658), a dimeric Z18754 variant linked in the hinge region by disulfides, was obtained by removing the IgG1 Fc part from PSI0536, see Table 22. This was achieved by incubation of purified PSI0536 with the IdeS protease (FabRICATOR, Genovis AB). The cleavage products were then purified using conventional chromatography methods such as ion exchange chromatography and affinity chromatography. The purified dimeric Z18754 variant was subjected to buffer exchange into PBS, which was also the formulation buffer used in subsequent experiments. The purity was analyzed by SDS-PAGE stained with Coomassie Blue and the molecular weight was analyzed using mass spectrometry (HPLC/MS or MALDI-TOF/MS).

Biolayer Interferometry (BLI) kinetic analysis: Binding of four IL-1R-I binding fusion proteins to human and cynomolgus IL-1R-I was analyzed using BLI. The Fc fused IL-1R-I binding Z variants denoted PSI0536, PSI0537, PSI0534 and PSI0535 (SEQ ID NO:1648, 1649, 1646, 1647) were loaded onto a Protein A sensor (Pall, ForteBio cat. no. 18-5010) at 0.5 µg/ml for 150 s in each cycle using an OctetRED96 instrument (Pall, ForteBio). Subsequently, these sensors were exposed to different and increasing concentrations of human IL-1R-I (R&D systems cat. no. 269-1R/CF) ranging from 0.15 to 5 nM or cynomolgus IL-1R-I (SEQ ID NO:1665) ranging from 2.5

to 80 nM. Association was recorded for 300 s and dissociation for 300 s (human) or 90 s (cynomolgus) and spectrograms were recorded and analyzed according to a 1:1 Langmuir model using global fit (Octet System Data Analysis 8.2 software, Pall, ForteBio). Each sensor was referenced to a sensor with the same ligand loaded onto it but exposed to buffer only. Following each association/dissociation cycle, all sensors were regenerated by three pulses of 10 mM glycine at pH 2.5 for 10 s each. All steps were carried out at 25 °C at a shaking speed of 1000 rpm and all dilutions of fusion proteins (Z-Fc fusion proteins) and analytes (human or cynomolgus IL-1R-I) were in 1 x kinetics buffer (Pall, ForteBio).

Results

Cultivation and purification: All the IL-1R-I binding fusion proteins (Table 22) were expressed to high levels in *E. coli* or CHO cells as soluble proteins. Purification resulted in protein preparations with high purity, which was analyzed by SDS-PAGE stained with Coomassie Blue. The correct identity and molecular weight of each Z variant were confirmed by mass spectrometry analysis.

BLI kinetic analysis: Four Z-Fc fusion protein variants (SEQ ID NO: 1648, 1649, 1646, 1647) were analyzed for the ability to bind human and cynomolgus IL-1R-I loaded onto protein A sensor using BLI technology on an OctetRED96 instrument. All four variants bound IL-1R-I according to a 1:1 model with B-max values ranging from 0.46 to 0.72 nm (human) or 0.31 to 0.37 nm (cynomolgus). The kinetic data; association rate constant (k_{on}), dissociation rate constant (k_{off}) and dissociation constant K_D for the Z-Fc fusion protein variants are presented in Table 23.

Table 23: Kinetic parameters for IL-1R-I binding fusion proteins

Fusion proteins and SEQ ID NO	Human IL-1R-I			Cynomolgus IL-1R-I		
	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)	k_{on} (1/Ms)	k_{off} (1/s)
PSI0536 (SEQ ID NO:1648)	7.5×10^{-10}	8.99×10^5	6.79×10^{-4}	1.4×10^{-8}	1.70×10^6	2.34×10^{-2}
PSI0537 (SEQ ID NO:1649)	1.2×10^{-9}	8.41×10^5	1.02×10^{-3}	3.1×10^{-8}	1.78×10^6	5.48×10^{-2}
PSI0534 (SEQ ID NO:1646)	1.6×10^{-9}	4.04×10^5	6.42×10^{-4}	2.8×10^{-8}	1.08×10^6	2.99×10^{-2}
PSI0535 (SEQ ID NO:1647)	7.2×10^{-10}	5.83×10^5	4.21×10^{-4}	1.1×10^{-8}	1.49×10^6	1.66×10^{-2}

Example 11:In vitro pharmacological activity analysis using a cell-based assay*Materials and methods*

5 The inhibitory effect of IL-1R-I binding fusion proteins on IL-1 β induced IL-6 production in Normal Human Dermal Fibroblasts (NHDF) cells was monitored.

Cells were seeded three days prior to treatment with proteins. Proteins (IL-1R-I binding fusion proteins or anakinra) were diluted to a starting
10 concentration of 100 nM and subsequently serially 1:4 nine times resulting in a concentration range of 100 nM to 0.38 pM in serum-free growth medium in the presence of 9 μ M recombinant human serum albumin (rHSA). The IL-1R-I binding fusion proteins or anakinra were tested in presence of a challenge dose of 3.4 pM IL-1 β and the cells were incubated for 22 hours with proteins
15 at 37 °C, followed by harvesting of medium. Harvested medium was diluted 41 X before IL-6 content was analyzed using a human IL-6 ELISA kit (R&D Systems) according to manufacturer's recommendations. Data was analyzed using XLfit and IC₅₀ values were calculated from concentration-response curves.

20 The inhibitory effect of His₆-tagged IL-1R-I binding Z variants, produced as described in Example 9, on IL-1 β induced IL-6 production in NHDF cells was similarly monitored and IC₅₀ values calculated.

Chemically synthesized protein: A chemically synthesized version of SEQ ID NO:1672, denoted PSI0558, was ordered from BACHEM AG. The
25 activity of PSI0558 was assessed according to the method set out above.

Results

The IL-1 β induced IL-6 release from NHDF cells was reduced in a concentration-dependent manner by the IL-1R-I binding fusion proteins as
30 well as by anakinra. Each IL-1R-I binding fusion protein was tested twice and the data from both experiments along with historical average of anakinra (n > 20) in this assay are presented in Table 24 and one of the two experiments is also presented in Figure 2.

Table 24: *In vitro* IC₅₀ values

Denotation	SEQ ID NO	IC ₅₀ (pM)
PSI0536	1648	66;45
PSI0537	1649	260;200
PSI0534	1646	140;110
PSI0535	1647	80;50
PSI0538	1650	87;70
PSI0539	1651	240;110
anakinra		Average 70

Some IL-1R-I binding fusion proteins were tested in the same manner but only one time. The results from this experiment are presented in Table 25.

5

Table 25: *In vitro* IC₅₀ values

Denotation	SEQ ID NO	IC ₅₀ (pM)
PSI0589	1658	1.8
PSI0582	1657	2.0
PSI0580	1655	1500
PSI0581	1656	1800

The IL-1 β inhibition ability of His₆-tagged IL-1R-I-binding Z variants, previously demonstrated in a TF-1 cell assay (Example 9, Table 20), was confirmed in this NHDF assay (results not shown).

10

The IC₅₀ value of the chemically synthesized PSI0558 was 690 pM.

Example 12

In vitro pharmacological activity analysis using a whole blood assay

15

The inhibitory effect of IL-1R-I binding fusion proteins on IL-1 β induced IL-6 production in whole blood from individual donors was measured.

Materials and methods

20

Blood from healthy donors was collected 1-3 hours prior to treatment with the IL-1R-I binding fusion proteins (SEQ ID NO:1648-1649). Proteins (IL-1R-I binding fusion proteins or anakinra) were diluted to starting concentration of 500 nM in serum free RPMI (ThermoFisher Scientific, RPMI 1640 Medium, GlutaMAX™ Supplement, Cat. No.: 61870010) and subsequently serially diluted 1:3 in a ten-step dilution series resulting in a concentration range of 500 nM to 25 pM. The IL-1R-I binding fusion polypeptides or anakinra were tested in presence of a challenge dose of 100 pM IL-1 β . The blood was incubated for 21-23 hours with proteins, followed by harvesting of plasma.

25

Harvested plasma was diluted 2 x and IL-6 content was analyzed by using a human IL-6 kit (V-PLEX Human IL-6 Kit Human interleukin-6, MSD) according to manufacturer's recommendations.

IL-6 concentrations (pg/ml) were calculated using a standard curve
5 (provided by the kit) and data was analyzed using XLfit and IC₅₀ values were calculated from the concentration-response curves.

Results

The IL-1 β induced IL-6 release in human whole blood was reduced in a
10 concentration-dependent manner by the IL-1R-I binding fusion proteins as well as by anakinra. IL-1R-I binding fusion proteins were tested in blood from five to six individual healthy donors and compared to anakinra data from ten individual blood donors (Figure 3). The median IC₅₀ values were 0.32, 1.25 and 0.31 nM for SEQ ID NO:1648 (PSI0536), SEQ ID NO:1649 (PSI0537)
15 and anakinra, respectively.

Example 13

In vivo pharmacokinetics of IL-1R-I binding fusion proteins in rats

20 In this Example, the pharmacokinetics of IL-1R-I-binding fusion proteins (SEQ ID NO:1646-1651) were evaluated in a single dose study in male rats.

Material and methods

Fusion proteins: The IL-1R-I binding fusion proteins PSI0534, PSI0535,
25 PSI0536, PSI0537, PSI0538 and PSI0539 (see Table 22, SEQ ID NO:1646-1651) were evaluated in this study. All six test items were constituted as a solution in 25 mM sodium phosphate and 125 mM sodium chloride, pH 7.0.

In-life phase: The pharmacokinetic properties of the six fusion proteins were investigated in male Sprague-Dawley rats. For each test item, three rats
30 were given an i.v. single dose of 15 mg/kg (2.5 ml/kg) injected in the lateral tail vein and another three rats were given a s.c. single dose of 30 mg/kg (5 ml/kg) injected in the neck region. Blood samples for serum preparation were collected pre dosing and at 5 and 20 min, 1, 4, 8, 24, 48, 72 and 96 hrs post i.v. dosing, or 20 min, 1, 4, 8, 24, 48, 72, 96 and 120 hrs post s.c. dosing.

35 Quantitative ELISA: Determination of fusion protein levels in rat serum samples was performed by enzyme-linked immunosorbent assay (ELISA).

The ELISA assay employed the quantitative sandwich enzyme immunoassay technique.

In brief; a goat polyclonal anti-Z antibody recognizing the Z variant domain of the IL-1R-I binding fusion protein (produced in house, Affibody AB) was coated onto a microplate. Unbound polyclonal antibody was washed away and casein was added as blocking agent to reduce unspecific binding to the plastic surface. After removal of unbound casein by a second wash step, standards and samples were pipetted to the wells and any fusion protein present was bound to the immobilized antibody. After washing away any unbound substances, a HRP labeled Swine anti-rabbit antibody (Dako, cat. no. P0399) was added. Following a wash to remove any unbound anti-rabbit HRP reagent, a substrate solution was added to the wells and color developed in proportion to the amount of fusion protein bound in the initial step. The color development was stopped and the intensity of the color was measured.

Pharmacokinetic analysis: The pharmacokinetic analysis was based on median serum concentration versus time data from each dose group. The observed maximum concentration (C_{max}) and the time to maximum serum concentration (t_{max}) were taken directly from the bioanalytical data. Other pharmacokinetic parameters, i.e. clearance (CL), apparent clearance following s.c. administration (CL/F), apparent volume of distribution at steady-state (V_{ss}), mean residence time (MRT) and terminal half-life ($t_{1/2z}$), were estimated by non-compartmental analysis using Phoenix WinNonlin software version 6.3 (Pharsight Corp., USA). Estimation of the terminal slope following i.v. dosing was based on four data points, from 24 to 96 hrs. Estimation of the terminal slope following s.c. dosing was based on five data points, from 24 to 120 hrs. Calculation of the subcutaneous bioavailability (F) was performed using Microsoft Excel.

Results

There was no significant difference in the pharmacokinetics between the six tested fusion proteins. The pharmacokinetics following i.v. administration was characterized by a clearance in the order of 2.4 ml/h·kg and a volume of distribution of about 140 ml/kg, translating into a mean residence time of ca 60 hrs (Table 26).

Table 26: Pharmacokinetic parameter estimates following an intravenous single dose administration, 15 mg/kg, to male rats

Parameter	PSI0534	PSI0535	PSI0536	PSI0537	PSI0538	PSI0539
CL (ml/h·kg)	2.83	2.40	2.68	2.06	2.36	2.03
V _{ss} (ml/kg)	159	149	143	136	146	113
MRT (hrs)	56.4	62.1	53.5	65.9	61.6	55.5
t _{1/2z} (hrs)	48.7	52.1	44.7	55.1	50.4	48.3

- 5 The subcutaneous bioavailability was on average 50 % and peak levels were observed at 24 hrs after dosing. The serum levels then declined with a half-life ranging from 45 to 59 hrs (Table 27).

Table 27: Pharmacokinetic parameter estimates following a subcutaneous single dose administration, 30 mg/kg, to male rats

10

Parameter	PSI0534	PSI0535	PSI0536	PSI0537	PSI0538	PSI0539
F (%)	41.5	49.6	46.7	60.3	47.2	52.2
C _{max} (nM)	828	866	948	1115	796	886
t _{max} (hrs)	24	24	24	24	24	24
CL/F (ml/h·kg)	6.81	5.70	6.05	4.69	5.98	5.42
V _z /F (ml/kg)	445	457	403	372	509	424
t _{1/2z} (hrs)	45.3	55.6	46.1	55.1	59.0	54.3
MRT (hrs)	72.4	87.3	74.5	87.4	91.7	86.2

Example 14

In vivo pharmacokinetics of an IL-1R-I binding fusion protein in monkeys

15 *Material and methods*

Fusion proteins: The IL-1R-I binding fusion protein denoted PSI0536 (SEQ ID NO:1648) was constituted as a solution in 25 mM sodium phosphate and 125 mM sodium chloride, pH 7.0.

- 20 In-life phase: The pharmacokinetic properties of PSI0536 were investigated in naïve male Cynomolgus monkeys. Three monkeys were given an i.v. single dose of 5 mg/kg (1 ml/kg) injected in the tail vein and another

three monkeys were given a s.c. single dose of 10 mg/kg (1 ml/kg) injected in the dorsal region. Blood samples for serum preparation were collected pre dosing and at 5 and 20 min, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240 and 504 hrs post i.v. dosing, or 20 min, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240 and 504 hrs post s.c. dosing.

Quantitative ELISA: Quantification of PSI0536 in serum from monkeys was performed according to the ELISA described in Example 13.

Pharmacokinetic analysis: Pharmacokinetic parameters were based on individual serum concentration *versus* time data and determined using WinNonlin software as described in Example 13. Estimation of the terminal slope following i.v. dosing was based on seven data points, from 72 to 504 hrs. Estimation of the terminal slope following s.c. dosing was based on eight data points, from 48 to 504 hrs. Calculation of the subcutaneous bioavailability (F) was performed using Microsoft Excel.

Results

The pharmacokinetics of PSI0536 (SEQ ID NO:1648) following i.v. administration was characterized by a low clearance (1.07 ml/h·kg) and a small volume of distribution (117 ml/kg), translating into a mean residence time of 109 hrs (Table 28).

Table 28: Mean ($\pm$ SD) pharmacokinetic parameter estimates of PSI0536 following an intravenous single dose of 5.04 ($\pm$ 0.01) mg/kg to three male monkeys

Parameter	Estimate
CL (ml/h·kg)	1.07 $\pm$ 0.04
V _{ss} (ml/kg)	117 $\pm$ 3
MRT (hrs)	109 $\pm$ 1
t _{1/2z} (hrs)	92.7 $\pm$ 3.7

The mean subcutaneous bioavailability of PSI0536 was 73.9%. Peak levels were observed at an average of 18.7 hrs after dosing. The serum levels then declined with a half-life of 77.3 hrs (Table 29).

Table 29: Mean ($\pm$ SD) pharmacokinetic parameter estimates of PSI0536 following a subcutaneous single dose of 10.1 ($\pm$ 0.1) mg/kg to three male monkeys

Parameter	Estimate
F (%)	73.9 $\pm$ 5.5
C _{max} (nM)	779 $\pm$ 159
t _{max} (hrs)	18.7 $\pm$ 7.5
CL/F (ml/h·kg)	1.46 $\pm$ 0.10
V _z /F (ml/kg)	163 $\pm$ 23
t _{1/2z} (hrs)	77.3 $\pm$ 6.3
MRT (hrs)	115 $\pm$ 14

5

Conclusion

Assuming a minimum target serum concentration of 100 nM or even 200 nM, the high subcutaneous bioavailability in combination with the low clearance facilitates a once weekly subcutaneous dose regimen of 10 mg/kg PSI0536 in monkey.

10

Example 15

Production and characterization of IL-1-R-I binding fusion proteins with mutations in the Fc portion

15

Four IL-1-R-I binding fusion proteins of the IL-1R-I binding polypeptide variant Z18754 (SEQ ID NO:1252) with mutated variants of the Fc portion of IgG1 or IgG4 were produced. In the IgG1 Fc portion, one mutation [N297A] was introduced in order to abolish effector functions through interaction with FC γ R3A. Fc-containing polypeptides produced in mammalian cells might otherwise cause such effector functions. In addition, in one fusion protein (SEQ ID NO:1735) two other residues were introduced, denoted LS (WO2009/086320), to increase affinity to FcRn, and in another fusion protein (SEQ ID NO:1736) three mutations denoted YTE (WO02060919) were introduced to increase affinity to FcRn. One fusion protein of Z18754 (SEQ ID NO:1252) with an IgG4 Fc a subtype, which is known to elicit low effector responses, was produced (SEQ ID NO:1737). One mutation, known as

20
25

S228P (van der Neut Kolfshoten M. et al., 2007, Science 317(5844):1554-7), was furthermore introduced in the hinge region of this fusion protein. This mutation abolishes the arm exchange that may take place for the IgG4 subclass of antibodies.

5

Material and methods

The fusion proteins PSI0653-PSI0656 (SEQ ID NO:1734-1737), see Table 30 for specifications, were produced in CHO cells according to Example 10.

10 The inhibitory effect of IL-1R-I binding fusion proteins on IL-1 β induced IL-6 production in Normal Human Dermal Fibroblasts (NHDF) cells was monitored as set out in Example 11.

The affinity towards FC γ R3A was analysed with Biolayer Interferometry essentially as disclosed in Example 10, with the exception that biotinylated
15 FC γ R3A (Sino Biological) was immobilized on a Streptavidin biosensor for kinetics (Pall/Fortebio) and the proteins were tested using concentrations of 100 and 1000 nM. In addition Human IgG (GammaNorm, Octapharma) was used as control in the measurements.

The affinity towards FcRn was assessed using Biacore essentially as
20 described in Example 9 with the exception that human biotinylated FcRn (Immunitrack ApS) was immobilized on a Biotin CAPture chip (GE Healthcare) and the analytes were tested in five concentrations, ranging from 2.5 - 200 nM.

25 *Table 30: Fusion proteins and expression systems*

SEQ ID NO	Fusion proteins	Construct	Expression system
1734	PSI0653	Z18754[N297A]-IgG1 Fc	CHO
1735	PSI0654	Z18754[N297A]-LS-IgG1 Fc	CHO
1736	PSI0655	Z18754[N297A]-YTE-IgG1 Fc	CHO
1737	PSI0656	Z18754[S228P]-IgG4 Fc	CHO

Results

30 Cultivation and purification: All the IL-1-R-I binding fusion proteins with mutated Fc portions (Table 30) were expressed at high levels in CHO cells as soluble proteins. Purification resulted in protein preparations with high purity, which were analyzed by SDS-PAGE stained with Coomassie Blue. The

correct identity and molecular weight of each Z variant were confirmed by mass spectrometry analysis.

- In vitro pharmacological activity: The IL-1 β induced IL-6 release from NHDF cells was reduced in a concentration-dependent manner by the IL-1R-I binding fusion proteins. The IL-1R-I binding fusion proteins were tested one time. The results from this experiment are accounted for in Table 31.

Table 31: In vitro IC₅₀ values

SEQ ID NO:	Fusion proteins	IC ₅₀ (pM)
1734	PSI0653	4.3
1735	PSI0654	2.9
1736	PSI0655	5.9
1737	PSI0656	8.4

- FC γ R3A affinity analysis: Human IgG bound to FC γ R3A with an affinity of 57 nM at 1000 nM concentration. The fusion proteins PSI0653-PSI0655 (SEQ ID NO 1734-1736) showed no binding at either concentration. PSI0656 (SEQ ID NO 1737) showed a weak binding at 1000 nM but no binding at 100 nM.

- Biacore FcRn affinity analysis: The affinity towards FcRn were in the order SEQ ID NO 1735 > SEQ ID NO 1736 > SEQ ID NO 1734 = SEQ ID NO 1737.

- Conclusion: The mutated Fc variants of the fusion proteins (SEQ ID NO:1734:1737) were equal to the previously produced proteins in terms of quality and activity (see Example 10). The removal of glycan attachment site removed the effector function of the IgG1 Fc portion in SEQ ID NO:1734-1736 as binding to FC γ R3A was abolished. The IgG4 Fc containing SEQ ID NO:1737 had low affinity towards FC γ R3A as expected for an Fc of that subclass. The FcRn affinity enhancing mutations in SEQ ID NO:1735 and 1736 displayed increased affinity, with SEQ ID NO:1735 showing the greatest increase.

Itemized listing of embodiments

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, 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;

15

X_6 is selected from F, H, I, Q, R, T, V and Y;

X_7 is selected from A, D, E, F, G, H, I, L, M, Q, S, T, V, W and Y;

X_{10} is selected from F and Y;

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

20

X_{16} is selected from N and T;

X_{18} is selected from K, R and S;

X_{21} is selected from Q, T and V;

X_{25} is selected from I, M, R, V and Y;

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

25

X_{28} 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 X_5 is I or V.

30

2. 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)

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

X_3 is selected from E and Y;

35

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

X_5 is selected from I and V;

X_6 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;
 5 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,
 10 and an amino acid sequence which has at least 93 % identity to the
 sequence defined in i).
3. IL-1R-I binding polypeptide according to any one of the preceding
 items, wherein sequence i) fulfills at least five of the ten conditions I-X:
- I. X₃ is E;
 15 II. X₅ is selected from I and V;
 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;
 20 VII. X₂₁ is T;
 VIII. X₂₅ is R;
 IX. X₂₆ is selected from K and S; and
 X. X₂₈ is selected from F and L.
4. IL-1R-I binding polypeptide according to item 3, wherein sequence i)
 25 fulfills at least six of the ten conditions I-X.
5. IL-1R-I binding polypeptide according to item 4, wherein sequence i)
 fulfills at least seven of the ten conditions I-X.
6. IL-1R-I binding polypeptide according to item 5, wherein sequence i)
 fulfills at least eight of the ten conditions I-X.
- 30 7. IL-1R-I binding polypeptide according to item 6, wherein sequence i)
 fulfills at least nine of the ten conditions I-X.
8. IL-1R-I binding polypeptide according to item 7, wherein sequence i)
 fulfills all of the ten conditions I-X.
9. IL-1R-I binding polypeptide according to any one of items 1-8,
 35 wherein X₂X₃X₆ is VEQ or VEY.
10. IL-1R-I binding polypeptide according to any one of items 1-8,
 wherein X₂X₃X₆ is IEQ or VEQ.

11. IL-1R-I binding polypeptide according to any one of items 1-8, wherein X_6X_{10} is selected from the group consisting of QF, QY, YF and YY.

12. IL-1R-I binding polypeptide according to any one of items 1-8, wherein X_6X_{10} is QF.

5 13. IL-1R-I binding polypeptide according to any one of items 1-8, wherein $X_{10}X_{18}$ is selected from the group consisting of FK, FR, YK and YR.

14. IL-1R-I binding polypeptide according to any one of items 1-8, wherein $X_{10}X_{18}$ is FK or FR.

10 15. IL-1R-I binding polypeptide according to any one of items 1-8, wherein $X_{18}X_{25}X_{28}$ is KRL or RRL.

16. IL-1R-I binding polypeptide according to any one of items 1-8, wherein X_5X_7 is IM or VM.

17. IL-1R-I binding polypeptide according to any preceding item, wherein sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1-1632, and 1679, such as the group consisting of SEQ ID NO:20-1632, and 1679.

18. IL-1R-I binding polypeptide according to any preceding item, 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.

19. IL-1R-I binding polypeptide according to any preceding item, 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.

20. IL-1R-I binding polypeptide according to item 19, wherein sequence i) corresponds to the sequence from position 8 to position 36 in SEQ ID NO:1252.

30 21. IL-1R-I binding polypeptide according to item 19, wherein sequence i) corresponds to the sequence from position 8 to position 36 in SEQ ID NO:1328.

22. IL-1R-I binding polypeptide according to item 19, wherein sequence i) corresponds to the sequence from position 8 to position 36 in SEQ ID NO:1435.

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

24. IL-1R-I binding polypeptide according to item 23, wherein said IL-
5 1R-I binding motif essentially forms part of two helices with an interconnecting loop, within said three-helix bundle protein domain.

25. IL-1R-I binding polypeptide according to item 24, wherein said three-helix bundle protein domain is selected from bacterial receptor domains.

26. IL-1R-I binding polypeptide according to item 25, wherein said
10 three-helix bundle protein domain is selected from domains of protein A from *Staphylococcus aureus* or derivatives thereof.

27. IL-1R-I binding polypeptide according to any preceding item, which comprises a binding module *BMod*, the amino acid sequence of which is selected from:

15

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

wherein

20

[BM] is an IL-1R-I binding motif as defined in any one of items 1-22;

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;

25

X_e is selected from D, E and S;

X_f is selected from A and S; and

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

30

28. IL-1R-I binding polypeptide according to any preceding item, wherein sequence iii) corresponds to the sequence 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.

35

29. IL-1R-I binding polypeptide according to item 28, wherein sequence iii) corresponds to the sequence from position 7 to position 55 in a sequence selected from the group consisting of SEQ ID NO:1206-1632 and

1670-1679, such as the group consisting of SEQ ID NO:1210-1632 and 1670-1679.

30. IL-1R-I binding polypeptide according to item 28, wherein 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, 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.

31. IL-1R-I binding polypeptide according to item 30, wherein sequence iii) corresponds to the sequence from position 7 to position 55 in SEQ ID NO:1672.

32. IL-1R-I binding polypeptide according to item 30, wherein sequence iii) corresponds to the sequence from position 7 to position 55 in SEQ ID NO:1675.

33. IL-1R-I binding polypeptide according to item 30, wherein sequence iii) corresponds to the sequence from position 7 to position 55 in SEQ ID NO:1676.

34. IL-1R-I binding polypeptide according to any preceding item, which comprises an amino acid sequence selected from:

20	ADNNFNK-[BM]-DPSQSANLLSEAKKLNESQAPK	SEQ ID NO:1695;
	ADNKFNK-[BM]-DPSQSANLLAEAKKLNDQAAPK	SEQ ID NO:1696;
	ADNKFNK-[BM]-DPSVSKEILAEAKKLNDQAAPK	SEQ ID NO:1697;
	ADAQQNNFNK-[BM]-DPSQSTNVLGEAKKLNESQAPK	SEQ ID NO:1698;
	AQHDE-[BM]-DPSQSANVLGEAQKLNDQAPK	SEQ ID NO:1699;
25	VDNKFNK-[BM]-DPSQSANLLAEAKKLNDQAAPK	SEQ ID NO:1700;
	AEAKYAK-[BM]-DPSESSELLSEAKKLNKSQAPK	SEQ ID NO:1701;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNDQAAPK	SEQ ID NO:1702;
	VDACYAK-[BM]-DPSQSSELLAEAKKLNDQAPK	SEQ ID NO:1703;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLNDQAPK	SEQ ID NO:1704;
30	AEAKYAK-[BM]-DPSQSSELLSEAKKLNDQAP	SEQ ID NO:1705;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLNDQAPK	SEQ ID NO:1706;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLNDQAP	SEQ ID NO:1707;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLNDQAAPK	SEQ ID NO:1708;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1709;
35	AEAKYAK-[BM]-DPSQSSELLSEAKKLSESQAP	SEQ ID NO:1710;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1711;
	AEAKFAK-[BM]-DPSQSSELLSEAKKLSESQAP	SEQ ID NO:1712;

	AEAKYAK-[BM]-DPSQSSELLAEAKKLSEAQAPK	SEQ ID NO:1713;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLESSQAPK	SEQ ID NO:1714;
	AEAKYAK-[BM]-DPSQSSELLSEAKKLESSQAP	SEQ ID NO:1715;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLESAQAPK	SEQ ID NO:1716;
5	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;
	VDACYAK-[BM]-DPSQSSELLSEAKKLNDSQAPK	SEQ ID NO:1721;
10	VDACYAK-[BM]-DPSQSSELLAEAKKLNDAQAPK	SEQ ID NO:1722;
	VDACYAK-[BM]-DPSQSSELLSEAKKLSESQAPK	SEQ ID NO:1723;
	VDACYAK-[BM]-DPSQSSELLAEAKKLSEAQAPK	SEQ ID NO:1724;
	VDACYAK-[BM]-DPSQSSELLSEAKKLESSQAPK	SEQ ID NO:1725;
	VDACYAK-[BM]-DPSQSSELLAEAKKLESAQAPK	SEQ ID NO:1726;
15	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;
	AEAKYAK-[BM]-DPSQSSELLAEAKKLNKAQAPK	SEQ ID NO:1731,
20	and	
	ADACYAK-[BM]-DPSQSSELLSEAKKLNDSQAPK	SEQ ID NO:1732,

wherein [BM] is an IL-1R-I binding motif as defined in any one of items 1-22.

35. IL-1R-I binding polypeptide according to any one of items 1-34,
 25 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 items 1-22; and

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

36. IL-1R-I binding polypeptide according to any one of items 1-34,
 which comprises an amino acid sequence selected from:

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

wherein [BM] is an IL-1R-I binding motif as defined in any one of items 1-22; and

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

37. IL-1R-I binding polypeptide according to item 35 or 36, 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.

38. IL-1R-I binding polypeptide according to item 37 wherein 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:1206-1632, 1667-1668 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1632, 1667-1668 and 1670-1679.

39. IL-1R-I binding polypeptide according to item 38, 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.

40. IL-1R-I binding polypeptide according to item 39, wherein sequence xxi) corresponds to the sequence from position 1 to position 58 in SEQ ID NO:1672.

41. IL-1R-I binding polypeptide according to item 39, wherein sequence xxi) corresponds to the sequence from position 1 to position 58 in SEQ ID NO:1675.

42. IL-1R-I binding polypeptide according to item 39, wherein sequence xxi) corresponds to the sequence from position 1 to position 58 in SEQ ID NO:1676.

43. IL-1R-I binding polypeptide according to any preceding item, which is capable of blocking IL-1R-I dependent signaling.

44. IL-1R-I binding polypeptide according to item 43, wherein the half maximal inhibitory concentration (IC_{50}) of the blocking is 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 5×10^{-10} M.

45. IL-1R-I binding polypeptide according to item 43 or 44, 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 .

46. IL-1R-I binding polypeptide according to any preceding item 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 1×10^{-8} M, such as at most 5×10^{-9} M, such as at most 1×10^{-10} M such as at most 5×10^{-10} M, such as at most 2×10^{-10} M.

47. IL-1R-I binding polypeptide according to any preceding item 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} .

48. IL-1R-I binding polypeptide according to any one of items 43-47, wherein said IL-1R-I is human IL-1R-I or cynomolgus IL-1R-I, such as human IL-1R-I.

49. IL-1R-I binding polypeptide according to any preceding item which comprises additional amino acids at the C-terminal and/or N-terminal end.

50. IL-1R-I binding polypeptide according to item 49, wherein said additional amino acid(s) improve(s) production, purification, stabilization *in vivo* or *in vitro*, coupling or detection of the polypeptide.

51. IL-1R-I binding polypeptide according to any preceding item in multimeric form, comprising at least two IL-1R-I binding polypeptide monomer units, the amino acid sequences of which are the same or different.

52. IL-1R-I binding polypeptide according to item 51, wherein said IL-1R-I binding polypeptide monomer units are covalently coupled together.

53. IL-1R-I binding polypeptide according to item 52, wherein the IL-1R-I binding polypeptide monomer units are expressed as a fusion protein.

54. IL-1R-I binding polypeptide according to any one of items 51-53, in dimeric form.

55. Fusion protein or conjugate comprising

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

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

56. Fusion protein or conjugate according to item 55, wherein said desired biological activity is a therapeutic activity.

57. Fusion protein or conjugate according to item 55, wherein said desired biological activity is a binding activity.

58. Fusion protein or conjugate according to item 55, wherein said desired biological activity is a binding activity modifying tissue distribution of said fusion protein or conjugate.

59. Fusion protein or conjugate according to item 57, wherein said
5 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.

60. Fusion protein or conjugate according to item 59, said *in vivo* half-life increasing activity is an albumin binding activity.

10 61. Fusion protein or conjugate according to item 60, wherein said albumin binding activity is provided by the albumin binding domain of streptococcal protein G or a derivative thereof.

62. Fusion protein or conjugate according to item 61, wherein said second moiety comprises a polypeptide having an amino acid sequence as
15 set out in SEQ ID NO:1659-1661, such as SEQ ID NO:1661.

63. Fusion protein or conjugate according to item 59, wherein said second moiety is serum albumin.

64. Fusion protein or conjugate according to item 59, wherein said second moiety is an Fc portion of an antibody, such as an IgG1 Fc or an IgG4
20 Fc.

65. Fusion protein or conjugate according to item 64, wherein said Fc is a mutated Fc which relative to an unmutated form of Fc displays improved affinity to FcRn and/or reduced effector response.

66. Fusion protein or conjugate according to item 58 or 59, wherein
25 said second moiety is transferrin.

67. Fusion protein or conjugate according to any one of items 59-65, comprising a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1639-1658 and 1734-1737, such as from the group consisting of SEQ ID NO:1646-1654 and 1734-1737.

30 68. Fusion protein or conjugate according to item 57, wherein said binding activity acts to block a biological activity.

69. Fusion protein or conjugate according to any one of items 55-68, further comprising at least one linker, said linker optionally being selected from the group consisting of flexible amino acid linkers, rigid amino acid
35 linkers and cleavable amino acid linkers.

70. Fusion protein or conjugate according item 69, wherein said linker is arranged between said first moiety and said second moiety.

71. Fusion protein or conjugate according item 69, wherein said linker is arranged within said first moiety.

72. Fusion protein or conjugate according item 69 or 70, wherein said linker is a flexible linker comprising at least one amino acid residue(s)
5 selected from the group consisting of glycine, serine and alanine.

73. Fusion protein or conjugate according to item 72, wherein said linker is selected from the group consisting of GS, VDSS, VDGS, VEGS, ASGS, (GGGGS)₂ (SEQ ID NO:1683), AS(GGGGS)₂ (SEQ ID NO:1684) and ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685).

10 74. Fusion protein or conjugate according to item 73, wherein said linker is selected from a AS(GGGGS)₂ (SEQ ID NO:1684) and ((KEAAA)₃KELAA)₂ (SEQ ID NO:1685).

75. A polynucleotide encoding a polypeptide or a fusion protein according to any one of items 1-74.

15 76. Expression vector comprising a polynucleotide according to item 75.

77. Host cell comprising an expression vector according to item 76.

78. Method of producing a polypeptide according to any one of items 1-77, comprising

20 - culturing a host cell according to item 77 under conditions permissive of expression of said polypeptide from said expression vector, and
- isolating said polypeptide.

79. Composition comprising an IL-1R-I binding polypeptide, fusion protein, or conjugate according to any one of items 1-74 and at least one
25 pharmaceutically acceptable excipient or carrier.

80. Composition according to item 79, further comprising at least one additional active agent, such as an agent selected from an immune response modifying agent and an anti-cancer agent.

81. Composition according to item 79 or 80, wherein said fusion protein
30 is a fusion protein according to any one of claims 59-67.

82. IL-1R-I binding polypeptide, fusion protein, or conjugate according to any one of items 1-74 or a composition according to any one of items 79-81 for use as a medicament, a diagnostic agent and/or a prognostic agent.

83. IL-1R-I binding polypeptide, fusion protein, conjugate or
35 composition according to item 82 for use as a medicament.

84. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to item 83, wherein said polypeptide, fusion protein, conjugate or composition modulates IL-1R-I function *in vivo*.

85. IL-1R-I binding polypeptide, fusion protein, conjugate or
5 composition according to item 82 for use as a diagnostic agent and/or a prognostic agent.

86. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to any one of items 82-85, in the treatment, prognosis or diagnosis of an IL-1R-I related disorder.

10 87. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to item 86, 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.

15 88. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to item 86 or 87, wherein 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);
20 periodic fever; aphthous stomatitis; 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
25 diabetes; dry eye syndrome; 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
30 the IL-1 receptor antagonist (DIRA), 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
35 syndrome with lymphedema (AISLE), Phospholipase C-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 (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; 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 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 osteitis (NBO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, and Majeed syndrome; relapsing polychondritis; idiopathic recurrent pericarditis (IRP); myocarditis; Erdheim-Chester disease; juvenile xanthogranuloma; islet-cell transplantation; haemodialysis-induced systemic inflammation; graft-versus-host disease; ANCA-associated glomerulonephritis and recurrent glomerulonephritis; Cogan syndrome; autoimmune inner-ear disease; chronic granulomatous disease (CGD); Castleman's disease; cardiac failure; diastolic cardiac failure; antisynthetase syndrome; acute ACL injury; acute haemorrhagic leukoencephalitis; AA amyloidosis; Di George syndrome; generalised fatigue; chronic fatigue syndrome (CFS); gulf-war illness (GWI); and narcolepsy.

89. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to item 87, wherein said IL-1R-I related disorder is cancer, such as a cancer selected from the group consisting of multiple myeloma, colon cancer, breast cancer, lung cancer, head and neck cancer, melanoma and prostate cancer.

90. IL-1R-I binding polypeptide, fusion protein, conjugate or composition for use according to any one of items 82-89, wherein said IL-1R-I

binding polypeptide, fusion protein, conjugate or composition is administered repeatedly within a 24 hour period from disease onset, such as at least two times within a 24 hour period from disease onset, such as at least three times within a 24 hour period from disease onset, such as continuously during 24
5 hours from disease onset, to a subject in need thereof.

91. Fusion protein, conjugate or composition for use according to any one of items 82-84, 86-89, wherein said fusion protein or conjugate is a fusion protein or conjugate according to any one of items 58-67 and said composition is a composition according to item 81.

10 92. Fusion protein, conjugate or composition for use according to item 91, wherein said fusion protein, conjugate or composition is administered once weekly to a subject in need thereof.

93. 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
15 binding polypeptide, fusion protein or conjugate according to any one of items 1-74 or a composition according to any one of items 79-81.

94. Method according to item 93, wherein said IL-1R-I related disorder is selected from the group consisting inflammatory disease, auto-inflammatory syndrome, autoimmune disease, infectious disease,
20 cardiovascular disease, ischaemic disease, cancer and diabetes.

95. Method according to item 93 or 94, wherein said IL-1R-I related disorder is selected from the group as defined in item 88.

96. Method according to item 94, wherein said IL-1R-I related disorder is cancer, such as a cancer selected from the group consisting of selected
25 from the group consisting of multiple myeloma, colon cancer, breast cancer, lung cancer, head and neck cancer, melanoma and prostate cancer.

97. Method according to any one of items 93-96, wherein said IL-1R-I binding polypeptide, fusion protein or conjugate or composition is administered repeatedly within a 24 h period from disease onset, such as at
30 least two times within a 24 hour period from disease onset, such as at least three times within a 24 hour period from disease onset, such as continuously during 24 hours from disease onset, to a subject in need thereof.

98. Method according to any one of claims 93-96, wherein said fusion protein or conjugate is a fusion protein or conjugate according to any one of
35 items 59-67 and said composition is a composition according to item 81.

99. Method according to item 97, wherein said fusion protein, conjugate or composition is administered once weekly to a subject in need thereof.

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) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
(SEQ ID NO:1686)

wherein, independently from each other,

10

X₂ is selected from A, I, L, T and V;

X₃ is selected from E and Y;

X₄ is selected from A, E, I, K, Q, R, T, V and Y;

X₅ is selected from I and V;

15

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;

20

X₁₈ is selected from K and R;

X₂₁ is selected from T and V;

X₂₅ is selected from I and R;

X₂₆ is selected from K and S, and

X₂₈ is selected from F and L,

25

and

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

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) EX₂X₃X₄X₅X₆X₇EIX₁₀X₁₁LPNLX₁₆RX₁₈QYX₂₁AFIX₂₅X₂₆LX₂₈D
(SEQ ID NO:1686)

wherein, independently from each other,

35

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

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

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

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

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

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

4. IL-1R-I binding polypeptide according to any preceding claim,
 wherein sequence i) corresponds to the sequence from position 8 to position
 36 in a sequence selected from the group consisting of SEQ ID NO:1-1632,
 35 and 1679, such as the group consisting of SEQ ID NO:20-1632 and 1679.

5. IL-1R-I binding polypeptide according to claim 4, wherein sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1206-1632 and 1679, such as the group consisting of SEQ ID NO:1210-1632 and 1679.

5

6. IL-1R-I binding polypeptide according to claim 5, wherein sequence i) corresponds to the sequence from position 8 to position 36 in a sequence selected from the group consisting of SEQ ID NO:1252, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1679, such as the group consisting of SEQ ID NO:1252, 1328, 1435 and 1679.

10

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

15

8. IL-1R-I binding polypeptide according to claim 7, wherein said three-helix bundle protein domain is selected from bacterial receptor domains, preferably from domains of protein A from *Staphylococcus aureus* or derivatives thereof.

20

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

25

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

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

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

30

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

35

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

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

11. IL-1R-I binding polypeptide according to claims 9 or 10, wherein
5 sequence xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1-1632, 1667-1668 and 1670-1679; such as the group consisting of SEQ ID NO:20-1632, 1667-1668 and 1670-1679.

10 12. IL-1R-I binding polypeptide according to claim 11 wherein xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting SEQ ID NO:1206-1632, 1667-1668 and 1670-1679, such as the group consisting of SEQ ID NO:1210-1632, 1667-1668 and 1670-1679.

15 13. IL-1R-I binding polypeptide according to claim 12, wherein sequence xix) or xxi) corresponds to the sequence from position 1 to position 58 in a sequence selected from the group consisting of SEQ ID NO:1252, 1285, 1307, 1308, 1328, 1331, 1415, 1421, 1435, 1594 and 1670-1679, such
20 as the group consisting of SEQ ID NO:1252, 1328, 1435, 1672, 1675-1676 and 1679.

14. IL-1R-I binding polypeptide according to any preceding claim,
which is capable of blocking the interaction of IL-1R-I with IL-1 cytokines,
25 such as the interaction of IL-1R-I with IL-1 α and/or IL-1 β .

15. IL-1R-I binding polypeptide according to any preceding claim which
is capable of binding to IL-1R-I such that the K_D value of the interaction is at
most 1×10^{-6} M, such as at most 1×10^{-7} M, such as at most 1×10^{-8} M, such
30 as at most 1×10^{-9} M, such as at most 9×10^{-10} .

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

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

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

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

10

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

21. Fusion protein or conjugate according to claim 18, wherein said

15 desired biological activity is a binding activity modifying tissue distribution of said fusion protein or conjugate.

22. Fusion protein or conjugate according to claim 18, wherein said desired biological activity is an *in vivo* half-life increasing activity such that

20 said second moiety increases *in vivo* half-life of the fusion protein or conjugate.

23. Fusion protein or conjugate according to claim 18, wherein said second moiety is selected from the group consisting of the albumin binding

25 domain of streptococcal protein G or a derivative thereof; serum albumin; an Fc portion of an antibody, and transferrin.

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

30 Fc.

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

35

26. Fusion protein or conjugate according to any one of claims 18-25, comprising a polypeptide having an amino acid sequence selected from the

group consisting of SEQ ID NO:1639-1658 and 1734-1737, such as from the group consisting of SEQ ID NO:1648-1654 and 1734-1737.

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

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

29. Host cell comprising an expression vector according to claim 28.
10

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

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

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

33. IL-1R-I binding polypeptide, fusion protein or conjugate according
to any one of claims 1-26 or a composition according to any one of claims 30-
32 for use as a medicament, a diagnostic agent and/or a prognostic agent.
25

34. IL-1R-I binding polypeptide, fusion protein, conjugate or
composition according to claim 33 for use as a medicament.

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

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

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

FIGURE 1A

DESIGNATION	SEQUENCE	SEQ ID NO
Z12964	VDKYAKEAEDATMEIYNLPNLTTRRQYVAFI IKLLDDPSQSSELLSEAKKLNDSQAPK	1
Z12933	VDKYAKEAKTAQIEIYDLPNLTTRRQYVAFIRKLLDDPSQSSELLSEAKKLNDSQAPK	2
Z12922	VDKYAKEDEQAQLEIFNLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	3
Z12941	VDKYAKEVLAYWEIFALPNLTTRKQYTA FIRKLMDDPSQSSELLSEAKKLNDSQAPK	4
Z12915	VDKYAKEVKWAHHEIFQLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	5
Z12975	VDKYAKEAHNAQQEIIYRLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	6
Z12905	VDKYAKEARAQQEIIYALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	7
Z12974	VDKYAKEADHAQQEII FALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	8
Z12967	VDKYAKEAHRAQMEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	9
Z12912	VDKYAKEALLAQQEII FALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	10
Z12910	VDKYAKEALSQQEII FALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	11
Z12895	VDKYAKEALSQQEII FALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	12
Z12884	VDKYAKEASLAQHEIFALPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	13
Z12920	VDKYAKEAVYARDEIYLLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	14
Z12917	VDKYAKEARQAYAEIYLLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	15
Z12961	VDKYAKEARSAYAEIYGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	16
Z12929	VDKYAKEQADAYAEIYSLPNLTTRKQYVAFIRKLI DDPSQSSELLSEAKKLNDSQAPK	17
Z12911	VDKYAKEHEKAI LEIFHLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	18
Z12891	VDKYAKEQSQAYHEIFKLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	19
Z15810	VDKYAKEVTDAQLEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	20
Z15811	VDKYAKEVEEAQMEIFELPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	21
Z15812	VDKYAKEVESAQMEIFYLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	22
Z15813	VDKYAKEVDEAYMEIYRLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	23
Z15814	VDKYAKELENAYMEIYLLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	24
Z15815	VDKYAKELEESAYMEIFNLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	25
Z15816	VDKYAKEVEEAQMEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	26
Z15817	VDKYAKETEDAQMEIFALPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	27
Z15818	VDKYAKEVEEAQMEIYNLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	28

FIGURE 1B

Z15819	VDKYYAKEAYVAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	29
Z15820	VDKYYAKEAYNAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	30
Z15821	VDKYYAKELEEAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	31
Z15822	VDKYYAKEIEAAQMEIFTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	32
Z15823	VDKYYAKEVEEAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	33
Z15824	VDKYYAKEIEEAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	34
Z15825	VDKYYAKETYN AQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	35
Z15826	VDKYYAKEVERAQMEIFDLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	36
Z15827	VDKYYAKEIESAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	37
Z15828	VDKYYAKEVHAAQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	38
Z15829	VDKYYAKETYE AQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	39
Z15830	VDKYYAKEIEDAYMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	40
Z15831	VDKYYAKEAERAQMEIFDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	41
Z15832	VDKYYAKEVEIAQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	42
Z15833	VDKYYAKEVEFAQMEIFKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	43
Z15834	VDKYYAKEVITAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	44
Z15835	VDKYYAKEIEEAQMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	45
Z15836	VDKYYAKETEAAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	46
Z15837	VDKYYAKEIENAQMEIYYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	47
Z15839	VDKYYAKETVEAYEEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	48
Z15840	VDKYYAKEVEVAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	49
Z15841	VDKYYAKEVEDAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	50
Z15842	VDKYYAKEIEVAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	51
Z15843	VDKYYAKEVEQAQMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	52
Z15844	VDKYYAKEVDQAYMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	53
Z15845	VDKYYAKEVEDAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	54
Z15846	VDKYYAKEIEEAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	55
Z15847	VDKYYAKEVYVAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	56
Z15848	VDKYYAKEIEEAQMEIFRLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	57

FIGURE 1C

Z15849	VDKYYAKEVEHAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	58
Z15850	VDKYYAKEIEIAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	59
Z15851	VDKYYAKEVV EAYQEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	60
Z15852	VDKYYAKEAEFFAQMEIFELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	61
Z15853	VDKYYAKEVELAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	62
Z15854	VDKYYAKEVEVAQMEIYGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	63
Z15855	VDKYYAKEIESAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	64
Z15856	VDKYYAKEVERAQFEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	65
Z15857	VDKYYAKEVKEAQDEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	66
Z15858	VDKYYAKEVEKAQMEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	67
Z15859	VDKYYAKEVEFFAQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	68
Z15860	VDKYYAKEVEEAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	69
Z15861	VDKYYAKEVENAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	70
Z15862	VDKYYAKEVEIAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	71
Z15863	VDKYYAKEIESAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	72
Z15864	VDKYYAKEIEN AQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	73
Z15865	VDKYYAKEIEDAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	74
Z15866	VDKYYAKELEKAQMEIYRLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	75
Z15867	VDKYYAKET YEAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	76
Z15868	VDKYYAKEVEWAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	77
Z15869	VDKYYAKEVQAAQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	78
Z15870	VDKYYAKEVEY AQMEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	79
Z15871	VDKYYAKEVELAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	80
Z15872	VDKYYAKEVEKAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	81
Z15873	VDKYYAKEAEIAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	82
Z15874	VDKYYAKEVEKAYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	83
Z15875	VDKYYAKELEDAYFEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	84
Z15877	VDKYYAKEVEEAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	85
Z15878	VDKYYAKEAADAYQEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	86

FIGURE 1D

Z15879	VDKYYAKEVEIAQMEIFGLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	87
Z15880	VDKYYAKEVEIAQMEIFSLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	88
Z15881	VDKYYAKEIEKAQMEIFRLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	89
Z15882	VDKYYAKEVEEAQMEIFGLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	90
Z15883	VDKYYAKETEIAQMEIFGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	91
Z15884	VDKYYAKEIHDAQMEIFGLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	92
Z15885	VDKYYAKETEKAQMEIFGLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	93
Z15886	VDKYYAKEVERAQMEIFALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	94
Z15887	VDKYYAKEVKEAQMEIFVLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	95
Z15888	VDKYYAKEVEDAQMEIFSLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	96
Z15889	VDKYYAKEVEAAQMEIFSLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	97
Z15890	VDKYYAKEAEKAYFEIYELPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	98
Z15891	VDKYYAKEIKDAYMEIFRLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	99
Z15892	VDKYYAKETEY AQMEIFNLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	100
Z15893	VDKYYAKEVEQAQMEIFHLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	101
Z15894	VDKYYAKEVEIAQMEIFILPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	102
Z15895	VDKYYAKEIEQAQMEIFGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	103
Z15896	VDKYYAKELDEAYMEIFGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	104
Z15897	VDKYYAKETEN AQMEIFALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	105
Z15898	VDKYYAKEVES AQMEIFGLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	106
Z15899	VDKYYAKEIEN AQMEIFNLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	107
Z15900	VDKYYAKEVID AQMEIFNLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	108
Z15901	VDKYYAKEL YEAQMEIFALPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	109
Z15902	VDKYYAKEVETAQMEIFALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	110
Z15903	VDKYYAKEVEFAQMEIYALPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	111
Z15904	VDKYYAKEVEEAQQEIQALPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	112
Z15905	VDKYYAKEVES AQMEIYNLPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	113
Z15906	VDKYYAKETEQAQMEIFALPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	114
Z15907	VDKYYAKELEAAAYFEIYELPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	115

FIGURE 1E

Z15908	VDAKYAKEVEEEAYMEIYNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	116
Z15909	VDAKYAKEVEVEAYMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	117
Z15910	VDAKYAKEIEQAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	118
Z15911	VDAKYAKEIEVAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	119
Z15912	VDAKYAKEVEAAQMEIFVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	120
Z15913	VDAKYAKEVEAAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	121
Z15914	VDAKYAKEVETAQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	122
Z15915	VDAKYAKEAENAQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	123
Z15916	VDAKYAKEIERAQHEIFNLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	124
Z15917	VDAKYAKEVEEAQMEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	125
Z15918	VDAKYAKELEAAQMEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	126
Z15919	VDAKYAKEVVSQAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	127
Z15920	VDAKYAKEVEDAQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	128
Z15921	VDAKYAKEVEEAQMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	129
Z15922	VDAKYAKEIEKAQMEIFKLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	130
Z15923	VDAKYAKETYA QMEIFTLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	131
Z15924	VDAKYAKETYE A QMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	132
Z15925	VDAKYAKEIEEAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	133
Z15926	VDAKYAKEVQEAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	134
Z15927	VDAKYAKEIEEAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	135
Z15928	VDAKYAKELEAA YMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	136
Z15929	VDAKYAKETERAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	137
Z15930	VDAKYAKEIEHAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	138
Z15933	VDAKYAKEVEDAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	139
Z15935	VDAKYAKEVEAAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	140
Z15936	VDAKYAKEVVAA YQEIYQLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	141
Z15937	VDAKYAKETYAAQMEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	142
Z15938	VDAKYAKEVEQAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	143
Z15939	VDAKYAKEIEKAQMEIYQLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	144

FIGURE 1F

Z15940	VDKYYAKEAEVAYFEIYKLPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	145
Z15941	VDKYYAKEAIDAYDEIYALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	146
Z15942	VDKYYAKEVEDAQMEIYFLPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	147
Z15943	VDKYYAKEIEN AQMEIFYLPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	148
Z15944	VDKYYAKEVDDAYMEIFRLPNLTNRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	149
Z15945	VDKYYAKEVEEAQMEIFS LPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	150
Z15946	VDKYYAKEVES AQMEIFKLPNLTNRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	151
Z15947	VDKYYAKETEIAQMEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	152
Z15948	VDKYYAKEVERAQMEIFDLPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	153
Z15949	VDKYYAKETETAQMEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	154
Z15950	VDKYYAKEIEYAQMEIFALPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	155
Z15951	VDKYYAKELEERAQMEIYHLPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	156
Z15952	VDKYYAKESEIAQMEIFALPNLTNRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	157
Z15953	VDKYYAKETEK AQMEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	158
Z15954	VDKYYAKEVENAQMEIFNLPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	159
Z15955	VDKYYAKEVEEAQLEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	160
Z15956	VDKYYAKEVKEAQLEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	161
Z15957	VDKYYAKEVQEAQMEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	162
Z15958	VDKYYAKEVQFAYMEIFHLPNLTNRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	163
Z15959	VDKYYAKELEHAYMEIYALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	164
Z15960	VDKYYAKETEAAQMEIFALPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	165
Z15961	VDKYYAKEVETAQMEIFALPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	166
Z15962	VDKYYAKELEKAQMEIYYLPNLTNRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	167
Z15963	VDKYYAKEIEEAQMEIYDLPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	168
Z15964	VDKYYAKELESAYMEIYSLPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	169
Z15965	VDKYYAKEIEVAQMEIFS LPNLTNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	170
Z15966	VDKYYAKEVELAQMEIFE LPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	171
Z15967	VDKYYAKEIEEAQMEIFTLPNLTNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	172
Z15968	VDKYYAKEIEAAQMEIYYLPNLTNRKQYTA FIKLDDPSQSSELLSEAKKLND SQAPK	173

FIGURE 1G

Z15969	VDKYYAKEIEEAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	174
Z15970	VDKYYAKEVEFAQLEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	175
Z15971	VDKYYAKEIEEAAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	176
Z15972	VDKYYAKEVEEQAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	177
Z15973	VDKYYAKEAFTAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	178
Z15974	VDKYYAKETHQAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	179
Z15976	VDKYYAKEVEDAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	180
Z15977	VDKYYAKEVEQAQMEIYVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	181
Z15978	VDKYYAKEVEAAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	182
Z15979	VDKYYAKEVEEAAQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	183
Z15980	VDKYYAKEIEEAAQMEIYALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	184
Z15981	VDKYYAKEIEQAQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	185
Z15982	VDKYYAKETEAAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	186
Z15983	VDKYYAKEIERAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	187
Z15984	VDKYYAKEIEEAAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	188
Z15985	VDKYYAKEVEAAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	189
Z15986	VDKYYAKEVEEAAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	190
Z15987	VDKYYAKEVEEAAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	191
Z15988	VDKYYAKEVEEKAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	192
Z15989	VDKYYAKEVEEQAQMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	193
Z15990	VDKYYAKELEHAYHEIYILPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	194
Z15991	VDKYYAKEIEEAAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	195
Z15992	VDKYYAKEVEDAQQEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	196
Z15993	VDKYYAKEIEIAQMEIYALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	197
Z15994	VDKYYAKEVEWAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	198
Z15995	VDKYYAKEVLDAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	199
Z15996	VDKYYAKEVESAAQMEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	200
Z15997	VDKYYAKEIEEAAQMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	201
Z15998	VDKYYAKEIEDAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	202

FIGURE 1H

Z15999	VDKAYAKEVEIEIAYMEIFHLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	203
Z16000	VDKAYAKEAYRAQMEIFALPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	204
Z16001	VDKAYAKEVELAQMEIFSLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	205
Z16002	VDKAYAKETEHQAQMEIYNLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	206
Z16003	VDKAYAKEVYIAQMEIYGLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	207
Z16004	VDKAYAKEVEVAQMEIFSLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	208
Z16005	VDKAYAKELEDAQMEIFKLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	209
Z16006	VDKAYAKEIEQAQMEIFALPNLTTRKQYTAFAIKLFDDPSQSSELLSEAKKLNDSQAPK	210
Z16007	VDKAYAKEVEIAQMEIFSLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	211
Z16008	VDKAYAKEVEVAQMEIFNLPNLTTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	212
Z16009	VDKAYAKEVEEAQLEIFGLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	213
Z16010	VDKAYAKETEQAQMEIFNLPNLTTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	214
Z16011	VDKAYAKEIEVAQMEIFALPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	215
Z16012	VDKAYAKEVEQAQMEIFFLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	216
Z16013	VDKAYAKEIESAQMEIFDLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	217
Z16014	VDKAYAKEIEKAQMEIFYLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	218
Z16015	VDKAYAKEVEEAQMEIYYLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	219
Z16016	VDKAYAKEVEDAQMEIYYLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	220
Z16017	VDKAYAKEVEEAQMEIYDLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	221
Z16018	VDKAYAKEVELAQMEIFNLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	222
Z16019	VDKAYAKETEYAQMEIFALPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	223
Z16020	VDKAYAKEVEAAQMEIYGLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	224
Z16021	VDKAYAKEVEVAQMEIFALPNLTTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	225
Z16022	VDKAYAKEIEFAQMEIFALPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	226
Z16023	VDKAYAKEVEEAQMEIFALPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	227
Z16024	VDKAYAKEVEEAQMEIFTLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	228
Z16025	VDKAYAKEVEVAQMEIYNLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	229
Z16026	VDKAYAKEVEKAQMEIYYLPNLTTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	230
Z16027	VDKAYAKEVYQAQMEIFYLPNLTTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	231

FIGURE 1I

Z16028	VDKYYAKEIRDAQMEIFDLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	232
Z16029	VDKYYAKEIEDAQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	233
Z16030	VDKYYAKEVEYQAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	234
Z16031	VDKYYAKEAYYAQMEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	235
Z16032	VDKYYAKEAEDAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	236
Z16033	VDKYYAKEIEDAYMEIYRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	237
Z16034	VDKYYAKEVEEAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	238
Z16035	VDKYYAKELEEAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	239
Z16036	VDKYYAKEVETAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	240
Z16037	VDKYYAKEIEDAQMEIFQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	241
Z16038	VDKYYAKEVEDAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	242
Z16039	VDKYYAKEVEEAQMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	243
Z16040	VDKYYAKEVQDAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	244
Z16041	VDKYYAKEIETAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	245
Z16042	VDKYYAKEVEDAQMEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	246
Z16043	VDKYYAKETEEAQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	247
Z16044	VDKYYAKEVERAQMEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	248
Z16045	VDKYYAKEAEAQAQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	249
Z16046	VDKYYAKEIYSAQMEIFKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	250
Z16047	VDKYYAKEIEKAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	251
Z16048	VDKYYAKEIEEAQMEIYYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	252
Z16049	VDKYYAKEVEQAQMEIFSLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	253
Z16050	VDKYYAKEVEAAQMEIFNLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	254
Z16051	VDKYYAKEVESAQMEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	255
Z16052	VDKYYAKEIEAAQMEIFDLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	256
Z16053	VDKYYAKEETERAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	257
Z16054	VDKYYAKEAEVAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	258
Z16055	VDKYYAKEIEEAQMEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	259
Z16056	VDKYYAKEVEQAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	260

FIGURE 1J

Z16057	VDKYYAKEAEAAQMEIFTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	261
Z16058	VDKYYAKEVEEAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	262
Z16059	VDKYYAKETYYAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	263
Z16060	VDKYYAKEVEEAQMEIYSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	264
Z16061	VDKYYAKEIEAAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	265
Z16062	VDKYYAKEIEEAQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	266
Z16063	VDKYYAKEIESAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	267
Z16065	VDKYYAKEVEEAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	268
Z16066	VDKYYAKEAEAAQMEIYFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	269
Z16067	VDKYYAKEVEIAQMEIAYFEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	270
Z16068	VDKYYAKEVEVAQLEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	271
Z16069	VDKYYAKEVEEAQMEIYFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	272
Z16070	VDKYYAKEIEEAQMEIYRLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	273
Z16071	VDKYYAKEVRAAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	274
Z16072	VDKYYAKEVEIAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	275
Z16073	VDKYYAKEAERAQMEIWKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	276
Z16074	VDKYYAKETESAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	277
Z16075	VDKYYAKEVEEAQMEIFALPNLTRKQYTA FIKLFDDPSQSSELLSEAKKLND SQAPK	278
Z16076	VDKYYAKELEAAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	279
Z16077	VDKYYAKEVEVAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	280
Z16078	VDKYYAKEVEVAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	281
Z16079	VDKYYAKEVEEAQMEIFFLPNLTRKQYTA FIKLDDPSQSSELLSEAKKLND SQAPK	282
Z16080	VDKYYAKEVEAAQMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	283
Z16081	VDKYYAKEAEYAYEIIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	284
Z16082	VDKYYAKEVESAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	285
Z16083	VDKYYAKELEQAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	286
Z16084	VDKYYAKEIEIAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	287
Z16086	VDKYYAKEVESAQMEIFALPNLTRKQYTA FIKLFDDPSQSSELLSEAKKLND SQAPK	288
Z16087	VDKYYAKEAENAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	289

FIGURE 1K

Z16088	VDAKYAKEVTTAYE IYNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	290
Z16089	VDAKYAKEIESAYE IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	291
Z16090	VDAKYAKEVEEAAQME IFYLPNLTRRQYTA FI IKLLDDPSQSSELLSEAKKLND SQAPK	292
Z16092	VDAKYAKEIEQAQME IYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	293
Z16093	VDAKYAKETEEAAQME IFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	294
Z16094	VDAKYAKEVEEAAQME IFYLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	295
Z16095	VDAKYAKEAAAAHWE IYNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	296
Z16096	VDAKYAKEVERAAQME IFGLPNLTRRQYTA FI IKLLDDPSQSSELLSEAKKLND SQAPK	297
Z16097	VDAKYAKETERAAQME IFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	298
Z16098	VDAKYAKEVEEAAQME IYVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	299
Z16099	VDAKYAKEAENAYHE IFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	300
Z16101	VDAKYAKEAYAAQME IYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	301
Z16102	VDAKYAKEVETAQME IYQLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	302
Z16103	VDAKYAKEAEDAQLE IFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	303
Z16104	VDAKYAKEAQEAYE IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	304
Z16105	VDAKYAKEVEHAYME IYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	305
Z16106	VDAKYAKEVEDAQME IFKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	306
Z16107	VDAKYAKEVEEAAQME IYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	307
Z16108	VDAKYAKEIEYAQME IFDLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	308
Z16109	VDAKYAKEAEWAYME IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	309
Z16110	VDAKYAKEVEEAAQYE IFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	310
Z16111	VDAKYAKEIEAAQME IFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	311
Z16112	VDAKYAKEVENAYME IFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	312
Z16113	VDAKYAKEVEHAYQE IFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	313
Z16114	VDAKYAKEVEDAYME IYVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	314
Z16115	VDAKYAKEVEDAQME IFGLPNLTRKQYTA FI IKLLDDPSQSSELLSEAKKLND SQAPK	315
Z16116	VDAKYAKEVEAAQME IFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	316
Z16117	VDAKYAKEIEKAQFE IFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	317
Z16118	VDAKYAKEVEDAQME IYSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	318

FIGURE 1L

Z16119	VDKYYAKEAESAYLEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	319
Z16120	VDKYYAKEVVVEAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	320
Z16121	VDKYYAKEVEDAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	321
Z16122	VDKYYAKEAEADAYMEIYSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	322
Z16125	VDKYYAKEAQDAYMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	323
Z16126	VDKYYAKEIEAAQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	324
Z16127	VDKYYAKEIEIAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	325
Z16128	VDKYYAKEVEHAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	326
Z16129	VDKYYAKEAEAAQYEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	327
Z16130	VDKYYAKEVVYHAQMEIFKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	328
Z16131	VDKYYAKEVEIAQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	329
Z16132	VDKYYAKELEERAYAEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	330
Z16133	VDKYYAKEVDEAYMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	331
Z16134	VDKYYAKEFHRA YSEIYLLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	332
Z16135	VDKYYAKEVELAQHEIFQLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	333
Z16136	VDKYYAKEVES AQMEIFELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	334
Z16137	VDKYYAKEAEIAYYEIYSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	335
Z16138	VDKYYAKEVEDAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	336
Z16139	VDKYYAKETFKAQQEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	337
Z16140	VDKYYAKEAEQAYWEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	338
Z16141	VDKYYAKEVVQAYDEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	339
Z16142	VDKYYAKEASDAYEEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	340
Z16143	VDKYYAKEIEAAQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	341
Z16144	VDKYYAKEAEAAQYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	342
Z16145	VDKYYAKEVEHAQYEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	343
Z16146	VDKYYAKEAEKAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	344
Z16147	VDKYYAKEVDAA YMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	345
Z16148	VDKYYAKEVEIAQMEIYNLPNLTRKQYTA I IKLDDPSQSSELLSEAKKLND SQAPK	346
Z16149	VDKYYAKEVENAYFEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	347

FIGURE 1M

Z16150	VDKYYAKEVEDAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	348
Z16152	VDKYYAKEVEKAYFEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	349
Z16154	VDKYYAKEIEAAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	350
Z16155	VDKYYAKEFTWYAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	351
Z16156	VDKYYAKEIERAQMEIFS LPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	352
Z16157	VDKYYAKEVD DAYMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	353
Z16158	VDKYYAKEVEAA YVEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	354
Z16159	VDKYYAKEFSEAYFEIYSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	355
Z16160	VDKYYAKEVAKAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	356
Z16161	VDKYYAKEVEYAQMEIYSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	357
Z16162	VDKYYAKEAESAYWEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	358
Z16163	VDKYYAKEVERAQMEIFE LPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	359
Z16164	VDKYYAKEVEEAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	360
Z16165	VDKYYAKEIEVAQMEIYSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	361
Z16166	VDKYYAKEVR I AQFEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	362
Z16167	VDKYYAKEVEQAQHEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	363
Z16168	VDKYYAKEAVSAYWEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	364
Z16169	VDKYYAKETE EAQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	365
Z16170	VDKYYAKEADAA YMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	366
Z16171	VDKYYAKETA AAQAEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	367
Z16172	VDKYYAKEAFDAYWEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	368
Z16173	VDKYYAKEIEAAYAEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	369
Z16174	VDKYYAKEVIDAYFEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	370
Z16175	VDKYYAKEVESAQMEIYRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	371
Z16176	VDKYYAKETE EAYQEIFDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	372
Z16177	VDKYYAKEVEI AQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	373
Z16178	VDKYYAKEVEEAQMEIFFLPNLTRKQYTA FIKLFDDPSQSSELLSEAKKLND SQAPK	374
Z16179	VDKYYAKEIEI AQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	375
Z16180	VDKYYAKETYWAQQEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	376

FIGURE 1N

Z16181	VDKYYAKEAESQAQMEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	377
Z16182	VDKYYAKELETAQFEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	378
Z16183	VDKYYAKEVEDAQMEIFYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	379
Z16184	VDKYYAKELELAQOEIYALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	380
Z16185	VDKYYAKEIVAAQWEIYYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	381
Z16186	VDKYYAKEVEEAYMEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	382
Z16187	VDKYYAKEIDSAYFEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	383
Z16188	VDKYYAKEAEQAQOEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	384
Z16189	VDKYYAKEAYRAQMEIFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	385
Z16190	VDKYYAKEVEDAYFEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	386
Z16191	VDKYYAKEIEAAQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	387
Z16192	VDKYYAKEAYEAQMEIFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	388
Z16193	VDKYYAKEVVDAQFEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	389
Z16194	VDKYYAKEVEEAQMEIFKLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	390
Z16195	VDKYYAKETEKAQMEIFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	391
Z16196	VDKYYAKETYQAQMEIFGLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	392
Z16197	VDKYYAKEVESQAQMEIFALPNLTRKQYTA FIKLLDDPSQSSELLSEAKKLNDSQAPK	393
Z16198	VDKYYAKEIEDAQMEIFGLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	394
Z16199	VDKYYAKEVEKAQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	395
Z16200	VDKYYAKEIEQAQFEIFYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	396
Z16201	VDKYYAKETEVAQMEIFKLPNLTRKQYTA FIKLFDDPSQSSELLSEAKKLNDSQAPK	397
Z16202	VDKYYAKEVEQAQMEIFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	398
Z16203	VDKYYAKEVEIAQHEIFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	399
Z16204	VDKYYAKEVELAYMEIYKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	400
Z16205	VDKYYAKEVVQAYDEIFQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	401
Z16206	VDKYYAKEVEEAQMEIFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	402
Z16207	VDKYYAKEVEEAQMEIYNLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	403
Z16208	VDKYYAKEVEKAQMEIFDLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	404
Z16209	VDKYYAKEVEEAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	405

FIGURE 10

Z16210	VDKAYAKEAETAYHEIYILPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	406
Z16211	VDKAYAKEAEAEQAQMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	407
Z16212	VDKAYAKEVEFEAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	408
Z16213	VDKAYAKEARQAYWEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	409
Z16214	VDKAYAKETETAQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	410
Z16215	VDKAYAKEIEEAQHEIFRLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	411
Z16216	VDKAYAKEVSNAYMEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	412
Z16217	VDKAYAKEIEEAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	413
Z16218	VDKAYAKEVTDAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	414
Z16219	VDKAYAKEIEHAQLEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	415
Z16220	VDKAYAKEVEQAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	416
Z16221	VDKAYAKEAEWAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	417
Z16222	VDKAYAKEVHAAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	418
Z16223	VDKAYAKEVEFAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	419
Z16224	VDKAYAKEVIDAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	420
Z16225	VDKAYAKEVEDAYMEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	421
Z16227	VDKAYAKEVEAAQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	422
Z16228	VDKAYAKETVAAAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	423
Z16229	VDKAYAKEVVDAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	424
Z16230	VDKAYAKETEEAAYWEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	425
Z16231	VDKAYAKEVETAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	426
Z16232	VDKAYAKEVVDAYYEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	427
Z16233	VDKAYAKEVQEAAYMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	428
Z16234	VDKAYAKEVEDAYYEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	429
Z16235	VDKAYAKEVVEAYDEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	430
Z16236	VDKAYAKETEEAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	431
Z16237	VDKAYAKEVIDAYDEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	432
Z16238	VDKAYAKEVVDAYYEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	433
Z16239	VDKAYAKEVEEAAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	434

FIGURE 1P

Z16240	VDAKYAKEVESAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	435
Z16241	VDAKYAKEVEDAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	436
Z16242	VDAKYAKEAESAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	437
Z16243	VDAKYAKEVEEAYMEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	438
Z16244	VDAKYAKEVEHAYFEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	439
Z16245	VDAKYAKEVETAYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	440
Z16246	VDAKYAKEVEDAYMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	441
Z16247	VDAKYAKEAHDAYWEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	442
Z16248	VDAKYAKEVEDAYMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	443
Z16249	VDAKYAKEVEEAYEEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	444
Z16250	VDAKYAKEVEIAYMEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	445
Z16251	VDAKYAKEVEQAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	446
Z16252	VDAKYAKEVEEAYMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	447
Z16253	VDAKYAKEVEEAYEIIYLLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	448
Z16255	VDAKYAKETEDAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	449
Z16256	VDAKYAKEVEHAYFEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	450
Z16257	VDAKYAKEVEEAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	451
Z16258	VDAKYAKEVETAYMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	452
Z16259	VDAKYAKEVEDAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	453
Z16260	VDAKYAKEIEEAYMEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	454
Z16261	VDAKYAKEVEDAYFEIYTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	455
Z16262	VDAKYAKEVEEAYFEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	456
Z16263	VDAKYAKEAEKAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	457
Z16264	VDAKYAKEVEVAYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	458
Z16265	VDAKYAKEVEEAYFEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	459
Z16266	VDAKYAKEVTDAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	460
Z16268	VDAKYAKEVEVAYWEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	461
Z16269	VDAKYAKEVEYAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	462
Z16270	VDAKYAKEVEEAYMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	463

FIGURE 1Q

Z16271	VDKYYAKEVEDAYWEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	464
Z16272	VDKYYAKEVVDAYYEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	465
Z16273	VDKYYAKEATAAYMEIYFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	466
Z16274	VDKYYAKEASDAYQEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	467
Z16275	VDKYYAKEAQTAAYMEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	468
Z16276	VDKYYAKETVDAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	469
Z16277	VDKYYAKEVEDAYYEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	470
Z16278	VDKYYAKEVVEAYWEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	471
Z16279	VDKYYAKEADEAYWEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	472
Z16280	VDKYYAKEVEFFAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	473
Z16281	VDKYYAKEVVDAYYEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	474
Z16282	VDKYYAKEVEAAAYFEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	475
Z16283	VDKYYAKEVEDAYMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	476
Z16284	VDKYYAKEAELAYWEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	477
Z16285	VDKYYAKEVEKAYMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	478
Z16286	VDKYYAKEQEFFAYFEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	479
Z16287	VDKYYAKELDAYMEIYGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	480
Z16288	VDKYYAKEAEQAYYEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	481
Z16289	VDKYYAKEHVEAYFEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	482
Z16290	VDKYYAKEVTAAYYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	483
Z16291	VDKYYAKEVEIAYFEIYNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	484
Z16292	VDKYYAKEAQDAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	485
Z16293	VDKYYAKEVITAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	486
Z16294	VDKYYAKEVENAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	487
Z16295	VDKYYAKEHVDAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	488
Z16296	VDKYYAKEVTNAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	489
Z16297	VDKYYAKEAAEAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	490
Z16298	VDKYYAKEVHEAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	491
Z16299	VDKYYAKEADIAAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	492

FIGURE 1R

Z16300	VDAKYAKEVEVAYMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	493
Z16301	VDAKYAKEIEAAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	494
Z16302	VDAKYAKEVETAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	495
Z16303	VDAKYAKEAQQAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	496
Z16304	VDAKYAKEIDKAYFEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	497
Z16305	VDAKYAKEVESAYFEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	498
Z16306	VDAKYAKELYLAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	499
Z16307	VDAKYAKEAVEAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	500
Z16308	VDAKYAKEAVNAYWEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	501
Z16309	VDAKYAKELEYAYFEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	502
Z16311	VDAKYAKEVQAAAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	503
Z16312	VDAKYAKEVEKAQMEIFDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	504
Z16313	VDAKYAKETYAAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	505
Z16314	VDAKYAKELEAAAYEIEYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	506
Z16315	VDAKYAKEHVDAAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	507
Z16316	VDAKYAKETIHAYDEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	508
Z16317	VDAKYAKEQEEAYWEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	509
Z16318	VDAKYAKEVEEAYEIEYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	510
Z16319	VDAKYAKEIEEAQMEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	511
Z16320	VDAKYAKEVEDAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	512
Z16321	VDAKYAKEIEEAQMEIYTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	513
Z16322	VDAKYAKEVERAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	514
Z16324	VDAKYAKEVVIAAYHEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	515
Z16325	VDAKYAKEAYDAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	516
Z16327	VDAKYAKEIIQAYYEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	517
Z16328	VDAKYAKEVV SAYFEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	518
Z16329	VDAKYAKEVEDAYFEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	519
Z16330	VDAKYAKEVV EAYHEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	520
Z16331	VDAKYAKEAEVAYYEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	521

FIGURE 1S

Z16332	VDAKYAKEVEEEAYMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	522
Z16333	VDAKYAKEAEWAYFEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	523
Z16334	VDAKYAKEAEAAWEIYALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	524
Z16335	VDAKYAKEAYVAYEINYLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	525
Z16336	VDAKYAKELEYAYHEIFALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	526
Z16337	VDAKYAKESESAWWEIYALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	527
Z16338	VDAKYAKEVEEAYQEIFNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	528
Z16339	VDAKYAKEIEEAYMEIFNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	529
Z16340	VDAKYAKEVVDAYSEIYLLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	530
Z16341	VDAKYAKELEAAQMEIFALPNLT R R R QYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	531
Z16342	VDAKYAKEVEVAYMEIFELPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	532
Z16343	VDAKYAKEVHEAYFEIFALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	533
Z16344	VDAKYAKEVENAYYEIYELPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	534
Z16345	VDAKYAKEVEHAYYEIYRLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	535
Z16346	VDAKYAKEAEADAYMEIFHLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	536
Z16347	VDAKYAKETYAAQMEIYRLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	537
Z16348	VDAKYAKEAEYAYFEIFALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	538
Z16349	VDAKYAKEVVEAYYEIYELPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	539
Z16351	VDAKYAKEVVHAYFEIFSLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	540
Z16352	VDAKYAKEIENAQMEIFYLPNLT R R R QYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	541
Z16353	VDAKYAKEVEAAAYFEITYLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	542
Z16354	VDAKYAKETLHAYDEIYQLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	543
Z16356	VDAKYAKEVEEAYMEIFRLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	544
Z16357	VDAKYAKEVEEAQMEIFNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	545
Z16358	VDAKYAKETVDAYYEIYALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	546
Z16360	VDAKYAKEAEAYFEIYGLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	547
Z16361	VDAKYAKEIEIAQMEIFTLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	548
Z16362	VDAKYAKEVEIAYFEIFALPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	549
Z16363	VDAKYAKEVEEAQMEIFRLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	550

FIGURE 1T

Z16364	VDAKYAKEVQDAYWEIYQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	551
Z16365	VDAKYAKETE EAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	552
Z16366	VDAKYAKEVEAAYFEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	553
Z16367	VDAKYAKEIEDAQMEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	554
Z16368	VDAKYAKEVEVAYFEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	555
Z16369	VDAKYAKEIETAYMEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	556
Z16370	VDAKYAKEADAAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	557
Z16371	VDAKYAKEVEQAYYEIYHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	558
Z16372	VDAKYAKEIEKAYYEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	559
Z16373	VDAKYAKEVVAAAYYEIYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	560
Z16376	VDAKYAKEVVSAAYEINYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	561
Z16377	VDAKYAKETERAQMEIFYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	562
Z16378	VDAKYAKEVESAYFEIFKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	563
Z16379	VDAKYAKEVEKAYMEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	564
Z16380	VDAKYAKETEDAYMEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	565
Z16381	VDAKYAKEAE EAYFEIYNLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	566
Z16382	VDAKYAKETLEAYDEIYQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	567
Z16383	VDAKYAKELEVAYMEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	568
Z16384	VDAKYAKEVEIAQMEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	569
Z16385	VDAKYAKEVVEAYQEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	570
Z16386	VDAKYAKEAE EAYYEIYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	571
Z16387	VDAKYAKEVEAAYMEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	572
Z16388	VDAKYAKEHE DAYMEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	573
Z16389	VDAKYAKELEKAYFEIYNLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	574
Z16390	VDAKYAKEVEIAQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	575
Z16391	VDAKYAKEVELAYMEIFNLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	576
Z16392	VDAKYAKEVFEAQMEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	577
Z16393	VDAKYAKEVEDAYMEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	578
Z16394	VDAKYAKETESAYFEIFKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	579

FIGURE 1U

Z16395	VDAKYAKELEEEAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	580
Z16396	VDAKYAKEVVTA YQE IYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	581
Z16397	VDAKYAKEVEAA YFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	582
Z16398	VDAKYAKEVEWAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	583
Z16399	VDAKYAKETEYAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	584
Z16400	VDAKYAKEVETAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	585
Z16401	VDAKYAKEVEFFAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	586
Z16402	VDAKYAKEVEAA YFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	587
Z16403	VDAKYAKEVERAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	588
Z16404	VDAKYAKETVIA YFEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	589
Z16405	VDAKYAKETEDAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	590
Z16406	VDAKYAKEADSA YWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	591
Z16407	VDAKYAKEVELAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	592
Z16409	VDAKYAKEVEQAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	593
Z16410	VDAKYAKEAVDAYYEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	594
Z16411	VDAKYAKELQEA YMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	595
Z16412	VDAKYAKEHVDA YMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	596
Z16413	VDAKYAKEVEHA YEEIYALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	597
Z16414	VDAKYAKEVVVA YHEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	598
Z16415	VDAKYAKEHWKA YLEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	599
Z16416	VDAKYAKEVYDA QMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	600
Z16417	VDAKYAKEVEAA YMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	601
Z16418	VDAKYAKEHLTA YYEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	602
Z16419	VDAKYAKEVKDA YFEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	603
Z16420	VDAKYAKETEYA QMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	604
Z16421	VDAKYAKEIEDA YMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	605
Z16422	VDAKYAKELEEA YYEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	606
Z16423	VDAKYAKETENA YMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	607
Z16424	VDAKYAKEIESA YFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	608

FIGURE 1V

Z16425	VDKAYAKEVYIAQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	609
Z16426	VDKAYAKEVEEAYFEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	610
Z16427	VDKAYAKEA INAHHEIFLLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	611
Z16428	VDKAYAKEIEDAQMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	612
Z16429	VDKAYAKEAYEAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	613
Z16430	VDKAYAKEAEDAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	614
Z16431	VDKAYAKEVEQAYFEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	615
Z16432	VDKAYAKEIEEAQMEIYFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	616
Z16433	VDKAYAKE TVSAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	617
Z16434	VDKAYAKETE EAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	618
Z16435	VDKAYAKEADRAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	619
Z16436	VDKAYAKETYKAQOEIYKLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	620
Z16437	VDKAYAKEVEVAYWEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	621
Z16438	VDKAYAKELE RAYYEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	622
Z16439	VDKAYAKEA IDAYWEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	623
Z16440	VDKAYAKEVESAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	624
Z16441	VDKAYAKEAENAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	625
Z16442	VDKAYAKEADAAYWEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	626
Z16443	VDKAYAKEATEAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	627
Z16444	VDKAYAKEVHDAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	628
Z16446	VDKAYAKELEFFAYQEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	629
Z16447	VDKAYAKEHVAAAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	630
Z16448	VDKAYAKEVEVAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	631
Z16449	VDKAYAKEVEQAYSEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	632
Z16450	VDKAYAKEAEVAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	633
Z16451	VDKAYAKEVEIAYYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	634
Z16452	VDKAYAKEVENAYYEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	635
Z16453	VDKAYAKEAYEAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	636
Z16454	VDKAYAKEADQAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	637

FIGURE 1W

Z16455	VDAKYAKELHHAYDEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	638
Z16456	VDAKYAKEVEEAYQEIFHLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	639
Z16457	VDAKYAKEVEEAAYYEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	640
Z16458	VDAKYAKEVEIAQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	641
Z16459	VDAKYAKEVEEAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	642
Z16460	VDAKYAKETESAYWEIYKLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	643
Z16461	VDAKYAKEVERAYYEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	644
Z16462	VDAKYAKEAEFEAYMEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	645
Z16463	VDAKYAKEVERAQMEIFELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	646
Z16464	VDAKYAKETEQA YMEIYALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	647
Z16465	VDAKYAKEVERAYFEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	648
Z16466	VDAKYAKEVEQA YFEIFELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	649
Z16467	VDAKYAKEVQKAYFEIYDLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	650
Z16468	VDAKYAKEVEEAA YMEIYELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	651
Z16469	VDAKYAKEVEEAYFEIYALPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	652
Z16470	VDAKYAKELEDA YMEIYSLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	653
Z16471	VDAKYAKEVVDA YDEIFHLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	654
Z16472	VDAKYAKEVVDA YDEIFRLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	655
Z16473	VDAKYAKEVEDA YEEIYALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	656
Z16474	VDAKYAKEAEAEAYWEIYELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	657
Z16475	VDAKYAKEVEVA QMEIFDLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	658
Z16476	VDAKYAKEVEVA QMEIFGLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	659
Z16477	VDAKYAKELEAA QMEIFELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	660
Z16478	VDAKYAKEVEEAYFEIYNLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	661
Z16479	VDAKYAKEVEQA YMEIYELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	662
Z16480	VDAKYAKEVHDA YEEIFILPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	663
Z16481	VDAKYAKEVEVA YMEIFNLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	664
Z16482	VDAKYAKEAEHA YFEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	665
Z16483	VDAKYAKEIEVA QMEIYNLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	666

FIGURE 1X

Z16484	VDKYYAKEAEADAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	667
Z16485	VDKYYAKEVEHAYFEI FALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	668
Z16486	VDKYYAKE TENAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	669
Z16487	VDKYYAKEVEQAYFEI FALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	670
Z16488	VDKYYAKEAEADAYMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	671
Z16489	VDKYYAKEVEDAYEEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	672
Z16490	VDKYYAKELESAYFEIYGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	673
Z16491	VDKYYAKEVV TAYYEI FELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	674
Z16492	VDKYYAKEQEDAYWEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	675
Z16493	VDKYYAKEVQAAYFEI FALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	676
Z16494	VDKYYAKEAVNAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	677
Z16495	VDKYYAKEVEHAQMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	678
Z16496	VDKYYAKEVEAAAYFEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	679
Z16497	VDKYYAKEIEIAQMEI FALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	680
Z16498	VDKYYAKELENAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	681
Z16499	VDKYYAKEVEAAAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	682
Z16500	VDKYYAKELEWAQMEI FYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	683
Z16501	VDKYYAKEADDAAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	684
Z16502	VDKYYAKEVELAQMEI FKLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	685
Z16503	VDKYYAKEIHEAQMEI FKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	686
Z16505	VDKYYAKEVEYAYFEI FKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	687
Z16506	VDKYYAKEAYTAQMEI FSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	688
Z16507	VDKYYAKEAENAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	689
Z16509	VDKYYAKEVERAYMEI FGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	690
Z16510	VDKYYAKEIEEAQMEI FWLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	691
Z16511	VDKYYAKEIEDAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	692
Z16512	VDKYYAKEVV KAYYEIYELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	693
Z16513	VDKYYAKELENAYAEI FHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	694
Z16514	VDKYYAKEQI SAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	695

FIGURE 1Y

Z16515	VDAKYAKETEDAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	696
Z16516	VDAKYAKEVE DAYMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	697
Z16517	VDAKYAKEVE DAYQYEIFDL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	698
Z16518	VDAKYAKEVE DAYQYEIFDL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	699
Z16519	VDAKYAKEAHEA QMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	700
Z16520	VDAKYAKETYN AQQEIFNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	701
Z16521	VDAKYAKEVE DAYQYEIFAL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	702
Z16522	VDAKYAKEIEKA QMEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	703
Z16523	VDAKYAKEIEKA QMEIFGL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	704
Z16524	VDAKYAKEVE LAQMEIFAL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	705
Z16525	VDAKYAKEVE HAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	706
Z16526	VDAKYAKETE SAQMEIFGL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	707
Z16527	VDAKYAKEIEVA QLEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	708
Z16528	VDAKYAKEVE TAQMEIFAL PNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	709
Z16529	VDAKYAKEIE SAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	710
Z16530	VDAKYAKETE EAQMEIFGL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	711
Z16531	VDAKYAKEVE VAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	712
Z16532	VDAKYAKEVI VA YEEIFQL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	713
Z16533	VDAKYAKEVE TAQMEIFSL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	714
Z16534	VDAKYAKEIEA AQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	715
Z16535	VDAKYAKEIEKA QMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	716
Z16536	VDAKYAKETE SAQMEIFAL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	717
Z16537	VDAKYAKEIE SAQMEIFAL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	718
Z16538	VDAKYAKETE DAQMEIYRL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	719
Z16539	VDAKYAKEIY VAQMEIFGL PNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	720
Z16540	VDAKYAKETE QAQMEIFSL PNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	721
Z16541	VDAKYAKEA YKAQMEIFKLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	722
Z16542	VDAKYAKEIE DAQMEIFEL PNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	723
Z16543	VDAKYAKEVE I AQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	724

FIGURE 1Z

Z16544	VDKYYAKEVEFAYMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	725
Z16545	VDKYYAKEIERAQMEIYELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	726
Z16546	VDKYYAKEVDEAYMEIYNLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	727
Z16547	VDKYYAKEVEEAQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	728
Z16548	VDKYYAKETHDAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	729
Z16549	VDKYYAKETEDAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	730
Z16550	VDKYYAKETERAYYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	731
Z16551	VDKYYAKEVEDAQMEIYYLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	732
Z16552	VDKYYAKEAEQAYFEIYELPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	733
Z16554	VDKYYAKEVEEAQMEIFNLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	734
Z16555	VDKYYAKEVEVAQMEIFNLPNLT RKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	735
Z16556	VDKYYAKEIEAQQMEIYFLPNLT RKQYTA I IKLFDDPSQSSELLSEAKKLND SQAPK	736
Z16557	VDKYYAKEVEWAQMEIFYLPNLT RKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	737
Z16558	VDKYYAKEVESAQMEIFKLPNLT RKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	738
Z16559	VDKYYAKEAEVAQMEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	739
Z16560	VDKYYAKEIEKAQMEIYYLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	740
Z16561	VDKYYAKEIEKAQLEIFALPNLT RKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	741
Z16562	VDKYYAKETERAQMEIFQLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	742
Z16563	VDKYYAKEVQDAQMEIFYLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	743
Z16564	VDKYYAKEIEAAQMEIFVLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	744
Z16565	VDKYYAKELQRAQMEIFELPNLT RRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	745
Z16566	VDKYYAKELEEAQMEIFLLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	746
Z16567	VDKYYAKEIEHAQMEIFALPNLT RKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	747
Z16568	VDKYYAKEVYQAQMEIFGLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	748
Z16569	VDKYYAKEIEAAQMEIFYLPNLT RRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	749
Z16570	VDKYYAKEAKDAQMEIFGLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	750
Z16572	VDKYYAKEVEETAQMEIYYLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	751
Z16573	VDKYYAKEVEAAQMEIYALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	752
Z16574	VDKYYAKEVEAAQWEIFKLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	753

FIGURE 1AA

Z16575	VDKYYAKEIEQAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	754
Z16576	VDKYYAKETE EAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	755
Z16577	VDKYYAKEVEWAQMEIFKLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	756
Z16578	VDKYYAKEIEIAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	757
Z16579	VDKYYAKEAEAAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	758
Z16580	VDKYYAKEVVSA YEEIFHLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	759
Z16581	VDKYYAKETEDAQMEIFALPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	760
Z16582	VDKYYAKEVEFFAQMEIFELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	761
Z16583	VDKYYAKEVQNAQMEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	762
Z16584	VDKYYAKEAQRAYMEIYQLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	763
Z16585	VDKYYAKEIEDAQMEIYGLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	764
Z16586	VDKYYAKEVEYAQMEIFSLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	765
Z16587	VDKYYAKEAEADAQMEIFALPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	766
Z16588	VDKYYAKEVES AQMEIFDLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	767
Z16589	VDKYYAKEVDVAYMEIFGLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	768
Z16590	VDKYYAKEVEDAQMEIFSLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	769
Z16591	VDKYYAKEVEAAQMEIFDLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	770
Z16592	VDKYYAKEVEDAYFEIYLLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	771
Z16593	VDKYYAKEVEKAQMEIFTLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	772
Z16594	VDKYYAKELEKAYFEIYELPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	773
Z16595	VDKYYAKEVEAAQMEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	774
Z16596	VDKYYAKEIREAQMEIFGLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	775
Z16597	VDKYYAKEVENAQMEIYNLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	776
Z16598	VDKYYAKEVEDAQMEIYDLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	777
Z16599	VDKYYAKEVEVAQMEIFGLPNLT RRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	778
Z16600	VDKYYAKEVEHAQMEIYYLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	779
Z16601	VDKYYAKEAETAQMEIFALPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	780
Z16602	VDKYYAKEIEQAQMEIFRLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	781
Z16603	VDKYYAKEVEAAQMEIFYLPNLT RKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	782

FIGURE 1AB

Z16604	VDAKYAKEVHEAQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	783
Z16605	VDAKYAKEVEHAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	784
Z16606	VDAKYAKEIEKAQMEIFDLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	785
Z16607	VDAKYAKETEAAQMEIYNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	786
Z16608	VDAKYAKEVHEAQMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	787
Z16609	VDAKYAKEIQDAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	788
Z16610	VDAKYAKEVEQAQMEIFLLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	789
Z16611	VDAKYAKETEIAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	790
Z16612	VDAKYAKEIEEAQLEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	791
Z16613	VDAKYAKELEERAQMEIFVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	792
Z16614	VDAKYAKETEIAQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	793
Z16615	VDAKYAKEAEDAYMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	794
Z16616	VDAKYAKEVEQAQLEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	795
Z16617	VDAKYAKEIEFAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	796
Z16618	VDAKYAKEIEEAQMEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	797
Z16619	VDAKYAKETYHAQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	798
Z16620	VDAKYAKEAEQAYHEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	799
Z16621	VDAKYAKETETAQMEIFS LPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	800
Z16622	VDAKYAKEAEFAQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	801
Z16623	VDAKYAKETEVAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	802
Z16624	VDAKYAKEVEIAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	803
Z16625	VDAKYAKELEERAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	804
Z16626	VDAKYAKEVYAAAYDEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	805
Z16627	VDAKYAKEAEFAQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	806
Z16628	VDAKYAKEVQAAYYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	807
Z16629	VDAKYAKEVYNAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	808
Z16630	VDAKYAKEAEIAQMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	809
Z16631	VDAKYAKEVEVAQMEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	810
Z16632	VDAKYAKEVEQAQMEIYYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	811

FIGURE 1AC

Z16633	VDKYYAKEVEVENAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	812
Z16634	VDKYYAKEVEIEIAYIEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	813
Z16635	VDKYYAKEVEVAQFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	814
Z16636	VDKYYAKEIERAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	815
Z16637	VDKYYAKEIEDAQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	816
Z16638	VDKYYAKEIENAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	817
Z16639	VDKYYAKELEAAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	818
Z16640	VDKYYAKEIERAQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	819
Z16641	VDKYYAKEITYRAQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	820
Z16642	VDKYYAKEVEEAQMEIYSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	821
Z16643	VDKYYAKEVEKAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	822
Z16644	VDKYYAKEAHAAAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	823
Z16645	VDKYYAKEIERAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	824
Z16646	VDKYYAKELEAAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	825
Z16647	VDKYYAKEVEVAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	826
Z16648	VDKYYAKEAEAWAYMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	827
Z16649	VDKYYAKEITEYAQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	828
Z16650	VDKYYAKEVEDAQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	829
Z16652	VDKYYAKEIEEAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	830
Z16653	VDKYYAKEVERAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	831
Z16654	VDKYYAKEAEAAAYE IYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	832
Z16655	VDKYYAKETEEAQMEIYRLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	833
Z16656	VDKYYAKETEDAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	834
Z16657	VDKYYAKEIKQAQMEIYSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	835
Z16658	VDKYYAKEVEEAQMEIYNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	836
Z16659	VDKYYAKETEQAQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	837
Z16660	VDKYYAKEIEDAQMEIYYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	838
Z16661	VDKYYAKESEQAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	839
Z16662	VDKYYAKEVEVAQMEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	840

FIGURE 1AD

Z16663	VDKYYAKEIERAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	841
Z16664	VDKYYAKEAEQAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	842
Z16665	VDKYYAKELEYAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	843
Z16666	VDKYYAKEVEFAQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	844
Z16667	VDKYYAKETEEAQMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	845
Z16668	VDKYYAKETYN AQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	846
Z16669	VDKYYAKEISVAQFEIYHLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	847
Z16671	VDKYYAKEIKAAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	848
Z16672	VDKYYAKEVEYAYQEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	849
Z16675	VDKYYAKEVEIAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	850
Z16676	VDKYYAKEI DDAYLEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	851
Z16677	VDKYYAKEAYIAQQEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	852
Z16678	VDKYYAKEVEVAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	853
Z16679	VDKYYAKEVVTAQMEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	854
Z16680	VDKYYAKEVVIAQHEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	855
Z16681	VDKYYAKEVEYAYEIEFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	856
Z16682	VDKYYAKEAEFAAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	857
Z16683	VDKYYAKELEKAYEIEYELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	858
Z16684	VDKYYAKETHNAYQEIYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	859
Z16685	VDKYYAKEVIEAYEEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	860
Z16686	VDKYYAKEVEAAAYFEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	861
Z16687	VDKYYAKEAEDAYHEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	862
Z16688	VDKYYAKEVKDAQFEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	863
Z16689	VDKYYAKEADFAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	864
Z16690	VDKYYAKEVQDAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	865
Z16691	VDKYYAKEAVQAYHEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	866
Z16692	VDKYYAKEATEAYDEIYLLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	867
Z16693	VDKYYAKEATEAYMEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	868
Z16694	VDKYYAKETESAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	869

FIGURE 1AE

Z16695	VDKYYAKEAEKAYMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	870
Z16696	VDKYYAKEVETAQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	871
Z16697	VDKYYAKELYS AQMEIYGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	872
Z16699	VDKYYAKEAE EAYMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	873
Z16700	VDKYYAKEAQEA YDEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	874
Z16701	VDKYYAKEHVEAY YEIYNLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	875
Z16702	VDKYYAKETEQAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	876
Z16703	VDKYYAKEVEQAQMEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	877
Z16704	VDKYYAKEATSA YFEIYALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	878
Z16705	VDKYYAKELEAAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	879
Z16706	VDKYYAKEAEADAYMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	880
Z16708	VDKYYAKEAESAYMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	881
Z16709	VDKYYAKELEAA YFEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	882
Z16710	VDKYYAKEAEAY YFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	883
Z16711	VDKYYAKETHSAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	884
Z16712	VDKYYAKETERAQMEIFDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	885
Z16713	VDKYYAKEAYS AQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	886
Z16714	VDKYYAKEIEDAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	887
Z16715	VDKYYAKEVYSAQLEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	888
Z16716	VDKYYAKEVEQA YYEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	889
Z16717	VDKYYAKEIEEAYMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	890
Z16718	VDKYYAKEIEKAQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	891
Z16719	VDKYYAKEAVVAYSEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	892
Z16720	VDKYYAKEIEVAYSEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	893
Z16721	VDKYYAKEVDEAYMEIYELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	894
Z16722	VDKYYAKEIEHAQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	895
Z16723	VDKYYAKEISDAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	896
Z16724	VDKYYAKEVEEAQMEIFVLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	897
Z16725	VDKYYAKELEEA YMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	898

FIGURE 1AF

Z16726	VDKAYAKEVELAYFEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	899
Z16727	VDKAYAKETVSAYWEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	900
Z16728	VDKAYAKEIKEAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	901
Z16729	VDKAYAKELFEAQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	902
Z16730	VDKAYAKEIEDAYMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	903
Z16731	VDKAYAKEVEIAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	904
Z16732	VDKAYAKEAESAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	905
Z16733	VDKAYAKEVEEAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	906
Z16734	VDKAYAKEAVDAYWEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	907
Z16735	VDKAYAKEVEIAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	908
Z16736	VDKAYAKEVINAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	909
Z16737	VDKAYAKEVEEAYMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	910
Z16738	VDKAYAKEVEEAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	911
Z16739	VDKAYAKEVEDAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	912
Z16740	VDKAYAKEIEDAYMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	913
Z16741	VDKAYAKEVEDAQMEIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	914
Z16742	VDKAYAKEVEDAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	915
Z16743	VDKAYAKEQESAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	916
Z16745	VDKAYAKETEEAYQE IYQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	917
Z16746	VDKAYAKEELEAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	918
Z16747	VDKAYAKEVQDAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	919
Z16748	VDKAYAKEVENAYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	920
Z16749	VDKAYAKEVEEAYYEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	921
Z16750	VDKAYAKEVEHAYFEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	922
Z16751	VDKAYAKEVHEAYMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	923
Z16752	VDKAYAKEVEQAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	924
Z16753	VDKAYAKEVVDAYYEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	925
Z16754	VDKAYAKEAQIAYFEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	926
Z16755	VDKAYAKEVEEFAYYEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	927

FIGURE 1AG

Z16756	VDKYYAKEVVVEAYYEIYDLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	928
Z16757	VDKYYAKEIEEAYMEIYELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	929
Z16758	VDKYYAKEVQTAYMEIYHLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	930
Z16759	VDKYYAKEAEYAYFEIYKLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	931
Z16760	VDKYYAKEAYIAQMEIFELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	932
Z16761	VDKYYAKEAEERAYWEIYELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	933
Z16762	VDKYYAKETHDAYYEIYGLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	934
Z16763	VDKYYAKELEDAYYEIFGLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	935
Z16764	VDKYYAKEVEDAYQEIFQLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	936
Z16765	VDKYYAKEAHNAYYEIYALPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	937
Z16766	VDKYYAKEVEDAYFEIYWLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	938
Z16767	VDKYYAKEVTEAYFEIYRLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	939
Z16768	VDKYYAKEVEKAYEEIYKLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	940
Z16769	VDKYYAKEVDYAYFEIYKLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	941
Z16770	VDKYYAKETEAAYFEIFHLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	942
Z16771	VDKYYAKEVEVAYMEIFQLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	943
Z16772	VDKYYAKEVEQAYMEIFGLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	944
Z16773	VDKYYAKEVEYAYFEIYGLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	945
Z16774	VDKYYAKEAEVAYWEIYALPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	946
Z16775	VDKYYAKEVEIAYYEIYRLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	947
Z16776	VDKYYAKEVIQAYFEIYELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	948
Z16777	VDKYYAKEAEDAYWEIFKLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	949
Z16778	VDKYYAKEVTEAYFEIYALPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	950
Z16779	VDKYYAKEVEEAYFEIYRLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	951
Z16780	VDKYYAKEVQEAYFEIFGLPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	952
Z16781	VDKYYAKEVVVEAYEEIYALPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	953
Z16782	VDKYYAKEVQVAYFEIFALPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	954
Z16783	VDKYYAKEVEDAYIEIYELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	955
Z16784	VDKYYAKEVEAAYYEIYELPNLTRLRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	956

FIGURE 1AH

Z16785	VDKYYAKEVEIAYDEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	957
Z16786	VDKYYAKEHEEAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	958
Z16787	VDKYYAKEVYLAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	959
Z16788	VDKYYAKETEK AQMEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	960
Z16789	VDKYYAKELEEEAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	961
Z16790	VDKYYAKEVVEAYDEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	962
Z16791	VDKYYAKETIEAYEEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	963
Z16792	VDKYYAKEHIEAYDEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	964
Z16793	VDKYYAKEAQLAYWEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	965
Z16794	VDKYYAKEVFDAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	966
Z16795	VDKYYAKEIEEAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	967
Z16796	VDKYYAKEVEKAYFEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	968
Z16797	VDKYYAKEVEVAYYEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	969
Z16798	VDKYYAKEVEYAYFEIYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	970
Z16799	VDKYYAKEVIAAYYEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	971
Z16800	VDKYYAKEVVDA YMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	972
Z16801	VDKYYAKEAETAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	973
Z16802	VDKYYAKEVEEAQMEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	974
Z16803	VDKYYAKEAEAAAYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	975
Z16804	VDKYYAKEVEAAQMEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	976
Z16805	VDKYYAKELEWAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	977
Z16806	VDKYYAKEQKQAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	978
Z16808	VDKYYAKEAEDAYYEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	979
Z16809	VDKYYAKEQHEAYWEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	980
Z16810	VDKYYAKEVEDAYMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	981
Z16811	VDKYYAKEVDHAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	982
Z16812	VDKYYAKEAIEAYDEIFLLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	983
Z16813	VDKYYAKEVV EAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	984
Z16814	VDKYYAKETEDAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	985

FIGURE 1A1

Z16815	VDKAYAKEVIDAYYEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	986
Z16816	VDKAYAKEAIDAYHEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	987
Z16817	VDKAYAKETHDAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	988
Z16818	VDKAYAKEIESAYMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	989
Z16819	VDKAYAKEIEKAYMEIYHLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	990
Z16820	VDKAYAKEAEDAYQEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	991
Z16821	VDKAYAKEVEEAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	992
Z16822	VDKAYAKEVEDAQMEIFELPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	993
Z16823	VDKAYAKEVENAQYEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	994
Z16824	VDKAYAKEVEVAYMEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	995
Z16825	VDKAYAKESEQAYWEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	996
Z16826	VDKAYAKETVDAYEEIFTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	997
Z16827	VDKAYAKEIEEAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	998
Z16829	VDKAYAKEVVVAYEEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	999
Z16830	VDKAYAKEAVNAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1000
Z16831	VDKAYAKESEKAYMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1001
Z16832	VDKAYAKEVEEAYFEIYLLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1002
Z16833	VDKAYAKEIEAAQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1003
Z16834	VDKAYAKEQEKAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1004
Z16835	VDKAYAKEVEIAYYEIFALPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1005
Z16836	VDKAYAKEVYAAAYEEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1006
Z16837	VDKAYAKEVESAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1007
Z16838	VDKAYAKELEVAYMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1008
Z16839	VDKAYAKETINAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1009
Z16840	VDKAYAKEAETAYWEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1010
Z16852	VDKAYAKETEAAAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1011
Z16853	VDKAYAKEIQKAYMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1012
Z16854	VDKAYAKELEVAYFEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1013
Z16855	VDKAYAKEVEYAYWEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1014

FIGURE 1AJ

Z16856	VDAKYAKETEEAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1015
Z16857	VDAKYAKELESAYMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1016
Z16858	VDAKYAKEVEVAYMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1017
Z16859	VDAKYAKEVEDAYMEIYELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1018
Z16860	VDAKYAKEHVDAYYEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1019
Z16861	VDAKYAKEHERAYFEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1020
Z16862	VDAKYAKEATEAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1021
Z16863	VDAKYAKEVYKAQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1022
Z16864	VDAKYAKEVERAYMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1023
Z16865	VDAKYAKELEHAQLEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1024
Z16866	VDAKYAKEAQAAYDEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1025
Z16867	VDAKYAKEVEEAQMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1026
Z16868	VDAKYAKEVEEAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1027
Z16869	VDAKYAKEVEHAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1028
Z16870	VDAKYAKEVESAQMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1029
Z16871	VDAKYAKEVEKAQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1030
Z16873	VDAKYAKEVDEAYMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1031
Z16874	VDAKYAKETEEAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1032
Z16875	VDAKYAKEAFAAYFEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1033
Z16876	VDAKYAKELEDAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1034
Z16877	VDAKYAKEVEVAYEEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1035
Z16878	VDAKYAKEAVEAYWEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1036
Z16879	VDAKYAKELEEAYMEIYFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1037
Z16880	VDAKYAKEVENAYMEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1038
Z16881	VDAKYAKETVKAYEEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1039
Z16882	VDAKYAKELEKAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1040
Z16883	VDAKYAKETEK AQLEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1041
Z16884	VDAKYAKEVELAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1042
Z16886	VDAKYAKEAENAYWEIYELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1043

FIGURE 1AK

Z16887	VDKAYAKEVVIQAYWEIYHLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1044
Z16888	VDKAYAKEAEYAYMEIFRLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1045
Z16889	VDKAYAKEVESAYMEIYHLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1046
Z16890	VDKAYAKETEDAYMEIFRLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1047
Z16891	VDKAYAKEVDAAAYFEIFNLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1048
Z16892	VDKAYAKEAEDAYFEIYSLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1049
Z16893	VDKAYAKELEDAYMEIFGLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1050
Z16894	VDKAYAKEVEAAAYFEIYGLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1051
Z16895	VDKAYAKEVEFAYYEIFALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1052
Z16896	VDKAYAKEVV SAYWEIYALPNLTNRQYTAFAIRKLLDDPSQSSELLSEAKKLND	1053
Z16897	VDKAYAKETEKAYFEIYALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1054
Z16898	VDKAYAKEAEYAYMEIYNLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1055
Z16899	VDKAYAKEVESAYMEIYRLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1056
Z16900	VDKAYAKEVEVAYMEIYGLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1057
Z16901	VDKAYAKEIEFAYMEIFHLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1058
Z16902	VDKAYAKEVVEAYFEIYELPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1059
Z16903	VDKAYAKEIEAAQMEIFALPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1060
Z16904	VDKAYAKEVEDAQMEIFGLPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1061
Z16905	VDKAYAKEIEEAQMEIYGLPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1062
Z16906	VDKAYAKETLDAQMEIFALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1063
Z16907	VDKAYAKETQEAQMEIFALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1064
Z16908	VDKAYAKEVEEAQMEIFALPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1065
Z16909	VDKAYAKEVEDAQMEIFALPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1066
Z16910	VDKAYAKEVESAQMEIFYLPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1067
Z16911	VDKAYAKEIEDAQMEIFALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1068
Z16912	VDKAYAKEVEAAQMEIFFLPNLTNRQYTAFAIRKLLDDPSQSSELLSEAKKLND	1069
Z16913	VDKAYAKEVEEAQLEIFALPNLTNRKQYTAFIKLFDDPSQSSELLSEAKKLND	1070
Z16914	VDKAYAKETEDAQMEIFALPNLTNRKQYTAFAIRKLLDDPSQSSELLSEAKKLND	1071
Z16915	VDKAYAKEIEIAQMEIFRLPNLTNRKQYTAFAIRKLFDDPSQSSELLSEAKKLND	1072

FIGURE 1AL

Z16916	VDKYYAKEVEIAQMEIFALPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1073
Z16917	VDKYYAKEIEIAQMEIFSPLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1074
Z16918	VDKYYAKETEAAQMEIFYLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1075
Z17171	VDKYYAKEIEDAQMEIFALPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1076
Z17173	VDKYYAKEVEHAQMEIFDLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1077
Z17174	VDKYYAKEVVSAQMEIFGLPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1078
Z17175	VDKYYAKELDEAYFEIYGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1079
Z17176	VDKYYAKEVEHAQLEIFRLPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1080
Z17177	VDKYYAKEAYKAQMEIFGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1081
Z17178	VDKYYAKEIEIAQMEIFFLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1082
Z17179	VDKYYAKEVEHAQMEIFTLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1083
Z17180	VDKYYAKEVKIAQMEIYELPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1084
Z17181	VDKYYAKEAEDAYQEIFGLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1085
Z17182	VDKYYAKEAENAYDEIYKLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1086
Z17183	VDKYYAKEIEAAQIEIFHLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1087
Z17184	VDKYYAKEVVDAQQEIFNLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1088
Z17185	VDKYYAKEIEWAQMEIFALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1089
Z17186	VDKYYAKEIEDAQMEIYELPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1090
Z17187	VDKYYAKEAEKAQIEIFYLPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1091
Z17188	VDKYYAKEAEWAQMEIYSLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1092
Z17189	VDKYYAKEVEAAQMEIFQLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1093
Z17190	VDKYYAKEVEIAQMEIYSLPNLTRRQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1094
Z17191	VDKYYAKEIKAAQMEIFALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1095
Z17192	VDKYYAKEVEYAAQMEIFNLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1096
Z17193	VDKYYAKEVYAAQQEIFHLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1097
Z17194	VDKYYAKEAEQAYMEIFRLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1098
Z17195	VDKYYAKEVDVAYQEIFNLPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1099
Z17196	VDKYYAKEVYHAQMEIFSPLPNLTRKQYTAFAIRKLFDDPSQSSELLSEAKKLNDSQAPK	1100
Z17197	VDKYYAKEAEDAQMEIYALPNLTRKQYTAFAIRKLLDDPSQSSELLSEAKKLNDSQAPK	1101

FIGURE 1AM

Z17198	VDKAYAKEVQEAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1102
Z17199	VDKAYAKEHEFA YMEIYHLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1103
Z17200	VDKAYAKEAE EAYVEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1104
Z17201	VDKAYAKEIEKAQFEIYYLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1105
Z17202	VDKAYAKEVYKAQMEIFALPNLT R KQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1106
Z17203	VDKAYAKEVEKAQMEIYYLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1107
Z17204	VDKAYAKEVEAAQLEIFELPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1108
Z17205	VDKAYAKET YQAQMEIYSLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1109
Z17206	VDKAYAKELEDA YQEIFHLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1110
Z17207	VDKAYAKEVEEAQLEIFSLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1111
Z17208	VDKAYAKEIYLAQMEIFKLPNLT R RQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1112
Z17209	VDKAYAKEIEEAQMEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1113
Z17210	VDKAYAKETEQA YMEIYQLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1114
Z17211	VDKAYAKEAEAA YYEIYHLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1115
Z17212	VDKAYAKETEAA YDEIYGLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1116
Z17213	VDKAYAKEVEEA YFEIFRLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1117
Z17214	VDKAYAKEVVKA YFEIYHLPNLT R RQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1118
Z17215	VDKAYAKEVYEAQMEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1119
Z17216	VDKAYAKEVEDA YIEIYKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1120
Z17217	VDKAYAKEVEWAQMEIFNLPNLT R RQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1121
Z17218	VDKAYAKELEKAQMEIFYLPNLT R KQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1122
Z17219	VDKAYAKETE EA YQEIFHLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1123
Z17220	VDKAYAKEAEADAQMEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1124
Z17221	VDKAYAKEIEEAQLEIFNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1125
Z17222	VDKAYAKEVEDA YHEIFLLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1126
Z17223	VDKAYAKEVEYA YHEIFKLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1127
Z17224	VDKAYAKETVEAQMEIFNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1128
Z17225	VDKAYAKEVEDA YMEIYFLPNLT R RQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1129
Z17226	VDKAYAKETETAQMEIYNLPNLT R KQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1130

FIGURE 1AN

Z17227	VDAKYAKEVEIEAQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1131
Z17228	VDAKYAKEVHLAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1132
Z17229	VDAKYAKEVEYAAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1133
Z17230	VDAKYAKEAEAEAAQHEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1134
Z17231	VDAKYAKEAYVAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1135
Z17232	VDAKYAKEVQKAQMEIFELPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1136
Z17233	VDAKYAKEAYAAQHEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1137
Z17234	VDAKYAKEVERAYYEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1138
Z17235	VDAKYAKEVEAAQMEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1139
Z17236	VDAKYAKELENAQMEIFTLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1140
Z17237	VDAKYAKELEAYAQQEIFHLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1141
Z17238	VDAKYAKEQLNAQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1142
Z17240	VDAKYAKEVIAAYYEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1143
Z17241	VDAKYAKEVVDAWYEIYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1144
Z17242	VDAKYAKEVEEAYQEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1145
Z17243	VDAKYAKEAEDAYFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1146
Z17244	VDAKYAKEVEDAYFEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1147
Z17245	VDAKYAKEVEVAYYEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1148
Z17246	VDAKYAKELEDAYMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1149
Z17247	VDAKYAKEVDEAYWEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1150
Z17248	VDAKYAKEAEWAYWEIYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1151
Z17249	VDAKYAKEVEVAYMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1152
Z17250	VDAKYAKETERAYMEIYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1153
Z17251	VDAKYAKEHIAAYFEIYELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1154
Z17252	VDAKYAKEVEEAYYEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1155
Z17253	VDAKYAKEVEDAYQEIQYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1156
Z17254	VDAKYAKETVEAYYEIYRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1157
Z17255	VDAKYAKEVEQAYYEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1158
Z17256	VDAKYAKEVVEAYDEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1159

FIGURE 1AO

Z17257	VDAKYAKEVEEEAYMEIYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1160
Z17258	VDAKYAKEVD DAYMEIFRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1161
Z17259	VDAKYAKEVQ DAYMEIYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1162
Z17260	VDAKYAKEAQQAYDEIFQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1163
Z17261	VDAKYAKEVEFAYMEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1164
Z17262	VDAKYAKEVEIAYFEIYQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1165
Z17263	VDAKYAKETEKAYFEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1166
Z17264	VDAKYAKEVTNAYMEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1167
Z17266	VDAKYAKETEAAAYFEIFKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1168
Z17267	VDAKYAKEVE TAYMEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1169
Z17268	VDAKYAKEAE DAYMEIYKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1170
Z17269	VDAKYAKEVEEAYQEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1171
Z17270	VDAKYAKETE EAYFEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1172
Z17271	VDAKYAKEA I SAYWEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1173
Z17272	VDAKYAKEVEEAYQEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1174
Z17273	VDAKYAKEVVYAQHEIFYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1175
Z17274	VDAKYAKEIEVAYMEIYHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1176
Z17275	VDAKYAKEVEYAYEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1177
Z17276	VDAKYAKEVEQAYMEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1178
Z17277	VDAKYAKEVEDAYDEIYQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1179
Z17278	VDAKYAKEIERAYEIDYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1180
Z17279	VDAKYAKEVEDAYFEIYYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1181
Z17280	VDAKYAKEVEQAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1182
Z17281	VDAKYAKEVEEAYQEIFKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1183
Z17282	VDAKYAKEAEHAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1184
Z17283	VDAKYAKEVEKAYEINYLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1185
Z17284	VDAKYAKEVEEAYMEIYKLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1186
Z17285	VDAKYAKEIEDAYQEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1187
Z17286	VDAKYAKEVENAYEIDFLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1188

FIGURE 1AP

Z17287	VDKYYAKEATEAYWEIYQLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1189
Z17288	VDKYYAKEADAAYFEIYHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1190
Z17289	VDKYYAKEVINAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1191
Z17290	VDKYYAKEAVDAYWEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1192
Z17291	VDKYYAKEVEEAYYEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1193
Z17292	VDKYYAKEVEYAYFEIYSLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1194
Z17293	VDKYYAKEAEKAYYEIFNLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1195
Z17294	VDKYYAKETIDAYYIEYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1196
Z17295	VDKYYAKEVEVAYAEIFNLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1197
Z17296	VDKYYAKEVEYAYFEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1198
Z17297	VDKYYAKEAYIAQMEIFGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1199
Z17298	VDKYYAKEVEEAYFEIYNLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1200
Z17299	VDKYYAKESEAAAYWEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1201
Z17300	VDKYYAKEAEDAYWEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1202
Z17301	VDKYYAKEVDAAAYWEIYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1203
Z17302	VDKYYAKETVDAYYIEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1204
Z18557	VDKYYAKEIEAVQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1205
Z15876	VDKYYAKEIEAAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1206
Z15932	VDKYYAKEVEEAQMEIFILPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1207
Z15934	VDKYYAKEVTVAQMEIFALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1208
Z15975	VDKYYAKEVEYTAQMEIFVLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1209
Z19134	VDKYYAKEAEDAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1210
Z19125	VDKYYAKEAIEAYWEIYALPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1211
Z19136	VDKYYAKEVVAAAYEIEFELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1212
Z19127	VDKYYAKEVVSAYYIEIYELPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1213
Z19138	VDKYYAKEIEIAYMEIFHLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1214
Z19101	VDKYYAKELDVAYMEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1215
Z19095	VDKYYAKEAEVAYMEIYRLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1216
Z19121	VDKYYAKELERAYYIEYGLPNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1217

FIGURE 1AQ

Z19122	VDAKYAKEAEIAYYE IYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1218
Z19120	VDAKYAKETEVAYYE IYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1219
Z19139	VDAKYAKEVEAAYYE IYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1220
Z19058	VDAKYAKEVEIAYME IYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1221
Z19124	VDAKYAKEVEVAYFE IYNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1222
Z19131	VDAKYAKEHEEAYME IYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1223
Z19103	VDAKYAKELERAYME IYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1224
Z19088	VDAKYAKEVEHAYME IYHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1225
Z19077	VDAKYAKEVQEA YME IFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1226
Z19111	VDAKYAKEVKIAQME IFNLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1227
Z19060	VDAKYAKEVEWAQME IFDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1228
Z19112	VDAKYAKEAHS AQME IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1229
Z19133	VDAKYAKEAERAQME IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1230
Z19094	VDAKYAKETEAAQME IYKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1231
Z19093	VDAKYAKELEQAQME IFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1232
Z19069	VDAKYAKEVES AQME IFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1233
Z19067	VDAKYAKEVEDAQME IYQLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1234
Z19183	VDAKYAKEIEDAQME IYDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1235
Z19079	VDAKYAKEVEQAQME IFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1236
Z19102	VDAKYAKEVEHAQME IYSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1237
Z19110	VDAKYAKEVEKAQME IFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1238
Z19087	VDAKYAKEIEDAQME IFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1239
Z19059	VDAKYAKEVEEAQME IYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1240
Z19123	VDAKYAKEIEKAQME IFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1241
Z19128	VDAKYAKETYVAQME IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1242
Z19137	VDAKYAKEVEIAQME IFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1243
Z19068	VDAKYAKEVKVAQME IFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1244
Z19086	VDAKYAKEVEYAQME IFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1245
Z19076	VDAKYAKEVETAQME IFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1246

FIGURE 1AR

Z19135	VDKYYAKEVEEAAQMEIFKLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1247
Z19078	VDKYYAKEIEAAQMEIFGLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1248
Z19066	VDKYYAKETEAAQMEIYALPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1249
Z18906	VDKYYAKEIETIQHEIYELPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1250
Z18912	VDKYYAKETEIEIQMEIFHLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1251
Z18754	VDKYYAKEVEEIQMEIFRLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1252
Z18767	VDKYYAKEVEEVYFEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1253
Z19174	VDKYYAKETEVQMEIYHLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1254
Z18802	VDKYYAKEAERVQMEIFGLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1255
Z18792	VDKYYAKEAEA IQMEIYDLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1256
Z18783	VDKYYAKETEVIQMEIFRLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1257
Z18753	VDKYYAKETEAIQMEIFQLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1258
Z18795	VDKYYAKETEAIQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1259
Z18929	VDKYYAKETEAVQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1260
Z19305	VDKYYAKETEAVQMEIFRLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1261
Z19303	VDKYYAKETEAVQMEIFTLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1262
Z18899	VDKYYAKETEAIQMEIFELPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1263
Z18824	VDKYYAKETEAVQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1264
Z18860	VDKYYAKETEIEIQMEIFLLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1265
Z18864	VDKYYAKETERVQMEIFYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1266
Z18778	VDKYYAKETERVQMEIFQLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1267
Z18798	VDKYYAKETEIEIQMEIFQLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1268
Z18821	VDKYYAKETEIEVQMEIFKLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1269
Z18920	VDKYYAKETEIEIQMEIFRLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1270
Z18806	VDKYYAKETEIEIQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1271
Z18966	VDKYYAKETEIEVQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1272
Z19304	VDKYYAKETEIQVQMEIFHLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1273
Z18766	VDKYYAKETEIQVQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1274
Z18825	VDKYYAKETEEKVQMEIFGLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1275

FIGURE 1AS

Z18819	VDKAYAKETEEVQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1276
Z18822	VDKAYAKETEEIQMEIYGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1277
Z18810	VDKAYAKETEEVQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1278
Z18892	VDKAYAKETEAVQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1279
Z18854	VDKAYAKETEVVQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1280
Z18758	VDKAYAKETEEVQMEIFGLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1281
Z18823	VDKAYAKETEEVQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1282
Z18958	VDKAYAKETEEIQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1283
Z18770	VDKAYAKETERVQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1284
Z18898	VDKAYAKELEAIQMEIFYLPNLTRRQYVAFIRKLDDPSQSSELLSEAKKLND SQAPK	1285
Z18876	VDKAYAKEIEEQIOMEIFYLPNLTRRQYVAFIRKLDDPSQSSELLSEAKKLND SQAPK	1286
Z18840	VDKAYAKELEKVQMEIFVLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1287
Z18900	VDKAYAKELEIRIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1288
Z18775	VDKAYAKELEKVQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1289
Z18952	VDKAYAKEVEQIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1290
Z18851	VDKAYAKEIEQIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1291
Z19152	VDKAYAKEIEQVQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1292
Z18765	VDKAYAKEIEQIQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1293
Z18885	VDKAYAKEVEEQIOMEIFYLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1294
Z18830	VDKAYAKEVEEQIOMEIFFLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1295
Z18828	VDKAYAKEVEEQIOMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1296
Z18833	VDKAYAKEVEEQIOMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1297
Z18853	VDKAYAKEIEEQIOMEIFYLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1298
Z18849	VDKAYAKEIEEQIOMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1299
Z18902	VDKAYAKELEEQIOMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1300
Z18877	VDKAYAKEVEEQIOMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1301
Z18878	VDKAYAKEVEEQIOMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1302
Z18909	VDKAYAKEIEEQIOMEIFFLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1303
Z18848	VDKAYAKEIEEQIOMEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1304

FIGURE 1AT

Z19166	VDKYYAKELEEEVQMEIYFLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1305
Z18873	VDKYYAKELEEEVQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1306
Z19147	VDKYYAKELEEEIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1307
Z18831	VDKYYAKEIEEEVQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1308
Z18843	VDKYYAKEIEEEIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1309
Z19153	VDKYYAKEIEEEIQMEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1310
Z18882	VDKYYAKEVEEVQMEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1311
Z18894	VDKYYAKEVEEEIQMEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1312
Z18940	VDKYYAKELEERIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1313
Z18759	VDKYYAKEIEKVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1314
Z18855	VDKYYAKELEKVQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1315
Z18837	VDKYYAKELEKVQMEIFHLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1316
Z18788	VDKYYAKEVEEKIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1317
Z18827	VDKYYAKETEKVQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1318
Z18761	VDKYYAKEIEEVQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1319
Z18786	VDKYYAKELEEVQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1320
Z18757	VDKYYAKEIEEEIQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1321
Z18858	VDKYYAKEIEEEIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1322
Z18785	VDKYYAKELEEEIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1323
Z18866	VDKYYAKEIEEEIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1324
Z19145	VDKYYAKELETVQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1325
Z18777	VDKYYAKEIEEQVQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1326
Z18803	VDKYYAKEIEEQIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1327
Z18800	VDKYYAKEIEEEIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1328
Z18804	VDKYYAKELEEEIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1329
Z18856	VDKYYAKELEEEIQMEIFHLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1330
Z18846	VDKYYAKEIEEEIQMEIFHLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1331
Z18871	VDKYYAKEVEEEIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1332
Z18782	VDKYYAKEVEEVQMEIFELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1333

FIGURE 1AU

Z19170	VDKYYAKEVEEIQMEIFELPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1334
Z18949	VDKYYAKEVEQVQMEIFHLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1335
Z18852	VDKYYAKEVEQIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1336
Z18838	VDKYYAKEVEEIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1337
Z18928	VDKYYAKEVEEVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1338
Z18769	VDKYYAKEVEEVQMEIFHLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1339
Z18832	VDKYYAKEVEEIQMEIFHLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1340
Z18771	VDKYYAKEVEEIQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1341
Z18808	VDKYYAKEVEEVQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1342
Z18817	VDKYYAKEVEEIQMEIFRLPNLTRRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1343
Z18889	VDKYYAKEVEEVQMEIFRLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1344
Z18930	VDKYYAKEVERIQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1345
Z18812	VDKYYAKEVEKIQMEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1346
Z18809	VDKYYAKEIETVQMEIFSLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1347
Z18768	VDKYYAKELETVQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1348
Z18844	VDKYYAKELEEIQMEIFSLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1349
Z18919	VDKYYAKEVEEIQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1350
Z18931	VDKYYAKELETVQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1351
Z18890	VDKYYAKELEKQVQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1352
Z18893	VDKYYAKEIEEIQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1353
Z18796	VDKYYAKELEEVQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1354
Z18881	VDKYYAKEIEEIQMEIFGLPNLTRRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1355
Z18826	VDKYYAKEIEEIQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1356
Z18959	VDKYYAKEIEEVQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1357
Z18897	VDKYYAKEVEEIQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1358
Z18841	VDKYYAKEVEEIQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1359
Z18918	VDKYYAKEVEEVQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1360
Z18834	VDKYYAKEVEEIQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1361
Z18863	VDKYYAKEVEEVQMEIFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1362

FIGURE 1AV

Z18847	VDKAYAKETEEVQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1363
Z19159	VDKAYAKETEEVQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1364
Z18789	VDKAYAKEIEIQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1365
Z18756	VDKAYAKEIEEVQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1366
Z18850	VDKAYAKEIEEIQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1367
Z18814	VDKAYAKEVEEIQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1368
Z18861	VDKAYAKEVEEVQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1369
Z18938	VDKAYAKEIEIQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1370
Z18801	VDKAYAKEIEQVQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1371
Z18927	VDKAYAKEIEEIQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1372
Z18951	VDKAYAKEIEEVQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1373
Z19144	VDKAYAKEIEEVQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1374
Z18813	VDKAYAKEVEEIQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1375
Z18859	VDKAYAKETEIVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1376
Z18797	VDKAYAKETE VVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1377
Z18781	VDKAYAKETEIVQMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1378
Z19160	VDKAYAKEIEIQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1379
Z18891	VDKAYAKEIEYIQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1380
Z18857	VDKAYAKEIEVVQMEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1381
Z18816	VDKAYAKEIEVIQMEIFELPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1382
Z18829	VDKAYAKEVEVIQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1383
Z18787	VDKAYAKEVEVIQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1384
Z18791	VDKAYAKEVEVVQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1385
Z18887	VDKAYAKEVEVIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1386
Z18773	VDKAYAKEIEVIQMEIFKLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1387
Z18967	VDKAYAKEIEVVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1388
Z18774	VDKAYAKEIEVIQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1389
Z18879	VDKAYAKEVEYIQMEIFRLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1390
Z18868	VDKAYAKEIEIVQMEIFHLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1391

FIGURE 1AW

Z18903	VDKYYAKELEIIQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1392
Z19180	VDKYYAKEVEIIQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1393
Z18901	VDKYYAKELEVIQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1394
Z18755	VDKYYAKELEVIQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1395
Z18883	VDKYYAKEVEIIQMEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1396
Z19164	VDKYYAKEVEIIQMEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1397
Z18845	VDKYYAKEVEVIQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1398
Z18965	VDKYYAKEVEVVQMEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1399
Z18807	VDKYYAKELEIVQMEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1400
Z18818	VDKYYAKEIEYIQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1401
Z19169	VDKYYAKEVEVIQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1402
Z18884	VDKYYAKEVEIIQMEIFGLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1403
Z18793	VDKYYAKEVETVQMEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1404
Z18811	VDKYYAKELETVQMEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1405
Z18880	VDKYYAKELEAIQMEIFTLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1406
Z19154	VDKYYAKEIEAIQMEIYYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1407
Z18869	VDKYYAKELEAIQMEIFYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1408
Z18941	VDKYYAKELEAVQMEIFYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1409
Z18872	VDKYYAKEIEAVQMEIFYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1410
Z18895	VDKYYAKEIEAIQMEIFYLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1411
Z19165	VDKYYAKEIEAIQMEIFFLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1412
Z18862	VDKYYAKEIEAIQMEIFFLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1413
Z18948	VDKYYAKEIEAIQMEIFYLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1414
Z18762	VDKYYAKELEAIQMEIFRLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1415
Z18910	VDKYYAKEIEAIQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1416
Z18820	VDKYYAKELEAIQMEIFRLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1417
Z18776	VDKYYAKEVEAIQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1418
Z19302	VDKYYAKEIEAVQMEIFHLPNLTTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1419
Z18875	VDKYYAKEIEAIQMEIFHLPNLTTRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1420

FIGURE 1AX

Z18874	VDKYYAKELEIAIQMEIFHLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1421
Z18888	VDKYYAKEVEA IQMEIFHLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1422
Z18799	VDKYYAKEVEA IQMEIFHLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1423
Z18794	VDKYYAKEVEAVQMEIFSLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1424
Z18939	VDKYYAKEIEAVQMEIFSLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1425
Z18815	VDKYYAKELEA IQMEIFSLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1426
Z18764	VDKYYAKEIEAVQMEIFSLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1427
Z18870	VDKYYAKEIEA IQMEIFGLPNLTTRRQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1428
Z18950	VDKYYAKEVEA IQMEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1429
Z18836	VDKYYAKEVEA IQMEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1430
Z18763	VDKYYAKEIEAVQMEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1431
Z18886	VDKYYAKEIEA IQMEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1432
Z18784	VDKYYAKETE A IQMEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1433
Z19146	VDKYYAKETE A VQMEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1434
Z18760	VDKYYAKETE A VQMEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1435
Z18896	VDKYYAKETE A IQMEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1436
Z18805	VDKYYAKEIEAVQMEIFALPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1437
Z18779	VDKYYAKEIEA IQMEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1438
Z18790	VDKYYAKEVEAVQMEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1439
Z18839	VDKYYAKEVEAVQMEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1440
Z18911	VDKYYAKEVEA IQMEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1441
Z19036	VDKYYAKEVVKIYFEIYDLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1442
Z19035	VDKYYAKEVIDVYFEIYYLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1443
Z19175	VDKYYAKEVVHIYFEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1444
Z19034	VDKYYAKEVVVEYFEIFYLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1445
Z19051	VDKYYAKEVVVEIYFEIFALPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1446
Z19027	VDKYYAKEVVVEYFEIFALPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1447
Z19062	VDKYYAKEIERIYFEIYGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1448
Z19096	VDKYYAKEIEKIYFEIYDLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1449

FIGURE 1AY

Z19070	VDKYYAKEIEKVYFEIYDLPLNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1450
Z19030	VDKYYAKEVEKIIYFEIYELPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1451
Z19050	VDKYYAKETEHVYFEIYQLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1452
Z19063	VDKYYAKETEKAYYFEIYDLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1453
Z18960	VDKYYAKETERVYFEIYSLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1454
Z19142	VDKYYAKETEIYVFEIFGLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1455
Z19055	VDKYYAKEVEFAWYFEIYALPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1456
Z19065	VDKYYAKEVEVVYFEIFALPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1457
Z19156	VDKYYAKEVESAYFEIYDLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1458
Z19116	VDKYYAKEVEAVYFEIYQLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1459
Z19083	VDKYYAKEVEVAYYFEIYGLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1460
Z19037	VDKYYAKEVEDVYFEIFELPLNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1461
Z18954	VDKYYAKEVETVYFEIFKLPLNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1462
Z19163	VDKYYAKEVEQVYFEIYFLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1463
Z19092	VDKYYAKEVEEIIYQEIYRLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1464
Z19157	VDKYYAKEVEEIIYFEIFGLPLNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1465
Z18978	VDKYYAKEIEAVQLEIFALPLNLTRKQYTA IIKLLDDPSQSSELLSEAKKLND SQAPK	1466
Z19041	VDKYYAKEIEKIQLEIFALPLNLTRKQYTA IIKLFDDPSQSSELLSEAKKLND SQAPK	1467
Z19113	VDKYYAKEVEEVQLEIFALPLNLTRKQYTA IIKLLDDPSQSSELLSEAKKLND SQAPK	1468
Z18924	VDKYYAKEVEDVQLEIFALPLNLTRKQYTA IIKLFDDPSQSSELLSEAKKLND SQAPK	1469
Z18996	VDKYYAKEIEEQVQLEIYKPLNLTRKQYTA IIKLFDDPSQSSELLSEAKKLND SQAPK	1470
Z19143	VDKYYAKEVEEIQLEIFHLPLNLTRRQYTA IIKLLDDPSQSSELLSEAKKLND SQAPK	1471
Z18968	VDKYYAKELEEVQLEIFRLPLNLTRRQYTA IIKLLDDPSQSSELLSEAKKLND SQAPK	1472
Z19179	VDKYYAKEIEDVQHEIFGLPLNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1473
Z19009	VDKYYAKEVEKVQOEIFGLPLNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1474
Z19003	VDKYYAKEIEAIIQHEIFALPLNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1475
Z18979	VDKYYAKEIEAIIQHEIFVLPLNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLND SQAPK	1476
Z18972	VDKYYAKEIERIIQHEIFALPLNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLND SQAPK	1477
Z18935	VDKYYAKEIEVIOQHEIFGLPLNLTRKQYTA FIRKLLDDPSQSSELLSEAKKLND SQAPK	1478

FIGURE 1AZ

Z18925	VDAKYAKETEDIQQEIFQLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1479
Z19098	VDAKYAKEVESIQQEIFQLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1480
Z19109	VDAKYAKEVERIQQEIFHLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1481
Z18923	VDAKYAKEIEEQQEIFHLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1482
Z18942	VDAKYAKEVETIQHEIFRLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1483
Z19167	VDAKYAKETE VVQFEIFRLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1484
Z19017	VDAKYAKETEAVQLEIFELPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1485
Z19011	VDAKYAKETEDVQLEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1486
Z18905	VDAKYAKEAEKIQFEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1487
Z18913	VDAKYAKETE EIQLEIYSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1488
Z19115	VDAKYAKETE EIQLEIFSLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1489
Z18975	VDAKYAKETE KIQYEIFSLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1490
Z19045	VDAKYAKEIEQIQYEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1491
Z18998	VDAKYAKEIETVQYEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1492
Z18992	VDAKYAKEIEAVQYEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1493
Z18932	VDAKYAKELEHIQYEIFFLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1494
Z19052	VDAKYAKEVEEQYEIFWLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1495
Z19042	VDAKYAKEVEEQYEIFFLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1496
Z19029	VDAKYAKEVEEVQIEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1497
Z19005	VDAKYAKEVEDVQLEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1498
Z19149	VDAKYAKEIEEVQLEIFVLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1499
Z19168	VDAKYAKEIERIQMEIFYLPNLTRRQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1500
Z19038	VDAKYAKELEQVQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1501
Z19148	VDAKYAKEVEEQFEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1502
Z19028	VDAKYAKEIEEQFEIFYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1503
Z19155	VDAKYAKEIEEQMEIFYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1504
Z19043	VDAKYAKEIEEQMEIYYLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1505
Z19141	VDAKYAKEVEEQHEIYDLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1506
Z19016	VDAKYAKEIETIQLEIFDLPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1507

FIGURE 1BA

Z18991	VDAKYAKEIETVQYEIYDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1508
Z18917	VDAKYAKEIEEIQFEIYDLPNLNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1509
Z18980	VDAKYAKEVEEIQLEIYDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1510
Z18947	VDAKYAKEVEEVQLEIFDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1511
Z19023	VDAKYAKEIEEVQLEIFDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1512
Z18907	VDAKYAKEIEEIQEIEIFDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1513
Z18981	VDAKYAKEVESVQFEIYHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1514
Z19091	VDAKYAKEIESIQEIEIFELPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1515
Z18943	VDAKYAKEIESIQLEIFHLPNLNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1516
Z19040	VDAKYAKEVEDIQLEIFDLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1517
Z19033	VDAKYAKEVEDIQEIEIFELPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1518
Z18914	VDAKYAKEVEDIQLEIEIFELPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1519
Z19089	VDAKYAKEIEDIQEIEIFELPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1520
Z18963	VDAKYAKEIEDIQLEIEIFELPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1521
Z19061	VDAKYAKEIEDIQLEIYHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1522
Z19100	VDAKYAKEIEDIQEIEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1523
Z18946	VDAKYAKEIEDVQIEIFQLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1524
Z19018	VDAKYAKEIEDIQLEIFKLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1525
Z19053	VDAKYAKEIEDVQLEIFKLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1526
Z18990	VDAKYAKEVEKIQFEIFKLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1527
Z19054	VDAKYAKEIEWVQLEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1528
Z19008	VDAKYAKELEIRIQLEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1529
Z18953	VDAKYAKELEKIQLEIYHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1530
Z18921	VDAKYAKEIEKVQIEIFQLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1531
Z18995	VDAKYAKEIEEIQLEIYHLPNLNRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1532
Z18922	VDAKYAKEIEEIQLEIFRLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1533
Z19108	VDAKYAKEIEEIQFEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1534
Z19007	VDAKYAKEIEEIQEIEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1535
Z18916	VDAKYAKEIEEIQLEIFHLPNLNRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1536

FIGURE 1BB

Z19105	VDKYYAKELEEEIQLEIYKLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1537
Z19104	VDKYYAKELEEEIQLEIYHLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1538
Z18976	VDKYYAKEIEQVQLEIFHLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1539
Z19090	VDKYYAKEIEEVQMEIFHLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1540
Z19019	VDKYYAKEVEEIQIEIFKLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1541
Z18997	VDKYYAKEVEEVQLEIFKLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1542
Z18973	VDKYYAKEVEEIQVEIFQLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1543
Z19048	VDKYYAKEVEEVQLEIFHLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1544
Z19150	VDKYYAKEVEEIQLEIFHLPNLTTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1545
Z19024	VDKYYAKEVEEVQIEIFQLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1546
Z18915	VDKYYAKEVEEVQIEIFELPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1547
Z19099	VDKYYAKEVEEIQLEIFRLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1548
Z19181	VDKYYAKEVEEVQLEIYSLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1549
Z19025	VDKYYAKEIEQIQLEIFSLPNLTTRRQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1550
Z19172	VDKYYAKELEEDVQLEIFSLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1551
Z19084	VDKYYAKEIEQIQMEIFSLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1552
Z18982	VDKYYAKEIEEVQLEIFSLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1553
Z19072	VDKYYAKEIEEIQLEIFSLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1554
Z18937	VDKYYAKEIEDIQVEIYGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1555
Z19049	VDKYYAKELETVQLEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1556
Z19080	VDKYYAKEIETIQLEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1557
Z19057	VDKYYAKEIEQVQLEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1558
Z18971	VDKYYAKEIESVQLEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1559
Z18986	VDKYYAKEIEEVQLEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1560
Z19071	VDKYYAKEVEEIQLEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1561
Z19020	VDKYYAKEVEEVQFEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1562
Z19082	VDKYYAKEVEEIQFEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1563
Z19085	VDKYYAKEVEEIQYEIFGLPNLTTRKQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1564
Z19015	VDKYYAKEVEEIQLEIFGLPNLTTRRQYTA FIRKLLDDPSQSSELLSEAKKLNDSQAPK	1565

FIGURE 1BC

Z19107	VDKAYAKETEEVQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1566
Z19081	VDKAYAKETEHQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1567
Z19001	VDKAYAKETEVQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1568
Z19000	VDKAYAKETEKIQFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1569
Z19014	VDKAYAKETEEIQLEIYALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1570
Z19158	VDKAYAKETEEIQMEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1571
Z18974	VDKAYAKEIESIQYEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1572
Z19074	VDKAYAKEIESVQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1573
Z19176	VDKAYAKEIESIQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1574
Z18962	VDKAYAKELESVQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1575
Z19021	VDKAYAKEIETIQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1576
Z19006	VDKAYAKEVEIVQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1577
Z19073	VDKAYAKEIEQIQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1578
Z19118	VDKAYAKEIEHVQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1579
Z19097	VDKAYAKEIEHIQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1580
Z18987	VDKAYAKEVEKVQLEIFALPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLND SQAPK	1581
Z18977	VDKAYAKEIEEVQLEIYALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1582
Z18955	VDKAYAKEVEVQFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1583
Z18933	VDKAYAKEVEQIQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1584
Z18988	VDKAYAKEVEEVQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1585
Z19056	VDKAYAKEVEEIQLEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1586
Z18904	VDKAYAKEVEEIQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1587
Z19012	VDKAYAKEVEEVQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1588
Z19047	VDKAYAKEVEEIQLEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1589
Z19064	VDKAYAKEIEEQFEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1590
Z18908	VDKAYAKEIEEQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1591
Z18989	VDKAYAKEIEDVQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1592
Z19171	VDKAYAKEIEDIQLEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1593
Z19151	VDKAYAKEVEDIQLEIFALPNLTRRQYTA FIRKLDDPSQSSELLSEAKKLND SQAPK	1594

FIGURE 1BD

Z19002	VDKAYAKETE	VVQYE	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1595						
Z18936	VDKAYAKEAE	I	V	Q	Y	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1596		
Z18969	VDKAYAKEVE	F	V	Q	Y	E	I	F	Q	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1597		
Z18983	VDKAYAKEI	E	I	V	Q	F	E	I	F	H	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1598	
Z19044	VDKAYAKEVE	I	I	Q	L	E	I	F	H	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1599		
Z19031	VDKAYAKEVE	T	I	Q	L	E	I	F	A	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1600		
Z19022	VDKAYAKEVE	Y	I	Q	L	E	I	F	A	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1601		
Z18970	VDKAYAKEI	E	I	L	I	Q	L	E	I	Y	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1602
Z18945	VDKAYAKEI	E	Y	V	Q	F	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1603	
Z19010	VDKAYAKEI	E	V	I	Q	Y	E	I	F	A	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1604	
Z18944	VDKAYAKEI	E	V	I	Q	L	E	I	F	A	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1605	
Z19026	VDKAYAKEI	E	V	I	Q	L	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1606	
Z19039	VDKAYAKEVE	Y	I	Q	M	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1607		
Z18934	VDKAYAKEVE	I	V	Q	F	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1608		
Z19178	VDKAYAKEVE	V	I	Q	L	E	I	Y	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1609		
Z19114	VDKAYAKEVE	V	I	Q	Y	E	I	F	A	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1610		
Z19032	VDKAYAKEVE	V	I	Q	L	E	I	F	S	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1611		
Z19162	VDKAYAKELE	I	I	Q	L	E	I	F	S	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1612		
Z18994	VDKAYAKEI	E	V	V	Q	L	E	I	F	G	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1613	
Z18984	VDKAYAKEI	E	V	V	Q	L	E	I	F	G	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1614	
Z19161	VDKAYAKEI	E	I	I	Q	M	E	I	F	G	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1615	
Z18985	VDKAYAKEVE	V	V	Q	F	E	I	Y	G	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1616		
Z18957	VDKAYAKEVE	V	Q	L	E	I	Y	G	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1617			
Z19075	VDKAYAKEVE	I	I	Q	Y	E	I	F	G	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1618		
Z19046	VDKAYAKELE	A	I	Q	M	E	I	F	V	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1619		
Z19173	VDKAYAKEVE	A	I	Q	M	E	I	F	F	L	P	N	L	T	R	R	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1620		
Z19004	VDKAYAKELE	A	I	Q	L	E	I	Y	E	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1621		
Z18993	VDKAYAKEVE	A	I	Q	F	E	I	F	Q	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1622		
Z19177	VDKAYAKEVE	A	I	Q	F	E	I	Y	H	L	P	N	L	T	R	K	Q	Y	T	A	F	I	R	K	L	D	D	P	S	Q	S	S	E	L	L	S	E	A	K	K	L	N	D	S	Q	A	P	K	1623		

FIGURE 1BE

Z18926	VDAKYAKEVEAIQLEIYHLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1624
Z18956	VDAKYAKEIEAVQIEIFRLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1625
Z18961	VDAKYAKEIEAIQLEIFHLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1626
Z18772	VDAKYAKEIEAIQMEIFHLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1627
Z19182	VDAKYAKEVEAIQMEIFQLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1628
Z18964	VDAKYAKEIEAIQYEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1629
Z19013	VDAKYAKEIEAIQLEIYALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1630
Z19117	VDAKYAKEIEAIQLEIFALPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1631
Z18999	VDAKYAKEVEAVQLEIFALPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1632
Z18581	AEAKYAKEAEAYEYIEFGLPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1633
Z18591	AEAKYAKEADAAAYMEIFGLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1634
Z18607	AEAKYAKEIEAVQMEIFYLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1635
Z18573	AEAKYAKEIEAAQMEIFGLPNLTRKQYTA FIRKLFDDPSQSSELLSEAKKLNDSQAPK	1636
Z18574	AEAKYAKEIEAAYMEIYYLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1637
Z18603	AEAKYAKEAEKAYEYIFNLPNLTRKQYTA FIRKLDDPSQSSELLSEAKKLNDSQAPK	1638
PSI0405	AEAKYAKEAHRAQMEIFALPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLSAQPKVEGSLAEAK EAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALP	1639
PSI0407	AEAKYAKEALSAAQMEIFALPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLSAQPKVEGSLAEAK EAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALP	1640
PSI0411	ASLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALPGSAEAKYAKEAHRAQMEIF ALPNLTR RQYTA FIRKLDDPSQSSELLSEAKKLSAQPK	1641
PSI0412	ASLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALPGGGGGSAEAKYAKEA HRAQMEIFALPNLTRRRQYTA FIRKLDDPSQSSELLSEAKKLSAQPK	1642
PSI0415	ASLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALPAEAKYAKEAHRAQMEIFAL PNLTRRQ YTAFIRKLDDPSQSSELLSEAKKLSAQPK	1643
PSI0416	ASLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGV EALKDAILAALPKYAKEAHRAQMEIFALPNL TRRRQYTA FIRKLDDPSQSSELLSEAKKLSAQPK	1644

FIGURE 1BF

PSI0417	ASLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGVEALKDAILAALPKEAAAKEAAAKELA AKEAAAKEAAAKEAAAKELAAAEAKYAKEAHRAQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLS EAKKLSAQAPK	1645
PSI0534	AEAKYAKEIEEVQMEIFYLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGG GGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1646
PSI0535	AEAKYAKEIEEIQMEIFHLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGG GGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1647
PSI0536	AEAKYAKEVEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGG GGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1648
PSI0537	AEAKYAKEVEDIQLEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGG GGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1649
PSI0538	AEAKYAKELEAIQMEIFHLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGG GGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1650

FIGURE 1BG

PSI0539	AEAKYAKETEAVQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGG GGSDKTHTCPPCAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1651
PSI0574	AEAKYAKEIEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGG GGSDKTHTCPPCAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1652
PSI0575	AEAKYAKELEAIQMEIFYLPNLTRRQYVAFIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGG GGSDKTHTCPPCAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1653
PSI0576	AEAKYAKELEEQMEIFYLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGG GGSDKTHTCPPCAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYITL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	1654
PSI0580	AEAKYAKEVEEQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGG GGSDAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDK SLHTLFGDKLCTVATIRETYGEMADCCAKQEPERNECFIQHKDDNP NLPRLVRPEVDVMTAFHDNE ETFLKKYLYEIAARRHPYFYAPELFFAKRYKAAFTCECCQAAADKAACLLPKLDELDEGKASSAKQRL KCASLQKFGERAFAKAWAVARLSORFPKAEFAEVSKLVDTLTKVHTECCHGDLLECADDRADLAKYIC ENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLLLR LAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKONCELFEQLG EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKKHPEAKRMFCAEDYLSVVLNQLCVLHEK TPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELV KHKPKATKEQLKAVMDFFAAAFVEKCKADDKETCFAEEGKKLVAASQAALGL	1655

FIGURE 1BH

PSI0581	AEAKYAKEVEEIQMEIFRLPNLRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQPKASGGGGGG GGSDAHKSEVAHRFKDLGEENFKALVLI AFAQYLQCCPFEDHVKLNVETFEAKTCVADESAENCDK SLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPNLPRLVPRVEDVMCTAFHDNE ETFLKKYLYEIAARRHPYFYAPELFFAKRYKAATECCQAADKAACLLPKLDELDEGKASSAKQRL KCASLOKFGERAFAKAWAVARLSQRFPAEFAEVSKLVTDLT KVHTECCCHGDLLECADDRADLAKYIC ENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLP SLAADFVESKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVVLRLRAKTYETTLKCCAAADPHECYAKVDFEFKPLVEEPQNLIKQNCSELFQLG EYKFQNALLVRYTKKVPQVSTPTLVEVRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEK TPVSDRVTKCCTESLVRNRRPCFSALEVDETYVPKEFNAETTFTHADICTLSEKERQIKKQTALVELV KHKPKATKEQLKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAA SQAALGL	1656
PSI0582	AEAKYAKEVEEIQMEIFRLPNLRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQPKASGGGGGG GGSVDPKTVRWCAVSEHEATKCQSFDRDHMKSVIPSDGPSVACVKKASYLDCIRAI AANEADAVTLDA GLVYDAYLAPNNLKPVVAEFGSKEDPQTFYAVAVVKKDSGFQMNQIRGKKSCHTGLGRSAGWNIP IGLLYCDLPEPRKPLEKAVANFFSGSCAPCADGTDFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDG AGDVA FVKHSTIFENLANKADRQYELLCLDNTRKPVDEYKDCHLAQVP SHTVVARSMGGKEDLIWE LLNQAQEHFGKDSKEFQLFSSPHGKDLLFKDSA HGFLLKVPPRMDAKMYLG YEYVTAIRNLREGTCP EAPTDECKPVKWCALSHHERLKCDEWSVNSVGKIECVSAETTEDCIAKIMNGEADAMS LDGGFVYIA GKGLVPVLAENYNKSDNCEDTPEAGYFAIAVVKKSASDLTWDNLGKKKSCHTAVGRTAGWNIPMGL LYNKINHC RFDEFFSEGCAPGSKKDSLCKLCMGSGNLNCEPNNKEGYGYTGAFRCLVEKGDVAFV KHQTVPQNTGKNPD PWAKNLNEKDYELLCLDGT RKPVEEYANCHLARAPNHAVVTRKDK EACVHKI LRQQQHLFGSNVTD CSGNFCLFRSETKDLLFRDDTVCLAKLHDRNTYEKYLGE EYVKAVGNLRKCST SSLLEACTFRRP	1657
PSI0589	AEAKYAKEVEEIQMEIFRLPNLRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQPKASGGGGGG GGSDKTHTCPPCPAPELLG	1658
ABD035	LA EAKVLANRELDKYGVSDFYKRLINKAKTVEGVEALKLHILAALP	1659
ABD001	LA EAKVLANRELDKYGVSDYKYNL INNAKTVEGVKALIDEILAALP	1660
PP013	LA EAKEAANAELDSYGVSDFYKRLIDKAKTVEGVEALKDAILAALP	1661

FIGURE 1BI

hIgG1 Fc	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVSVLTVLTQHQLWLNKEYSKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLYSKLTVDKSRWQQGN VFSCVMHEALHNHYTQKSLSLSPGK	1662
hAlbumin	DAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQCPFFEDHVKLVNEVTEFAKTCVADESAENCDKSLH TLFGDKLICTVATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRIVRPEVDVMTAFHDNEETF LKKYL YEIARRHPYFAPPELLFFAKRYKAFTTECCQAADKAACLLPKLDELDEGKASSAKQRLKCA SLQKFGERAFAKAWAVARLSQRFPKAEAEVSKLVTDLTKVHTECCGDDLLECADRADLAKYICENQ DSISSKLLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFGLMFLYEYA RRHPDYSVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCSELFELGEYK FQNALLVRYTKVPQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPV SDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHK PKATKEQLKAVMDDFAAFVEKCKCKADDKETCFAEEGKKLVAAASQAALGL	1663
hTransferrin	VPDKTVRWCAVSEHEATKCQSFDRDHMKSVIPSDGPSVACVKKASYLDCIRAI AANEADAVTLDAGLV YDAYLAPNNLKPVVAEFYGSKEDEPQTFYYAVAVVKKDSGFQMNQLRGKKSCHTGLGRSAGWNIPIGL LYCDLPEPRKPLEKAVANFFSGCAPCADGTFPQLCQLCPGCGCSTLNQYFGYSGAFKCLKDGAGD VAFVKHSTIFENLANKADRQYELLCLDNTRKPVDEYKDCHLAQVPSHTVVARSMSGKEDLIWELLN QAEHFGKDKSKEFQLFSSPHGKDLLFKDSAHGFLKVPPRMDAKMYLGYEYVTAIRNLREGTCPEAP TDECKPVKWCALSHHERLKCDEWSVNSVGKIECVSAETTEDCIAKIMNGEADAMSLDGGFVYIAGKC GLVPVLAENYNKSDNCEDTPEAGYFAIAVVKKASDLTWDNLKGKKSCHTAVGRTAGWNI PMGLLYN KINHCRFDEFFSEGCAPGSKKDSLCKLCMGSGNLCEPNNKEGYGYTGAFRCCLVEKGDVAFVKHQ TVPQNTGGKNPDPWAKNINEKDYELLCLDGTGRKPVVEYANCHLARA PNHAVVTRKDKEACVHKILRQ QQHLFGSNVTDCSGNFCLFRSETKDLLFRDDTVCLAKLHDRNTYEKYLGEYVKAVGNLRKCSSTSL LEACTFRRP	1664

FIGURE 1BJ

cIL-1R-I-HIS6	EADKCNEREKIIILVSSANEIDVRPCPLNPNEYKGTITWYKNDSKTPVSTEQASRIHQHKKKLWFVP AKVEDSGHYCVVRNSSYCLRIKITAKFVENEPNLCYNAEAI FKQRLPVAGDGLVCPYMEFFKDE NELPKLLWYKDKPLLLDNIHFSGVKDRLLVMNVAEKHRGNYTCHASYTYLGKQYPI TRVIEFITL ENKPTRPVI VSPANETIEVDLGSQIQLI CNVTGQLSDTAYWKWNGSFIDEDDPVLGEDYYSVENPA KRRSTLITVLNISETESRFYKHPFTCLARNTHGMDAAAYVQLIYPVTGSENLYFQGSDDTHTCPPCP KRRSTLITVLNISETESRFYKHPFTCLARNTHGMDAAAYVQLIYPVTGSENLYFQGSDDTHTCPPCP	1665
cIL-1R-I-Fc	LEADKCNEREKIIILVSSANEIDVRPCPLNPNEYKGTITWYKNDSKTPVSTEQASRIHQHKKKLWFV PAKVEDSGHYCVVRNSSYCLRIKITAKFVENEPNLCYNAEAI FKQRLPVAGDGLVCPYMEFFKDE NNELPKLLWYKDKPLLLDNIHFSGVKDRLLVMNVAEKHRGNYTCHASYTYLGKQYPI TRVIEFITL EENKPTRPVI VSPANETIEVDLGSQIQLI CNVTGQLSDTAYWKWNGSFIDEDDPVLGEDYYSVENPA NKRSTLITVLNISETESRFYKHPFTCLARNTHGMDAAAYVQLIYPVTGSENLYFQGSDDTHTCPPCP APELLGGPSVFLFPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHEA LHNHYTQKSLSLSPGK	1666
mut1	AEAKYAKEAHRAQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1667
mut2	AEAKYAKEALSQQEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1668
mut3	KYAKEAHRAQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1669
mut4	AEAKYAKEIEEVQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1670
mut5	AEAKYAKEIEEIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1671
mut6	AEAKYAKEVEEIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1672
mut7	AEAKYAKEVEDIQLEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1673
mut8	AEAKYAKELEAIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1674
mut9	AEAKYAKE TEAVQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1675
mut10	AEAKYAKEIEEIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1676
mut11	AEAKYAKELEAIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1677
mut12	AEAKYAKELEEIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1678
mut13	AEAKYAKEVEEIQMEIFALPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSQAPK	1679

FIGURE 1BK

GS-hIL-1B	GSAPVRSINCTLRDSQQKSLVMSGPYELKALHLQGDMEQQVVFMSFVQGEESNDKI PVALGLKEK NLYLSCVLKDDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEIINNKLFEFESAQFPNWIISTSQAENMPV FLGGTKGGQDITDFTMQFVSS	1733
PSI0653	AEAKYAKEVEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGGSDKTHTCP PCPAPELLGGPSVFLFPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWVVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKLSLSPGK	1734
PSI0654	AEAKYAKEVEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGGSDKTHTCP PCPAPELLGGPSVFLFPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWVVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVLHSHYTKLSLSLSPGK	1735
PSI0655	AEAKYAKEVEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGGSDKTHTCP PCPAPELLGGPSVFLFPKPKDTLYITREPEVTCVVDVSHEDPEVKFNWVVDGVEVHNAKTKPREEQYASTYRV SVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNNHYTQKLSLSLSPGK	1736
PSI0656	AEAKYAKEVEEIQMEIFRLPNLTRRQYTA FIRKLLDDPSQSSELLSEAKKLSAQAPKASGGGGGGGSGESKYGPC PPCPAPEFLGGPSVFLFPKPKDTLMISRTPEVTCVVDVSEQEDPEVQFNWVVDGVEVHNAKTKPREEQFNSTYR VSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFCSCVMHEALHNNHYTQKLSLSLGGK	1737

FIGURE 2

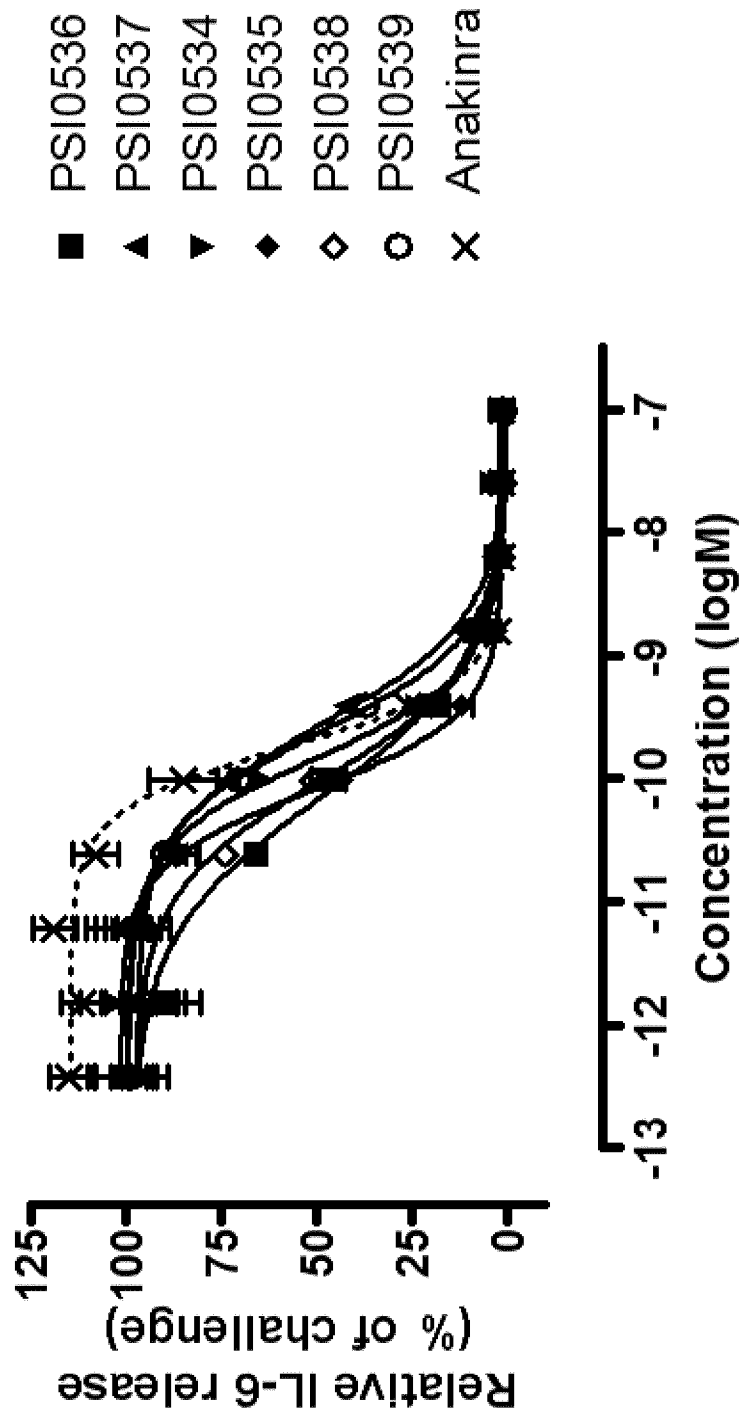
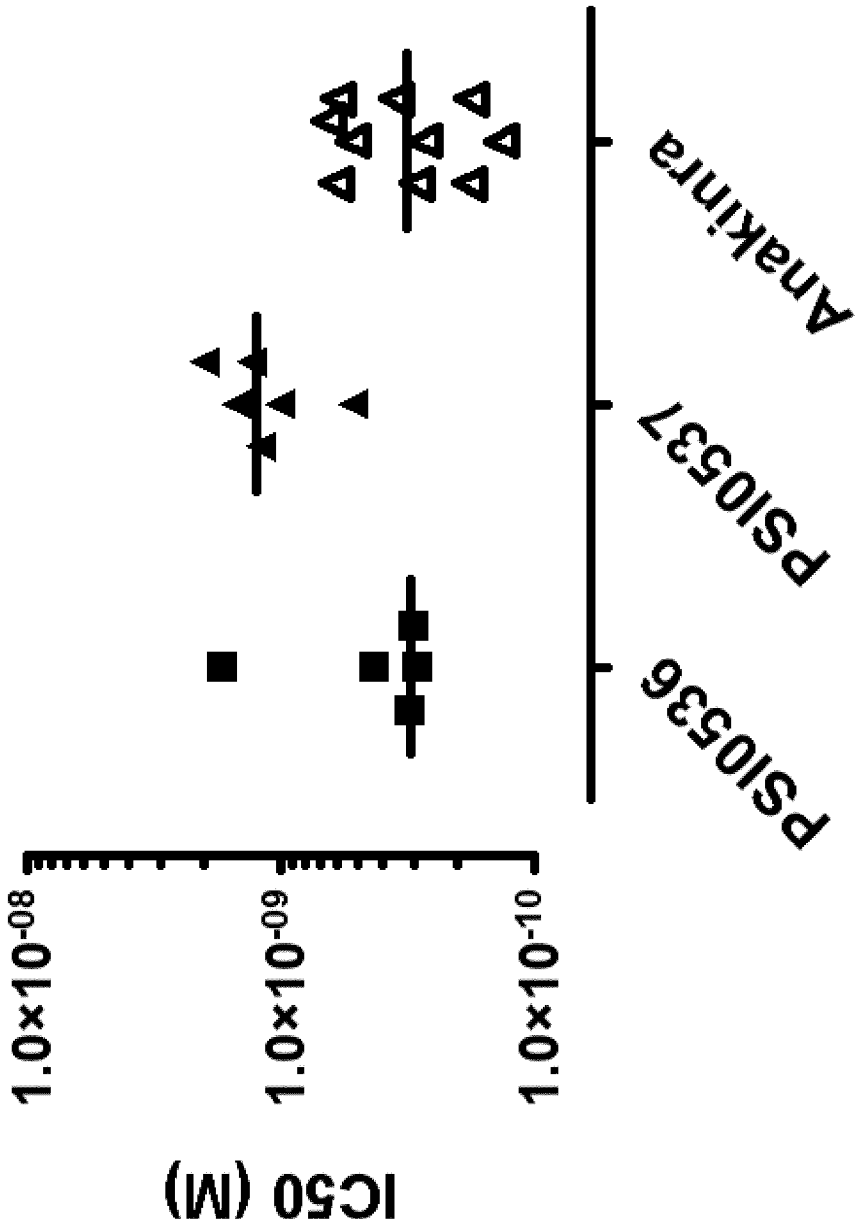


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/00 C07K14/31
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/063308 A2 (DOMANTIS LTD [GB]; DREW PHILIP D [GB]; DE WILDT RUDOLF M T [GB]; TOMLI) 7 June 2007 (2007-06-07) page 2, column 7 - page 3, column 16 page 16, line 18 - page 17, line 8 -----	1-39
A	NYGREN PER-AKE: "Alternative binding proteins: affibody binding proteins developed from a small three-helix bundle scaffold", FEBS JOURNAL, WILEY-BLACKWELL PUBLISHING LTD, GB, vol. 275, no. 11, 1 June 2008 (2008-06-01) , pages 2668-2676, XP002601623, ISSN: 1742-464X, DOI: 10.1111/J.1742-4658.2008.06438.X ----- -/-	1-39



Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Marinoni J-C

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/058448

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GRIMM S ET AL: "Selection and characterisation of affibody molecules inhibiting the interaction between Ras and Raf in vitro", NEW BIOTECHNOLOGY, ELSEVIER BV, NL, vol. 27, no. 6, 31 December 2010 (2010-12-31), pages 766-773, XP027539673, ISSN: 1871-6784 [retrieved on 2010-11-30] -----	1-39
A	WO 2013/126006 A1 (SWEDISH ORPHAN BIOVITRUM AB PUBL [SE]) 29 August 2013 (2013-08-29) -----	1-39
A	WO 2011/110515 A1 (AFFIBODY AB [SE]; ABRAHMSSEN LARS [SE]) 15 September 2011 (2011-09-15) -----	1-39
A	WO 2014/064237 A1 (AFFIBODY AB [SE]) 1 May 2014 (2014-05-01) -----	1-39
A	WO 2009/077175 A1 (AFFIBODY AB [SE]; LINDBORG MALIN [SE]; GUNNERIUSSON ELIN [SE]; LENDEL) 25 June 2009 (2009-06-25) -----	1-39
A	WO 2014/140366 A1 (AFFIBODY AB [SE]) 18 September 2014 (2014-09-18) -----	1-39
A	WO 2016/113246 A1 (AFFIBODY AB [SE]) 21 July 2016 (2016-07-21) -----	1-39
A	GRONWALL ET AL: "Selection and characterization of Affibody ligands binding to Alzheimer amyloid @b peptides", JOURNAL OF BIOTECHNOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 128, no. 1, 23 December 2006 (2006-12-23), pages 162-183, XP005734691, ISSN: 0168-1656, DOI: 10.1016/J.JBIOTEC.2006.09.013 -----	1-39

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2018/058448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007063308	A2	07-06-2007	
		AU 2006321364 A1	07-06-2007
		CA 2632866 A1	07-06-2007
		CN 101454344 A	10-06-2009
		CR 10022 A	22-09-2008
		EA 200801170 A1	30-12-2008
		EP 1957536 A2	20-08-2008
		JP 2009519011 A	14-05-2009
		KR 20080077238 A	21-08-2008
		MA 30300 B1	01-04-2009
		TW 200730539 A	16-08-2007
		US 2009155283 A1	18-06-2009
		WO 2007063308 A2	07-06-2007
WO 2013126006	A1	29-08-2013	
		AU 2013222836 A1	18-09-2014
		AU 2017245376 A1	02-11-2017
		CA 2863862 A1	29-08-2013
		CN 104114574 A	22-10-2014
		EP 2817329 A1	31-12-2014
		HK 1204790 A1	04-12-2015
		JP 6276202 B2	07-02-2018
		JP 2015508652 A	23-03-2015
		JP 2018052942 A	05-04-2018
		KR 20140129163 A	06-11-2014
		NZ 628625 A	31-03-2016
		PH 12014501604 A1	08-10-2014
		RU 2014137303 A	10-04-2016
		SG 11201404942U A	26-09-2014
		US 2015011474 A1	08-01-2015
		US 2018085428 A1	29-03-2018
		WO 2013126006 A1	29-08-2013
		ZA 201406773 B	31-08-2016
WO 2011110515	A1	15-09-2011	
		CA 2789738 A1	15-09-2011
		CN 102811782 A	05-12-2012
		CN 107686513 A	13-02-2018
		DK 2544785 T3	18-01-2016
		DK 2977088 T3	09-10-2017
		EP 2544785 A1	16-01-2013
		EP 2977088 A1	27-01-2016
		ES 2641896 T3	14-11-2017
		JP 5951509 B2	13-07-2016
		JP 2013528567 A	11-07-2013
		US 2013203962 A1	08-08-2013
		WO 2011110515 A1	15-09-2011
WO 2014064237	A1	01-05-2014	
		AU 2013336646 A1	28-05-2015
		CA 2889037 A1	01-05-2014
		CN 104854127 A	19-08-2015
		DK 2912054 T3	11-09-2017
		EP 2912054 A1	02-09-2015
		ES 2639099 T3	25-10-2017
		HK 1210793 A1	06-05-2016
		JP 2015534994 A	07-12-2015
		KR 20150077447 A	07-07-2015
		PL 2912054 T3	30-11-2017
		US 2015291668 A1	15-10-2015
		WO 2014064237 A1	01-05-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2018/058448

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009077175	A1	25-06-2009	AT 527353 T 15-10-2011
		DK 2231860 T3 05-12-2011	
		EP 2231860 A1 29-09-2010	
		ES 2373832 T3 09-02-2012	
		WO 2009077175 A1 25-06-2009	

WO 2014140366	A1	18-09-2014	AU 2014230018 A1 05-11-2015
		CA 2902657 A1 18-09-2014	
		CN 105209482 A 30-12-2015	
		DK 2970406 T3 05-02-2018	
		EP 2970406 A1 20-01-2016	
		ES 2660912 T3 26-03-2018	
		HK 1216756 A1 02-12-2016	
		JP 2016511280 A 14-04-2016	
		KR 20150132349 A 25-11-2015	
		LT 2970406 T 12-03-2018	
		RU 2015141224 A 21-04-2017	
		US 2016031967 A1 04-02-2016	
		US 2018118807 A1 03-05-2018	
		WO 2014140366 A1 18-09-2014	

WO 2016113246	A1	21-07-2016	AU 2016208161 A1 13-07-2017
		CA 2972683 A1 21-07-2016	
		CN 108064235 A 22-05-2018	
		EP 3245224 A1 22-11-2017	
		JP 2018508186 A 29-03-2018	
		KR 20170116023 A 18-10-2017	
		US 2017362290 A1 21-12-2017	
		WO 2016113246 A1 21-07-2016	
