SUMMARY

[0003a] In one aspect, the present disclosure relates to a polypeptide comprising a single-domain antibody (sdAb), the sdAb comprising a modified C-terminal amino acid sequence corresponding to the C-terminal endogenous sdAb amino acid residues $(T/L_{108})V_{109}T_{110}V_{111}S_{112}S_{113}$, as numbered according to the Kabat numbering scheme, wherein the modified amino acid sequence comprises the formula $X_{108}X_{109}X_{110}V_{111}X_{112}X_{113}Y$, wherein: X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of L, V, G, and N; X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; and X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) when X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the sdAb is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0003b] In another aspect, the present disclosure relates to a polypeptide of the formula VHH1-L_n-VHH2, wherein VHH1 is a VHH, L is a polypeptide linker comprising from 1-50 amino acids, n is 0 or 1, and VHH2 is a VHH of the disclosure.

[0003c] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a polypeptide of the disclosure.

[0003d] In another aspect, the present disclosure relates to a nucleic acid encoding a polypeptide of the disclosure.

[0003e] In another aspect, the present disclosure relates to a vector comprising the nucleic acid of the disclosure.

[0003f] In another aspect, the present disclosure relates to a host cell comprising the vector of the disclosure.

[0003g] In another aspect, the present disclosure relates to a cytokine receptor binding polypeptide of the formula VHH1-L_n-VHH2, wherein the cytokine receptor binding polypeptide comprises a first and second cytokine receptor subunits wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of a first cytokine receptor subunit and the other of VHH1 or VHH2 is a VHH that selectively binds to the extracellular

domain of a second cytokine receptor subunit, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0003h] In another aspect, the present disclosure relates to a nucleic acid sequence encoding a cytokine receptor binding polypeptide of the disclosure.

[0003i] In another aspect, the present disclosure relates to a bivalent IL6R/HSA binding polypeptide of the formula VHH1-L_n-VHH2, wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of IL6Ra and the other of VHH1 or VHH2 is a VHH that selectively binds human serum albumin, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0003j] In another aspect, the present disclosure relates to an anti-HSA VHH that selectively binds human serum albumin, wherein the a anti-HSA VHH comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to

the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0004] In one example, the present disclosure relates to modifications to the newly exposed C-terminal VTVSS (SEQ ID NO:1) amino acid sequence to eliminate or reduce recognition by and an immune response due to pre-existing antibodies.

[0005] In some examples, such amino acid sequence modifications to the C-terminal VTVSS (SEQ ID NO:1) amino acid sequence alters the neoepitope resulting from the newly exposed C-terminal VTVSS (SEQ ID NO:1) amino acid sequence on single-chain antibodies, such as a sdAb, VHH, multi-domain antibody comprising fusions of IgGs or HSA with another single-chain antibody, including bispecific antibodies comprising a single chain, an scFv, sdAb, Fab, diabody, cFab, or any other antigen binding domain or Fc- fusion protein that will expose a normally unexposed N- or C-terminal sequence.

[0006] In one example, the disclosure relates to an isolated single-domain antibody comprising a C-terminal modification, wherein the C-terminal modification comprises the substitution, addition, or deletion of at least one amino acid residue such that the modification to the single-domain antibody eliminates the interaction of at least one pre-existing antibody with the single-domain antibody without interfering with the binding of the single domain antibody with its target. In one example, the C-terminal amino acid sequence of the single-domain antibody is exposed such that the exposed C-terminal is available for interaction with the pre-existing antibody.

[0007] In one example, the present disclosure provides a polypeptide comprising a single domain antibody (sdAb) comprising a modified C-terminal amino acid sequence aligning to the endogenous sdAb amino acid residues $(T/L_{108})V_{109}T_{110}V_{111}S_{112}S_{113}$ (numbered according to the Kabat numbering scheme for human VH carboxy-terminal amino acid residues). In

accordance with the present disclosure, the modified amino acid sequence comprises the formula $X_{108}X_{109}X_{110}V_{111}X_{112}$ $X_{113}Y$, wherein:

X_{108} is selected from the group consisting of L, T, and Q;

X_{109} is selected from the group consisting of V, G, N, and L;

X_{110} is selected from the group consisting of T and Q;

X_{111} is V;

X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; and

X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent;

with the provisos that:

[0007a] when X_{109} is V, then X_{112} and X_{113} are not both S; and

[0007b] X_{112} and X_{113} are not both C; and

Y comprises a polypeptide comprising from 1-5 amino acids and wherein such amino acids are independently selected from the group consisting of A, G, S, T, L, and V, or is optionally absent.

[0008] In some examples, the sdAb is further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0009] In some examples of the disclosure, X_{108} is L; X_{109} is selected from the group consisting of V, G, and L; X_{110} is T; X_{112} is selected from the group consisting of S, T, and C; X_{113} is selected from the group consisting of S, T, C, and A; Y comprises a polypeptide comprising 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V; and wherein Y is optionally absent. In other examples, the amino acid sequence $X_{109}X_{110}V_{111}X_{112}$ X_{113} is $V_{109}T_{110}V_{111}S_{112}$ A_{113} and Y is AA.

[0010] In some examples, the sdAb comprises the amino acid sequence $X_{109}X_{110}V_{111}X_{112}$ X_{113} is selected from the group consisting of GTVSS (SEQ ID NO: 3), LTVSS EQ ID NO: 27), NTVSS (SEQ ID NO: 22), VTVCS (SEQ ID NO: 8), VTVSC (SEQ ID NO: 10), VTVTS (SEQ ID NO: 23), VTVTT (SEQ ID NO: 24).

[0011] In some examples, the polypeptides of the disclosure exhibit reduced binding to pre-existing antibodies.

[0012] In some examples, single domain antibody is a VHH. .

[0013] In another example, the disclosure relates to a polypeptide of the formula:

$$VHH1\text{-}L_n\text{-}VHH2$$

wherein VHH1 is a first VHH, L is a polypeptide linker comprising from 1-50 amino acids, n is 0 or 1, and VHH2 is a second VHH, which may be the same as or different from VHH1.

[0014] In some examples, VHH1 and VHH2 each independently bind to the extracellular domain of a cytokine receptor. In some examples, the cytokine receptors to which VHH1 and VHH2 bind is selected from the group consisting of IL2Rα, IL2Rβ, IL2Rγ, IL10Rα, IL10Rβ, IL12Rβ1, IL12Rβ2, IL18Rα, IL18Rβ, IL22R1, IL27Rα, gp130, IL23R, IL28Rα, IFNRγ1, IFNRγ2, IL21R. In some examples, VHH1 and VHH2 selectively bind to a pair

of cytokine receptors selected from the following pairs: IL10Rα/IL10Rβ, IL27Rα/gp130, IFNγR1/IFNγR2, IL10Rβ/IL28Rα, IL2Rβ/IL2Rγ, IL18Rα/IL18Rβ, IL22R1/IL10Rβ, IL10Rα/IL2Rγ, IL2Rβ/IL2Rγ, IL10R1/IFNRγ, IFNRγ/IL28Rα, IL12Rβ1/IL12Rβ2, IL12Rβ1/IL23R, and IL10Rα/IL2Rγ.

[0015] In the formula VHH1-L_n-VHH2 described above, the linker molecule L may be a GS linker. Various suitable GS linkers are described and exemplified herein.

[0016] In some examples, the polypeptide is PEGylated. In some examples, the polypeptide is conjugated to an Fc domain.

[0017] In some examples, the single-domain antibodies and antigen-binding fragments thereof can be conjugated to various other chemical entities, including antibody-drug conjugates (ADCs).

[0018] The single-domain antibodies or antigen-binding fragments described herein may also be used for diagnostic purposes.

[0019] The modified polypeptides of the present disclosure show reduced immunogenicity resulting from pre-existing antibodies when administered to a human subject, relative to a single-domain polypeptide having an endogenous heavy chain C-terminal amino acid sequence VTVSS (SEQ ID NO:1).

[0020] The present disclosure also includes methods of treating a mammalian subject suffering from a disease, disorder or condition, the method comprising the step of administering to the mammalian subject of a therapeutically effective amount of polypeptide of the present disclosure. In some examples, the present disclosure includes the administration of the polypeptides of the present disclosure, by the administration of an agent comprising a nucleic acid sequence encoding a polypeptide of the present disclosure with modifications to the C-terminus. In some examples, the present disclosure provides a method of reducing an immune response to single-domain antibodies. In some examples, the present disclosure includes methods of reducing the immunogenicity of single-domain antibodies resulting from pre-existing antibodies (an innate immune response) by use of a modified C-terminal amino acid sequence disclosed herein or reducing immunogenicity to B-cell derived antibodies (via acquired immunity), pharmaceutically acceptable formulations of the modified sdAbs and polypeptides described herein, nucleic acids encoding such sdAbs and polypeptides, vectors comprising such nucleic acids, and host cells comprising such vectors.

[0021] In some examples, a cytokine receptor binding polypeptide is providd of the formula VHH1-L_n-VHH2, wherein the cytokine receptor binding polypeptide comprises a first and second cytokine receptor subunits wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of a first cytokine receptor subunit and the other of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of a second cytokine receptor subunit, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X108 is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X112 and X113 are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

[0022] In some examples, the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ of VHH2 is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering scheme. In some examples, the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ in VHH2. In some examples, n=1 and L is a polypeptide linker of from 1-50 amino acids. In some examples, n=1 and L is a polypeptide linker selected from the group consisting of SEQ ID NOs: 25-48.

[0023] In some examples, the cytokine receptor binding polypeptide are modified to extend half-life in vivo. In some examples, the cytokine receptor binding polypeptide is PEGylated.

[0024] Also provided is a nucleic acid sequence encoding a cytokine receptor binding polypeptide as descried above or elsewhere herein.

[0025] In some examples, the cytokine receptor is the IL10 receptor, the first cytokine receptor subunit is IL10Ra and the second cytokine receptor subunit is IL10Rb. In some examples, the cytokine receptor binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-72. In some examples, the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to DR2485aa (SEQ ID NO:49). In some examples, the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-72. In some examples, the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 50-72. In some examples, the cytokine receptor is the IL18 receptor, the first cytokine receptor subunit is IL18Ra and the second cytokine receptor subunit is IL18Rb. In some examples, the cytokine receptor binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 111-134. In some examples, the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to R3905aa (SEQ ID NO:110). In some examples, the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 111-134. In some examples, the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 111-134.

[0026] In some examples, the cytokine receptor is the IL2 receptor, the first cytokine receptor subunit is IL2Rb (CD122) and the second cytokine receptor subunit is IL2Rg (CD132). In some examples, the cytokine receptor is the IL18 receptor, the first cytokine receptor subunit is IL18Ra and the second cytokine receptor subunit is IL18Rb. In some examples, the cytokine receptor is the IL27 receptor, the first cytokine receptor subunit is IL27Ra and the second cytokine receptor subunit is gp130. In some examples, the cytokine receptor is the IL22 receptor, the first cytokine receptor subunit is IL22Ra and the second cytokine receptor subunit is IL12Rb. In some examples, the cytokine receptor is the IL4 receptor, the first cytokine receptor subunit is IL4Ra and the second cytokine receptor subunit is IL2Rg (CD132). In some examples, the cytokine receptor is the IL7 receptor, the first cytokine receptor subunit is IL7Ra and the second cytokine receptor subunit is IL2Rg (CD132).

In some examples, the cytokine receptor is the IL9 receptor, the first cytokine receptor subunit is IL9Ra and the second cytokine receptor subunit is IL2Rg (CD132In some examples, the cytokine receptor is the IL12 receptor, the first cytokine receptor subunit is IL12Ra and the second cytokine receptor subunit is IL12Rb.

[0027] Also provided is a bivalent IL6R/HSA binding polypeptide of the formula VHH1-Ln-VHH2, wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of IL6Ra and the other of VHH1 or VHH2 is a VHH that selectively binds human serum albumin, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme. In some examples, the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ of VHH2 is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering scheme. In some examples, the bivalent IL6R/HSA binding polypeptide exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ in VHH2. In some examples, n=1 and L is a polypeptide linker of from 1-50 amino acids. In some examples, n=1 and L is a polypeptide linker selected from the group consisting of SEQ ID NOs: 25-48.

[0028] In some examples, the bivalent IL6R/HSA binding polypeptide is modified to extend half-life in vivo. In some examples, the bivalent IL6R/HSA binding polypeptide is PEGylated. In some examples, the bivalent IL6R/HSA binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid

sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-109. In some examples, the bivalent IL6R/HSA binding polypeptide exhibits immunogenicity relative to DR2514aa (SEQ ID NO:84). In some examples, the bivalent IL6R/HSA binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-109.

[0029] Also provided is an anti-HSA (human serum albumin) VHH that selectively binds human serum albumin, wherein the a anti-HSA VHH comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme. In some examples, the amino acid sequence $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering schemeIn some examples, the anti-HSA VHH exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$. In some examples, the anti-HSA is modified to extend half-life in vivo. In some examples, the anti-HSA is PEGylated. In some examples, the anti-HSA comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 160-194. In some examples, the anti-HSA VHH exhibits reduced immunogenicity relative to a polypeptide of SEQ ID NO:159. In some examples, the anti-HSA comprises an amino acid sequence an amino acid sequence selected from the group consisting of SEQ

CLAIMS

1. A polypeptide comprising a single-domain antibody (sdAb), the sdAb comprising a modified C-terminal amino acid sequence corresponding to the C-terminal endogenous sdAb amino acid residues (T/L_{108})$V_{109}T_{110}V_{111}S_{112}S_{113}$, as numbered according to the Kabat numbering scheme, wherein the modified amino acid sequence comprises the formula $X_{108}X_{109}X_{110}V_{111}X_{112}$ $X_{113}Y$, wherein:

X_{108} is selected from the group consisting of L, T, and Q;

X_{109} is selected from the group consisting of L, V, G, and N;

X_{110} is selected from the group consisting of T and Q;

X_{111} is V;

X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; and

X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that:

(a) when X_{109} is V, then X_{112} and X_{113} are not both S; and

(b) X_{112} and X_{113} are not both C; and

Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the sdAb is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

2. The polypeptide of claim 1, wherein

X_{108} is L;

X_{109} is selected from the group consisting of L, V, and G;

X_{110} is T;

X_{112} is selected from the group consisting of S, T, and C;

X_{113} is selected from the group consisting of S, T, C, and A;

Y is absent or is a dipeptide of the amino acid sequence AA.

3. The polypeptide of claim 2, wherein the amino acid sequence $X_{109}X_{110}V_{111}X_{112}$ X_{113} is selected from the group consisting of LTVSS (SEQ ID NO: 27), GTVSS (SEQ ID NO: 3),

VTVCS (SEQ ID NO: 8), VTVSC (SEQ ID NO: 10), NTVSS (SEQ ID NO: 22), VTVTS (SEQ ID NO: 23), and VTVTT (SEQ ID NO: 24).

4. The polypeptide of claims 1-3, wherein Y is AA.

5. The polypeptide of claim 2, wherein the amino acid sequence $X_{109}X_{110}V_{111}X_{112}$ X_{113} is VTVSA (SEQ ID NO: 6), and Y is AA.

6. The polypeptide of claims 1-5, wherein the sdAb is a fusion protein.

7. The polypeptide of claim 6, wherein the fusion protein comprises a first VHH joined to a second VHH.

8. The polypeptide of claim 7, wherein the first VHH has a C-terminus joined to an N-terminus of the second VHH.

9. A polypeptide of the formula VHH1-L_n-VHH2, wherein VHH1 is a VHH, L is a polypeptide linker comprising from 1-50 amino acids, n is 0 or 1, and VHH2 is a VHH of claims 1-5.

10. The polypeptide of claim 9, wherein the VHH1 and VHH2 each independently bind to the extracellular domain of a cytokine receptor.

11. The polypeptide of claim 9, wherein the cytokine receptor is selected from the group consisting of IL2Rα, IL2Rβ, IL2Rγ, IL10Rα, IL10Rβ, IL12Rβ1, IL12Rβ2, IL18Rα, IL18Rβ, IL22R1, IL27Rα, gp130, IL23R, IL28Rα, IFNRγ1, IFNRγ2, and IL21R.

12. The polypeptide of claim 11, wherein the VHH1 and VHH2 selectively bind to a pair of cytokine receptors selected from the following sets: IL10Rα/IL10Rβ, IL27Rα/gp130, IFNγR1/IFNγR2, IL10Rβ/IL28Rα, IL2Rβ/IL2Rγ, IL18Rα/IL18Rβ, IL22R1/IL10Rβ, IL10Rα/IL2Rγ, IL2Rβ/IL2Rγ, IL10R1/IFNRγ, IFNRγ/IL28Rα, IL12Rβ1/IL12Rβ2, IL12Rβ1/IL23R, IL12Rβ2/gp130, and IL10Rα/IL2Rγ.

13. The polypeptide of any one of claims 9-12, wherein L is a linker comprising the amino acids G and S.

14. The polypeptide of any one of claims 1-13 wherein the polypeptide is PEGylated.

15. The polypeptide of any one of claims 1-13 wherein the polypeptide is conjugated to an Fc domain.

16. The polypeptide of any one of claims 1-15 wherein the polypeptide has reduced immunogenicity to pre-existing antibodies of a human subject when administered to the human subject relative to a sdAb polypeptide comprising the corresponding native human sequence VTVSS (SEQ ID NO:1) (SEQ ID NO: 24).

17. A pharmaceutical composition comprising a polypeptide of any one of claims 1-16.

18. A nucleic acid encoding a polypeptide of any one of claims 1-16.

19. A vector comprising the nucleic acid of claim 18.

20. A host cell comprising the vector of claim 19.

21. A cytokine receptor binding polypeptide of the formula VHH1-L_n-VHH2, wherein the cytokine receptor binding polypeptide comprises a first and second cytokine receptor subunits wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of a first cytokine receptor subunit and the other of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of a second cytokine receptor subunit, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising

from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

22. The cytokine receptor binding polypeptide of claim 21 wherein the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ of VHH2 is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering scheme.

23. The cytokine receptor binding polypeptide of claims 21 or 22 wherein the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ in VHH2.

24. The cytokine receptor binding polypeptide of any one of claims 21-23 wherein n=1 and L is a polypeptide linker of from 1-50 amino acids.

25. The cytokine receptor binding polypeptide of any one of claims 21-24, n=1 and L is a polypeptide linker selected from the group consisting of SEQ ID NOs: 25-48.

26. The cytokine receptor binding polypeptide of any one of claims 21-25 modified to extend half-life in vivo.

27. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor binding polypeptide is PEGylated.

28. A nucleic acid sequence encoding a cytokine receptor binding polypeptide of any one of claim 21-26.

29. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL10 receptor, the first cytokine receptor subunit is IL10Ra and the second cytokine receptor subunit is IL10Rb.

30. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-72.

31. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to DR2485aa (SEQ ID NO:49).

32. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-72.

33. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 50-72.

34. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL18 receptor, the first cytokine receptor subunit is IL18Ra and the second cytokine receptor subunit is IL18Rb.

35. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 111-134.

36. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding polypeptide exhibits reduced immunogenicity relative to R3905aa (SEQ ID NO:110).

37. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 111-134.

38. The cytokine receptor binding polypeptide of claim 29 wherein the cytokine receptor binding protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 111-134.

39. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein cytokine receptor is the IL2 receptor, the first cytokine receptor subunit is IL2Rb (CD122) and the second cytokine receptor subunit is IL2Rg (CD132).

40. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL18 receptor, the first cytokine receptor subunit is IL18Ra and the second cytokine receptor subunit is IL18Rb.

41. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL27 receptor, the first cytokine receptor subunit is IL27Ra and the second cytokine receptor subunit is gp130.

42. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL22 receptor, the first cytokine receptor subunit is IL22Ra and the second cytokine receptor subunit is IL12Rb.

43. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL4 receptor, the first cytokine receptor subunit is IL4Ra and the second cytokine receptor subunit is IL2Rg (CD132).

44. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL7 receptor, the first cytokine receptor subunit is IL7Ra and the second cytokine receptor subunit is IL2Rg (CD132).

45. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL9 receptor, the first cytokine receptor subunit is IL9Ra and the second cytokine receptor subunit is IL2Rg (CD132).

46. The cytokine receptor binding polypeptide of any one of claims 21-26 wherein the cytokine receptor is the IL12 receptor, the first cytokine receptor subunit is IL12Ra and the second cytokine receptor subunit is IL12Rb.

47. A bivalent IL6R/HSA binding polypeptide of the formula VHH1-L_n-VHH2, wherein one of VHH1 or VHH2 is a VHH that selectively binds to the extracellular domain of IL6Ra and the other of VHH1 or VHH2 is a VHH that selectively binds human serum albumin, L is a polypeptide linker, n =0 (absent) or (1) present, and wherein the VHH2 comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

48. The bivalent IL6R/HSA binding polypeptide of claim 47 wherein the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ of VHH2 is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering scheme.

49. The bivalent IL6R/HSA binding polypeptide of claim 47 or 48 wherein the bivalent IL6R/HSA binding polypeptide exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ in VHH2.

50. The bivalent IL6R/HSA binding polypeptide of any one of claims 47-49, wherein n=1 and L is a polypeptide linker of from 1-50 amino acids.

51. The bivalent IL6R/HSA binding polypeptide of any one of claims 47-50, wherein n=1 and L is a polypeptide linker selected from the group consisting of SEQ ID NOs: 25-48.

52. The bivalent IL6R/HSA binding polypeptide of any one of claims 47-51, wherein polypeptide is modified to extend half-life in vivo.

53. The bivalent IL6R/HSA binding polypeptide of any one of claims 47-52 wherein the bivalent IL6R/HSA binding polypeptide is PEGylated.

54. The bivalent IL6R/HSA binding polypeptide of any one of claims 47-52 wherein the bivalent IL6R/HSA binding polypeptide comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-109.

55. The bivalent IL6R/HSA binding polypeptide of claim 54 wherein the bivalent IL6R/HSA binding polypeptide exhibits immunogenicity relative to DR2514aa (SEQ ID NO:84).

56. The bivalent IL6R/HSA binding polypeptide of claim 54 wherein the bivalent IL6R/HSA binding polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85-109.

57. An anti-HSA VHH that selectively binds human serum albumin, wherein the a anti-HSA VHH comprises an amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$, the amino acids numbered according to the Kabat numbering scheme, wherein X_{108} is selected from the group consisting of L, T, and Q; X_{109} is selected from the group consisting of V, G, N, and L;X_{110} is selected from the group consisting of T and Q; X_{111} is V; X_{112} is selected from the group consisting of S, C, T, A, and G, or optionally absent; X_{113} is selected from the group consisting of S, C, A, G, and T, or optionally absent; with the provisos that: (a) if X_{109} is V, then X_{112} and X_{113} are not both S; and (b) X_{112} and X_{113} are not both C; and Y comprises a polypeptide comprising from 1-5 amino acids independently selected from the group consisting of A, G, S, T, L, and V, or Y is optionally absent; and wherein the polypeptide is optionally

further modified to comprise an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, numbered in accordance with the Kabat numbering scheme.

58. The anti-HSA VHH of claim 57, wherein the amino acid sequence $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$ is selected from the group consisting of SEQ ID NOs:2-24, and optionally further comprises an amino acid substitution selected from the group consisting of L11S, L11Q, L11G, and P14A, amino acid residues numbered in accordance with the Kabat numbering scheme.

59. The anti-HSA VHH of claim 57 or 58, wherein the anti-HSA VHH exhibits reduced immunogenicity relative to the polypeptide absent the amino acid sequence of the formula $X_{108}V_{109}T_{110}V_{111}S_{112}S_{113}Y$.

60. The anti-HSA VHH of any one of claims 57-59 wherein the anti-HSA is modified to extend half-life in vivo.

61. The anti-HSA VHH of any one of claims 57-60 wherein the anti-HSA is PEGylated.

62. The anti-HSA VHH of any one of claims 57-61 wherein the anti-HSA comprises an amino acid sequence having at least 95%, alternatively at least 96%, alternatively at least 97%, alternatively at least 98%, alternatively at least 99%, or alternatively 100% amino acid sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 160-194.

63. The anti-HSA VHH of claim 62 wherein the anti-HSA VHH exhibits reduced immunogenicity relative to a polypeptide of SEQ ID NO:159.

64. The anti-HSA VHH of claim 62 wherein the anti-HSA comprises an amino acid sequence an amino acid sequence selected from the group consisting of SEQ ID NOs: 160-194.