aI-AI-bI-BI-cI-CI-dI-DI-eI-EI-fI-FI-gI-GI-hI

wherein the HRI is a fusion protein of a first human constant region of an immunoglobulin (1st CRI, acceptor) interspersed with amino acids of a second human constant region of an immunoglobulin (2nd CRI, donor), wherein the 1st CRI comprises seven antiparallel beta strands A1, B1, C1, D1, E1, F1, and G1, six intervening regions b1, c1, d1, e1, f1, and g1, a N-terminal region a1 and a C-terminal region h1 arranged from N- to C-terminus in the following order:

a1-A1-b1-B1-c1-C1-d1-D1-e1-E1-f1-F1-g1-G1-h1

wherein the 2nd CRI comprises seven antiparallel beta strands A2, B2, C2, D2, E2, F2, and G2, six intervening regions b2, c2, d2, e2, f2, and g2, a N-terminal region a2 and a C-terminal region h2 positioned from N- to C-terminus in the following order:

a2-A2-b2-B2-c2-C2-d2-D2-e2-E2-f2-F2-g2-G2-h2

wherein HRI has the amino acid sequence of the 1st CRI and wherein at least the following amino acids of the 1st CRI are replaced with the following amino acids of the 2nd CRI:

(i) at least 1 amino acid of a1 spanning IgLCRC positions 1 to 12 of the immunoglobulin is replaced with at least 1 amino acid of a2 spanning IgLCRC positions 1 to 12 of the immunoglobulin (Replacement 1);

(ii) at least 1 amino acid of c1 spanning IgLCRC positions 41 to 45 of the immunoglobulin is replaced with at least 1 amino acid of c2 spanning IgLCRC positions 41 to 45 of the immunoglobulin (Replacement 2); and

(iii) at least 1 amino acid of g1 spanning IgLCRC positions 109 to 127 of the immunoglobulin is replaced with at least 1 amino acid of g2 spanning IgLCRC positions 109 to 127 of the immunoglobulin (Replacement 3);

and

(b) the HRII comprises seven antiparallel beta strands AII, BII, CII, DII, EII, FII, and GII, six intervening regions bII, cII, dII, eII, fII, and gII, a N-terminal region aII and a C-terminal region hII positioned from N- to C-terminus in the following order:

aII-AII-bII-BII-cII-CII-dII-DII-eII-EII-fII-FII-gII-GII-hII

wherein the HRII is a fusion protein of a third human constant region of an immunoglobulin (3rd CRI, acceptor) interspersed with amino acids of a fourth human constant region of an immunoglobulin (4th CRI, donor), and wherein the 3rd CRI comprises seven antiparallel beta strands A3, B3, C3, D3, E3, F3, and G3, six intervening regions b3, c3, d3, e3, f3, and g3, a N-terminal region a3 and a C-terminal region h3 positioned from N- to C-terminus in the following order:

a3-A3-b3-B3-c3-C3-d3-D3-e3-E3-f3-F3-g3-G3-h3

wherein the 4th CRI comprises seven antiparallel beta strands A4, B4, C4, D4, E4, F4, and G4, six intervening regions b4, c4, d4, e4, f4, and g4, a N-terminal region a4 and a C-terminal region h4 positioned from N- to C-terminus in the following order:

a4-A4-b4-B4-c4-C4-d4-D4-e4-E4-f4-F4-g4-G4-h4

wherein HRII has the amino acid sequence of the 3rd CRI and wherein at least the following amino acids of the 3rd CRI are replaced with the following amino acids of the 4th CRI:

(i) at least 1 amino acid of a3 spanning IgLCRC positions 1 to 12 of the immunoglobulin is replaced with at least 1 amino acid of a4 spanning IgLCRC positions 1 to 12 of the immunoglobulin (Replacement 4);

(ii) at least 1 amino acid of c3 spanning IgLCRC positions 41 to 45 of the Immunoglobulin is replaced with at least 1 amino acid of c4 spanning IgLCRC positions 41 to 45 of the immunoglobulin (Replacement 5); and

(iii) at least 1 amino acid of g3 IgLCRC positions 109 to 127 of the immunoglobulin is replaced with at least 1 amino acid of g4 spanning IgLCRC positions 109 to 127 of the immunoglobulin (Replacement 6);

wherein the 1st CRI and the 3rd CRI are different from each other and specifically bind to each other under physiological conditions:

wherein in 1st, 2nd, 3rd and 4th CRI beta strand A spans IgLCRC positions 13 to 18, beta strand B spans IgLCRC positions 31 to 40, beta strand C spans IgLCRC positions 46 to 52, beta strand D spans IgLCRC positions 63 to 70, beta strand E spans IgLCRC positions 81 to 89, beta strand F spans IgLCRC positions 102 to 108, and beta strand G spans IgLCRC 20 positions 128 to 133; and

wherein in 1st, 2nd, 3rd and 4th CRI intervening regions “b”, “c”, “d”, “e”, “f” and “g” span IgLCRC positions 19 to 30, IgLCRC positions 41 to 45, IgLCRC positions 53 to 62, IgLCRC positions 71 to 80, IgLCRC positions 90 to 101, and IgLCRC positions 109 to 127, respectively.

In another aspect, the present disclosure provides the amino acid chain I or II as defined herein, preferably a combination of amino acid chains, wherein chain I and chain II have the amino acid sequence according to SEQ ID NO: 41 and SEQ ID NO: 42, SEQ ID NO: 34 and SEQ ID NO: 35, SEQ ID NO: 43 and SEQ ID NO: 44, SEQ ID NO: 36 and SEQ ID NO: 37 (scFv13.7-Fc1k), SEQ ID NO: 36 and SEQ ID NO: 38 (scFv13.7-CD3-Hinge-Fc1k), SEQ ID NO: 39 and SEQ ID NO: 38 (scFv3-43-CD3-Hinge-Fc1k) or SEQ ID NO: 40 and SEQ ID NO: 38 (scFvhuMCSP-CD3-Hinge-Fc1k).

Thus, in an example the present disclosure provides a protein complex comprising at least two amino acid chains I and II, which are non-covalently bound to each other through

heterodimerization region I (HRI) comprised in amino acid chain I and a heterodimerization region II (HRII) comprised in amino acid chain II and wherein HRI and HRII respectively comprise the heterodimerizing domains of a human constant region of an immunoglobulin or an immunoglobulin-like protein wherein each heterodimerizing domain is modified in that amino acid sequences of a further immunoglobulin or an immunoglobulin-like protein are inserted into at least two preferably at least three regions of the respective heterodimerizing domain that are outside the heterodimerization interphase of the respective HRI and HRII, i.e. which are preferably solvent accessible after heterodimerization of HRI and HRII.

More specifically the protein complex of the disclosure comprises at least two amino acid chains I and II, which are non-covalently bound to each other through a heterodimerization region I (HRI) comprised in amino acid chain I and a heterodimerization region II (HRII) comprised in amino acid chain II, wherein

(a) HRI comprises seven antiparallel beta strands AI, BI, CI, DI, EI, FI, and GI, six intervening regions bI, cI, dI, eI, fI, and gI, a N-terminal region aI and a C-terminal region hI positioned from N- to C-terminus in the following order:

aI-AI-bI-BI-cI-CI-dI-DI-eI-EI-fI-FI-gI-GI-hI,

Claims

1. A protein complex comprising at least two amino acid chains I and II, which are non-covalently bound to each other through a heterodimerization region I (HRI) comprised in amino acid chain I and a heterodimerization region II (HRII) comprised in amino acid chain II, wherein:

(a) HRI comprises seven antiparallel beta strands AI, BI, CI, DI, EI, FI, and GI, six intervening regions bI, cI, dI, eI, fI, and gI, a N-terminal region aI and a C-terminal region hI positioned from N- to C-terminus in the following order:

aI-AI-bI-BI-cI-CI-dI-DI-eI-EI-fI-FI-gI-GI-hI

wherein the HRI is a fusion protein of a first human constant region of an immunoglobulin (1st CRI, acceptor) interspersed with amino acids of a second human constant region of an immunoglobulin (2nd CRI, donor),
wherein the 1st CRI comprises seven antiparallel beta strands A1, B1, C1, D1, E1, F1, and G1, six intervening regions b1, c1, d1, e1, f1, and g1, a N-terminal region a1 and a C-terminal region h1 arranged from N- to C-terminus in the following order:

a1-A1-b1-B1-c1-C1-d1-D1-e1-E1-f1-F1-g1-G1-h1

wherein the 2nd CRI comprises seven antiparallel beta strands A2, B2, C2, D2, E2, F2, and G2, six intervening regions b2, c2, d2, e2, f2, and g2, a N-terminal region a2 and a C-terminal region h2 positioned from N- to C-terminus in the following order:

a2-A2-b2-B2-c2-C2-d2-D2-e2-E2-f2-F2-g2-G2-h2

wherein HRI has the amino acid sequence of the 1st CRI and wherein at least the following amino acids of the 1st CRI are replaced with the following amino acids of the 2nd CRI:

(i) at least 1 amino acid of a1 spanning IgLCRC positions 1 to 12 of the immunoglobulin is replaced with at least 1 amino acid of a2 spanning IgLCRC positions 1 to 12 of the immunoglobulin (Replacement 1);

(ii) at least 1 amino acid of c1 spanning IgLCRC positions 41 to 45 of the immunoglobulin is replaced with at least 1 amino acid of c2 spanning IgLCRC positions 41 to 45 of the immunoglobulin (Replacement 2); and

(iii) at least 1 amino acid of g1 spanning IgLCRC positions 109 to 127 of the immunoglobulin is replaced with at least 1 amino acid of g2 spanning IgLCRC positions 109 to 127 of the immunoglobulin (Replacement 3);

and

(b) the HRII comprises seven antiparallel beta strands AII, BII, CII, DII, EII, FII, and GII, six intervening regions bII, cII, dII, eII, fII, and gII, a N-terminal region aII and a C-terminal region hII positioned from N- to C-terminus in the following order:

aII-AII-bII-BII-cII-CII-dII-DII-eII-EII-fII-FII-gII-GII-hII

wherein the HRII is a fusion protein of a third human constant region of an immunoglobulin (3rd CRI, acceptor) interspersed with amino acids of a fourth human constant region of an immunoglobulin (4th CRI, donor), and wherein
the 3rd CRI comprises seven antiparallel beta strands A3, B3, C3, D3, E3, F3, and G3, six intervening regions b3, c3, d3, e3, f3, and g3, a N-terminal region a3 and a C-terminal region h3 positioned from N- to C-terminus in the following order:

a3-A3-b3-B3-c3-C3-d3-D3-e3-E3-f3-F3-g3-G3-h3

wherein the 4th CRI comprises seven antiparallel beta strands A4, B4, C4, D4, E4, F4, and G4, six intervening regions b4, c4, d4, e4, f4, and g4, a N-terminal region a4 and a C-terminal region h4 positioned from N- to C-terminus in the following order:

a4-A4-b4-B4-c4-C4-d4-D4-e4-E4-f4-F4-g4-G4-h4

wherein HRII has the amino acid sequence of the 3rd CRI and wherein at least the following amino acids of the 3rd CRI are replaced with the following amino acids of the 4th CRI:

(i) at least 1 amino acid of a3 spanning IgLCRC positions 1 to 12 of the immunoglobulin is replaced with at least 1 amino acid of a4 spanning IgLCRC positions 1 to 12 of the immunoglobulin (Replacement 4);

(ii) at least 1 amino acid of c3 spanning IgLCRC positions 41 to 45 of the immunoglobulin is replaced with at least 1 amino acid of c4 spanning IgLCRC positions 41 to 45 of the immunoglobulin (Replacement 5); and

(iii) at least 1 amino acid of g3 spanning IgLCRC positions 109 to 127 of the immunoglobulin is replaced with at least 1 amino acid of g4 spanning IgLCRC positions 109 to 127 of the immunoglobulin (Replacement 6);

wherein the 1st CRI and the 3rd CRI are different from each other and specifically bind to each other under physiological conditions;

wherein in 1st, 2nd, 3rd and 4th CRI beta strand A spans IgLCRC positions 13 to 18, beta strand B spans IgLCRC positions 31 to 40, beta strand C spans IgLCRC positions 46 to 52, beta strand D spans IgLCRC positions 63 to 70, beta strand E spans IgLCRC positions 81 to 89, beta strand F spans IgLCRC positions 102 to 108, and beta strand G spans IgLCRC positions 128 to 133; and

wherein in 1st, 2nd, 3rd and 4th CRI intervening regions “b”, “c”, “d”, “e”, “f” and “g” span IgLCRC positions 19 to 30, IgLCRC positions 41 to 45, IgLCRC positions 53 to 62, IgLCRC positions 71 to 80, IgLCRC positions 90 to 101, and IgLCRC positions 109 to 127, respectively.

2. The protein complex of claim 1, wherein the immunoglobulin is selected from IgG1, Ig Kappa, Ig Lambda, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, and IgM.

3. The protein complex of claim 1 or 2, wherein 1st CRI and 3rd CRI are independently selected from the group consisting of a constant region of heavy chain 1 (CH1) of IgG1, preferably having an amino acid sequence according to SEQ ID NO: 1; Igκ constant region, preferably having an amino acid sequence according to SEQ ID NO: 18; constant region of T cell receptor (TCR) α, preferably having an amino acid sequence according to SEQ ID NO: 10; constant region of TCR β, preferably having an amino acid sequence according to SEQ ID NO: 11; neonatal Fc receptor (FcRn) alpha 3, preferably having an amino acid sequence according to SEQ ID NO: 12; β 2 micro globulin, preferably having an amino acid sequence according to SEQ ID NO: 13; Igλ constant region, preferably having an amino acid sequence

according to SEQ ID NO: 19; IgG2, preferably having an amino acid sequence according to SEQ ID NO: 2, IgG3, preferably having an amino acid sequence according to SEQ ID NO: 3, IgG4, preferably having an amino acid sequence according to SEQ ID NO: 4, IgA1, preferably having an amino acid sequence according to SEQ ID NO: 5; IgA2, preferably having an amino acid sequence according to SEQ ID NO: 6; IgD, preferably having an amino acid sequence according to SEQ ID NO: 7; IgE, preferably having an amino acid sequence according to SEQ ID NO: 8; IgM, preferably having an amino acid sequence according to SEQ ID NO: 9; human leukocyte antigen (HLA) A, preferably having an amino acid sequence according to SEQ ID NO: 14, or HLA-B α3, preferably having an amino acid sequence according to SEQ ID NO: 15; HLA-D α2, preferably having an amino acid sequence according to SEQ ID NO: 16 and HLA-D β2, preferably having an amino acid sequence according to SEQ ID NO: 17,

wherein preferably the following combinations of 1st CRI and 3rd CRI are selected:

(i) 1st CRI: CH1 of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM and 3rd CRI: Igκ constant region and Igλ constant region;

(ii) 1st CRI: constant region of TCR α and 3rd CRI: constant region of TCR β;

(iii) 1st CRI: FcRn alpha 3; HLA-A α3; or HLA-B α3 and 3rd CRI: β 2 micro globulin; and

(iv) 1st CRI: HLA-D α2 and 3rd CRI: HLA-D β2.

4. The protein complex of any of claims 1 to 3, wherein

(i) 2nd CRI and 4th CRI are identical and selected from the group consisting of CH3 of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, CH1 of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM; or IgD; CH4 of IgE, or IgM; and Igκ or Igλ constant region, or

(ii) 2nd CRI and 4th CRI are selected individually from the group consisting of CH1 of IgG1, Igκ or Igλ constant region, CH1 of IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM; CH3 of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD and CH4 of IgE, or IgM.

5. The protein complex of any of claims 1 to 4,

(i) wherein in Replacement 1 and/or 4 all amino acids N-terminal to beta strand A (Ig like constant region consensus (IgLCRC, depicted in figure 4) positions 1 to 12) of the 1st CRI or 3rd CRI are replaced with all amino acids N-terminal to beta sheet A (IgLCRC positions 1 to 12) of the 2nd CRI or 4th CRI, respectively;

(ii) wherein in Replacement 2 and/or 5 amino acids at IgLCRC positions 41-45, 41-46, 41-47, 41-48, 41-49, 41-50, 41-51, 42-45, 42-46, 42-47, 42-48, 42-49, 42-50, 42-51, 43-

45, 43-46, 43-47, 43-48, 43-49, 43-50, 43-51, 44-45, 44-46, 44-47, 44-48, 44-49, 44-50, 44-51, 45-45, 45-46, 45-47, 45-48, 45-49, 45-50 or 45-51 of the 1st CRI or 3rd CRI are replaced with amino acids at IgLCRC positions 41-45, 41-46, 41-47, 41-48, 41-49, 41-50, 41-51, 42-45, 42-46, 42-47, 42-48, 42-49, 42-50, 42-51, 43-45, 43-46, 43-47, 43-48, 43-49, 43-50, 43-51, 44-45, 44-46, 44-47, 44-48, 44-49, 44-50, 44-51, 45-45, 45-46, 45-47, 45-48, 45-49, 45-50 or 45-51 of the 2nd CRI or 4th CRI, respectively; and

(iii) wherein in Replacement 3 and/or 6 amino acids at IgLCRC positions 103-127, 103-128, 103-129, 103-130, 103-131, 103-132, 104-127, 104-128, 104-129, 104-130, 104-131, 104-132, 105-127, 105-128, 105-129, 105-130, 105-131, 105-132, 106-127, 106-128, 106-129, 106-130, 106-131, 106-132, 107-127, 107-128, 107-129, 107-130, 107-131, 107-132, 108-127, 108-128, 108-129, 108-130, 108-131, 108-132, 109-127, 109-128, 109-129, 109-130, 109-131 or 109-132 of the 1st CRI or 3rd CRI are replaced with amino acids at IgLCRC positions 103-127, 103-128, 103-129, 103-130, 103-131, 103-132, 104-127, 104-128, 104-129, 104-130, 104-131, 104-132, 105-127, 105-128, 105-129, 105-130, 105-131, 105-132, 106-127, 106-128, 106-129, 106-130, 106-131, 106-132, 107-127, 107-128, 107-129, 107-130, 107-131, 107-132, 108-127, 108-128, 108-129, 108-130, 108-131, 108-132, 109-127, 109-128, 109-129, 109-130, 109-131 or 109-132 of the 2nd CRI or 4th CRI.

6. The protein complex of any of claims 1 to 5, wherein in addition to Replacement 1 to 6 the amino acids of 1st CRI and/or 3rd CRI, respectively, at IgLCRC positions 37 and/or 47 and/or 49 and/or 81 and/or 107 are replaced with amino acids of 2nd CRI and/or 4th CRI at IgLCRC positions 37 and/or 47 and/or 49 and/or 81 and/or 107.

7. The protein complex of any of claims 1 to 6, wherein HRI and HRII each comprise at least one Cys residue positioned to form a covalent bond between HRI and HRII at IgLCRC position 20 (CH1 of IgG2, IgG3, IgG4, or IgM), 21 (CH1 of IgD), 135 (CH1 of IgA1 or IgA2), 138 (CH1 of IgG1 or IgE, CL of Igκ, CL of Igλ), 139 (constant domain of TCR β) or 141 (constant domain of TCRa), as depicted in figure 4, resulting from the following combinations of 1st CRI and 3rd CRI:

(i) 1st CRI: CH1 of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM and 3rd CRI: Igκ constant region and/or Igλ constant region;

(ii) 1st CRI: constant region of TCR α and 3rd CRI: constant region of TCR β;

8. The protein complex of any of claims 1 to 7, wherein the HRI and HRII have the amino acid sequence according to SEQ ID NO: 20 and 21, SEQ ID NO: 22 and 23, SEQ ID NO: 24 and 25, SEQ ID NO: 26 and 27, SEQ ID NO: 28 and 32, SEQ ID NO: 28 and 33, SEQ ID NO: 31 and 29 and SEQ ID NO: 31 and 30, respectively, or heterodimerizing variants thereof having at least 70% sequence identity to the respectively indicated amino acid sequence.

9. The protein complex of any of claims 1 to 8, wherein amino acid chain I and/or amino acid chain II further comprise one or more amino acid elements selected from the group consisting of a CH2 or CH3 domain of an antibody; one or more antigen specific ligand (ASL), preferably selected from the group consisting of a Fv, a single-chain Fv (scFv), a disulfide-stabilized Fv, a disulfide-stabilized scFv, a Fab, a single-chain Fab, a single domain antibody, a variable heavy chain domain (V_H), a variable light chain domain (VL), T-cell receptor or antigen binding fragments thereof, a Nanobody, a VHH, one or more antibody-like binding proteins; an antibody hinge region (HR), one or more linker sequences (L), one or more cytokines, interleukines, interferons, growth factors, hormones, ligands, peptides, receptor fragments with ligand-binding activity, chelators, enzymes, coagulation factors, and anti-coagulants, and derivatives thereof,
wherein preferably amino acid chain I comprises one or more antigen specific ligands (ASL) and/or one or more effector molecules and amino acid chain II comprises one or more antigen specific ligands (ASL) and/or one or more effector molecules and, wherein the ASL modules are selected from a group of molecules, specifically binding to e.g. cell surface proteins (receptor, adhesion molecule, channel, transporter, etc.), hormones, growth factors, cytokines, ligands, serum proteins, coagulation factors, fibrinolytic factors, chemokines, enzymes and, wherein the effector molecules are selected from a group of molecules e.g. cell surface proteins (receptor, adhesion molecule, channel, transporter, etc.), hormones, growth factors, cytokines, ligands, serum proteins, coagulation factors, fibrinolytic factors, chemokines, enzymes.

10. Amino acid chain I or II as defined in claims 1 to 9, preferably a combination of amino acid chains, wherein chain I and chain II have the amino acid sequence according to SEQ ID NO: 41 and SEQ ID NO: 42, SEQ ID NO: 34 and SEQ ID NO: 35, SEQ ID NO: 43 and SEQ ID NO: 44, SEQ ID NO: 36 and SEQ ID NO: 37 (scFv13.7-Fc1k), SEQ ID NO: 36 and SEQ ID NO: 38 (scFv13.7-CD3-Hinge-Fc1k), SEQ ID NO: 39 and SEQ ID NO: 38 (scFv3-43-

CD3-Hinge-Fc1k) or SEQ ID NO: 40 and SEQ ID NO: 38 (scFvhuMCSP-CD3-Hinge-Fc1k).

11. A nucleic acid encoding the amino acid chain I and/or II of claim 10.

12. A vector comprising a nucleic acid of claim 11.

13. A method of defining the amino acid sequence of HRI of an amino acid chain I and/or of HRII of an amino acid sequence II comprising the steps of:

(i) selecting a 1st CRI, a 2nd CRI, a 3rd CRI, and a 4th CRI;

(ii) defining the seven beta strands A, B, C, D, E, F and G of the 1st CRI, 2nd CRI, 3rd CRI, and 4th CRI, intervening sequences b, c, d, e, f, and g of the 1st CRI, 2nd CRI, 3rd CRI, and 4th CRI, N- and C-terminal sequences a and h, respectively of the 1st CRI, 2nd CRI, 3rd CRI, and 4th CRI;

(iii) replacing at least 1 amino acid of a of the 1st CRI with at least 1 amino acid of a of the 2nd (Replacement 1); replacing at least 1 amino acid of c of the 1st CRI with at least 1 amino acids of c of the 2nd CRI (Replacement 2); replacing at least 1 amino acid of g of the 1st CRI with at least 1 amino acid of g of the 2nd CRI (Replacement 3); replacing at least 1 amino acid of a of the 3rd CRI with at least 1 amino acid of a of the 4th CRI (Replacement 4); replacing at least 1 amino acid of c of the 3rd with at least 1 amino acid of c of the 4th CRI (Replacement 5); and replacing at least 1 amino acid of g of the 3 with at least 1 amino acid g of the 4th CRI (Replacement 6),

wherein the 1st CRI and the 3rd CRI are different from each other and specifically bind to each other under physiological conditions.

14. Method of producing amino acid chain I comprising the HRI sequence defined in claim 13 and/or amino acid chain II with the HRII sequence defined in claim 13 comprising the step of introducing a nucleic acid encoding the amino acid chain I and/or amino acid chain II into a host cell and expressing amino acid chain I and/or II.

15. The protein complex of any of claims 1 to 9 or of amino acid chain I and/or II of claim 10 for use as a medicament, preferably for use in the prophylaxis, treatment or diagnosis of a disorder or disease such as but not limited to inflammatory diseases, autoimmune diseases, allergic diseases, proliferative diseases, cancer type diseases, cutaneous conditions,

endocrine diseases, eye diseases and disorders, genetic disorders, metabolic diseases, infectious diseases, intestinal diseases, neurological disorders, and mental illness.