CD3 BINDING POLYPEPTIDES

[001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 62/221,190, filed on September 21, 2015. The contents of this application are herein incorporated by reference in their entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[002] The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: APVO_052_01WO_SeqList_ST25.txt, date recorded: September 21, 2016, file size 544 kilobytes).

FIELD OF THE DISCLOSURE

[003] The present disclosure relates to molecules that specifically bind to CD3, which may have at least one humanized CD3-binding domain. A protein therapeutic binding to CD3 may be a monospecific protein therapeutic or a multispecific protein therapeutic. A multspecific protein therapeutic may bind both a tumor antigen and CD3 subunits of the T-cell receptor complex on T-cells to induce target-dependent T-cell cytotoxicity, activation and proliferation.

BACKGROUND OF THE DISCLOSURE

[004] Targeting the T-cell receptor complex (TCR) on human T-cells with anti-CD3 antibodies has been proposed for treatment of autoimmune disease and related disorders, such as for treatment of organ allograft rejection. In addition to monospecific therapeutics that target CD3, multispecific polypeptides that bind selectively to both T-cells and tumor cells could offer a mechanism to redirect T-cell cytotoxicity towards the tumor cells. Such multispecific polypeptides may be useful for treatment of cancer.

[005] Clinical use of some anti-CD3 antibodies has been hampered by serious side effects. For example, OKT3, a mouse monoclonal antibody specific for human CD3, induced T-cell proliferation and cytokine production in vitro and led to a large scale release of cytokine *in vivo* (Hirsch et al. (1989) J. Immunol 142: 737-43). The cytokine release (also referred to as "cytokine storm") in turn led to a "flu-like" syndrome, characterized by fever, chills, headaches, nausea, vomiting, diarrhea, respiratory distress, septic meningitis and hypotension (Chatenoud (2003) Nature Reviews 3:123-132).

[006] There is a need for CD3-binding molecules that have improved thermal stability with a favorable manufacturability profile and reduced adverse effects.

SUMMARY OF THE DISCLOSURE

[007] The disclosure encompasses CD3-binding domains and polypeptides that have an advantageous manufacturability profile. Polypeptides comprising CD3-binding domains disclosed herein may be thermally stable. In some cases, a polypeptide has an improved thermal stability compared to another CD3-binding polypeptide. CD3-binding domains and polypeptides disclosed herein may have reduced side effects (for example, may lead to release of low levels of cytokines when administered to a subject).

[008] In certain embodiments, the disclosure relates to a CD3-binding domain that binds specifically to human CD3 and that comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region; wherein the immunoglobulin light chain variable region comprises an amino acid sequence that is (a) at least about 93% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:88; or (b) at least about 94% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:89; and wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence that is at least about 82% identical, at least about 85% identical, at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:86. A CD3-binding domain may comprise an amino acid sequence that is at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:83 or SEQ ID NO:84. A CD3-binding domain may comprise SEQ ID NO:83 or SEQ ID NO:84.

[009] In one embodiment, a CD3-binding domain comprises an immunoglobulin light chain variable region that comprises an LCDR1 amino acid sequence of SEQ ID NO:94, an LCDR2 amino acid sequence of SEQ ID NO:95, and an LCDR3 amino acid sequence of SEQ ID NO:96 and an immunoglobulin heavy chain variable region that comprises an HCDR1 amino acid sequence of SEQ ID NO:91, an HCDR2 amino acid sequence of SEQ ID NO:92, and an HCDR3 amino acid sequence of SEQ ID NO:93. In another embodiment, a CD3-binding domain comprises an immunoglobulin light chain variable region that comprises an LCDR1 amino acid sequence of SEQ ID NO:202, an LCDR2 amino acid sequence of SEQ ID NO:203,

and an LCDR3 amino acid sequence of SEQ ID NO:204 and an immunoglobulin heavy chain variable region that comprises an HCDR1 amino acid sequence of SEQ ID NO:199, an HCDR2 amino acid sequence of SEQ ID NO:200, and an HCDR3 amino acid sequence of SEQ ID NO:201.

[0010] In certain aspects, a CD3-binding domain may comprise an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region that comprise framework regions and at least one of the immunoglobulin light chain variable region and the immunoglobulin heavy chain variable region may be humanized. In one embodiment, an immunoglobulin light chain variable region comprises framework regions based on the human IGKV3D-20*1 germline amino acid sequence. In another embodiment, an immunoglobulin heavy chain variable region comprises framework regions based on the human IGHV1-69*02 germline amino acid sequence.

[0011] In some embodiments, the amino acid residue at position 52 according to the IMGT numbering system of the immunoglobulin light chain variable region of a CD3-binding domain is arginine and/or the amino acid residue at position 53 according to the IMGT numbering system of the immunoglobulin light chain variable region of a CD3-binding domain is tryptophan. The amino acid residue at position 27 according to the IMGT numbering system of the immunoglobulin heavy chain variable region of a CD3-binding domain may be tyrosine. In some embodiments, a CD3-binding domain comprises one or more of the following: (a) the amino acid residue at position 9 according to the IMGT numbering system of the immunoglobulin heavy chain variable region is proline; (b) the amino acid residue at position 53 according to the IMGT numbering system of the immunoglobulin heavy chain variable region is isoleucine; and (c) the amino acid residue at position 21 according to the IMGT numbering system of the immunoglobulin light chain variable region is methionine. The amino acid residue at position 87 according to the IMGT numbering system of the immunoglobulin heavy chain variable region of a CD3-binding domain may be tyrosine. The amino acid residue at position 86 according to the IMGT numbering system of the immunoglobulin heavy chain variable region of a CD3-binding domain may be aspartic acid. In one embodiment, the amino acid residue at position 86 according to the IMGT numbering system of the immunoglobulin heavy chain variable region of a CD3-binding domain is aspartic acid and the amino acid residue at position 87 according to the IMGT numbering system of the immunoglobulin heavy chain variable region of a CD3-binding domain is tyrosine.

[0012] The disclosure encompasses a CD3-binding domain that is a single chain variable fragment (scFv). In some aspects, an scFv may comprise a linker between the heavy chain

variable region and the light chain variable region. In one embodiment, a linker between the heavy chain variable region and the light chain variable region comprises the amino acid sequence QRHNNSSLNTGTQMAGHSPNS (SEQ ID NO:148). In some embodiments, the heavy chain variable region of an scFv is amino-terminal to the light chain variable region of the scFv. In other embodiments, the light chain variable region of an scFv is amino-terminal to the heavy chain variable region of the scFv.

[0013] The disclosure encompasses a CD3-binding domain that has a thermal stability that is increased at least about 10% when compared to the thermal stability of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. The thermal transition midpoint (Tm) of a CD3-binding domain may be increased at least about 3°C, at least about 4°C, at least about 5°C, or at least about 6°C increased and up to about 20°C when compared to the Tm of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. The thermal transition midpoint of a CD3-binding domain may be at least about 54°C, at least about 55°C, at least about 56°C, or at least about 57°C and up to about 72°C. The thermal stability or the thermal transition midpoint of a CD3-binding domain may be measured by differential scanning calorimetry or differential scanning fluorimetry.

[0014] A CD3-binding domain as disclosed herein may have storage stability that is increased at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% and up to about 100% when compared to the storage stability of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. Storage stability may be measured after a CD3-binding domain is stored in PBS at about 25°C. In one embodiment, a CD3-binding domain is stable in storage in PBS at about 25°C for at least about 6 days, at least about 10 days, or at least about 13 days and up to about 90 days.

[0015] In some aspects, a CD3-binding domain as disclosed herein has a level of high molecular weight aggregates produced during recombinant expression that is at least about 5%, at least about 10%, at least about 20% decreased, at least about 30% decreased and up to about 50% decreased when compared to the level of high molecular weight aggregates produced during recombinant expression of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87.

[0016] The disclosure also relates to a CD3-binding domain that binds to human CD3 with an EC50 of about 10 nM or lower. In some embodiments, a CD3-binding domain of the disclosure may also bind specifically to cynomolgus CD3. For example, a CD3-binding domain may bind to cynomolgus CD3 with an EC50 of about 30 nM or lower.

[0017] The disclosure encompasses a CD3-binding domain that binds specifically to human CD3 and that comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region, wherein (a) the immunoglobulin light chain variable region comprises an LCDR1 amino acid sequence of SEQ ID NO:94, an LCDR2 amino acid sequence of SEQ ID NO:95, and an LCDR3 amino acid sequence of SEQ ID NO:96 and wherein the immunoglobulin heavy chain variable region comprises an HCDR1 amino acid sequence of SEQ ID NO:91, an HCDR2 amino acid sequence of SEQ ID NO:92, and an HCDR3 amino acid sequence of SEQ ID NO:93; or (b) the immunoglobulin light chain variable region comprises an LCDR1 amino acid sequence of SEQ ID NO:202, an LCDR2 amino acid sequence of SEQ ID NO:203, and an LCDR3 amino acid sequence of SEQ ID NO:204 and wherein the immunoglobulin heavy chain variable region comprises an HCDR1 amino acid sequence of SEQ ID NO:199, an HCDR2 amino acid sequence of SEQ ID NO:200, and an HCDR3 amino acid sequence of SEQ ID NO:201; and wherein the CD3-binding domain has any one or more of the properties described herein. For example, (i) the thermal transition midpoint of the CD3-binding domain (or a protein comprising the CD3-binding domain) is at least about 54°C, at least about 55°C, at least about 56°C, or at least about 57°C and up to about 72°C; (ii) the CD3-binding domain (or a protein comprising the CD3-binding domain) is stable in storage in PBS at about 25°C for at least about 6 days, at least about 10 days, or at least about 13 days and up to about 90 days; (iii) the CD3-binding domain (or a protein comprising the CD3-binding domain) binds to human CD3 with an EC50 of about 10 nM or lower; and (iv) the CD3-binding domain (or a protein comprising the CD3-binding domain) binds to cynomolgus CD3 with an EC50 of about 30 nM or lower.

[0018] The disclosure also relates to a CD3-binding polypeptide comprising any of the CD3-binding domains described herein. In some variations, a CD3-binding polypeptide may comprise an immunoglobulin constant region. This immunoglobulin constant region may comprise immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD. In some embodiments, an immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions L234A, L235A, G237A, and K322A, according to the EU numbering system. In certain embodiments, an immunoglobulin constant region comprises a human IgG1 CH2 domain comprising one or more of the substitutions L234A, L235A, G237A, and K322A,

according to the EU numbering system. In some embodiments, a CD3-binding polypeptide when bound to a CD3 protein on a T cell does not induce or induces a minimally detectable cytokine release from said T cell. In certain aspects, a CD3-binding protein or polypeptide exhibits reduced cytokine release in a patient as compared to the cytokine released when anti-CD3 antibody OKT3 is administered to a patient. In some cases, a CD3-binding polypeptide may induce T-cell activation or T-cell proliferation.

[0019] In certain aspects, a CD3-binding polypeptide further comprises a second binding domain. The second binding domain may be a single chain variable fragment (scFv). In some embodiments, the second binding domain binds or interacts with a tumor associated antigen (e.g., PSMA, CD19, CD20, CD37, CD38, CD123, Her2, ROR1, RON, glycoprotein A33 antigen (gpA33) or CEA).

[0020] The disclosure further encompasses a CD3-binding polypeptide comprising: (i) a CD3-binding domain and (ii) a second binding domain. In some embodiments, a CD3-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus or in order from carboxyl-terminus to amino-terminus, (i) a CD3-binding domain, (ii) a hinge region and (iii) an immunoglobulin constant region. In some embodiments, a CD3-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus, (i) a second binding domain, (ii) a hinge region, (iii) an immunoglobulin constant region, (iv) a carboxyl-terminus linker, and (v) a CD3-binding domain. In other embodiments, a CD3-binding polypeptide comprises, in order from carboxyl-terminus to amino-terminus, (i) a second binding domain, (ii) a hinge region, (iii) an immunoglobulin constant region, (iv) an amino-terminus linker, and (v) a CD3-binding domain. In certain variations, the first and/or the second binding domain is an scFv. Non-limiting examples of carboxyl-terminus and amino-terminus linkers include flexible linkers comprising glycine-serine (e.g., (Gly_4Ser)) repeats and linkers derived from (i) a stalk region of a type II C lectin or (ii) an immunoglobulin hinge region. In certain aspects, a carboxyl-terminus linker (or an amino-terminus linker) comprises or consists of SEQ ID NO:196. In some aspects, the disclosure relates to a CD3-binding polypeptide (e.g., multispecific), wherein (i) the CD3-binding domain comprises (a) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (b) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3; and (ii) the second binding domain comprises (a) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (b) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

[0021] The disclosure encompasses a CD3-binding polypeptide that induces redirected T-cell cytotoxicity (RTCC). For example, a CD3-binding polypeptide may induce RTCC with an EC50

of about 30 pM or lower. In some embodiments, a CD3-binding polypeptide does not exhibit or exhibits minimal antibody-dependent cell-mediated cytotoxicity (ADCC) activity and/or complement-dependent cytotoxicity (CDC) activity. In certain aspects, null ADCC and/or CDC activity is accomplished through mutations in the hinge region and Ig constant region (e.g, Fc).

[0022] A CD3-binding polypeptide may further comprise an immunoglobulin heterodimerization domain. In some embodiments, an immunoglobulin heterodimerization domain comprises an immunoglobulin CH1 domain or an immunoglobulin CL domain. In some aspects, a CD3-binding polypeptide is a heterodimeric CD3-binding protein comprising (i) a first polypeptide chain comprising, in order from amino-terminus to carboxyl-terminus or from carboxyl-terminus to amino-terminus, (a) a CD3-binding domain that specifically binds human CD3, (b) a first hinge region, (c) a first immunoglobulin constant region, and (d) a first immunoglobulin heterodimerization domain; and (ii) a second polypeptide chain comprising, in order from amino-terminus to carboxyl-terminus or from carboxyl-terminus to amino-terminus, (a') a second hinge region, (b') a second immunoglobulin constant region, and (c') a second immunoglobulin heterodimerization domain that is different from the first immunoglobulin heterodimerization domain of the first single chain polypeptide, wherein the first and second immunoglobulin heterodimerization domains associate with each other to form a heterodimer. In one embodiment, the first immunoglobulin heterodimerization domain comprises an immunoglobulin CH1 domain and the second immunoglobulin heterodimerization domain comprises an immunoglobulin CL domain, or wherein the first immunoglobulin heterodimerization domain comprises an immunoglobulin CL domain and the second immunoglobulin heterodimerization domain comprises an immunoglobulin CH1 domain. At least one of the first and second immunoglobulin constant regions may comprise immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD or any combination thereof; an immunoglobulin CH3 domain of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM or any combination thereof; or immunoglobulin CH3 and CH4 domains of IgE, IgM or a combination thereof. In some aspects, the second polypeptide chain of a heterodimeric CD3-binding protein may further comprise a second binding domain. In certain embodiments, the second binding domain may be amino-terminal or carboxy-terminal to the second hinge region.

[0023] In some variations, a CD3-binding polypeptide may be a bispecific single chain antibody molecule comprising a CD3-binding domain and a second binding domain, wherein the binding domains are arranged in the order VH CD3-VL CD3-VH second binding domain-VL second binding domain or VL CD3-VH CD3-VH second binding domain -VL second binding domain or

VH second binding domain-VL second binding domain-VH CD3-VL CD3 or VH second binding domain-VL second binding domain-VL CD3-VH CD3.

[0024] The disclosure also relates to an isolated nucleic acid molecule encoding a CD3-binding domain or a CD3-binding polypeptide described herein or a portion of said CD3-binding domain or polypeptide. In some aspects, the disclosure encompasses an expression vector comprising a nucleic acid segment encoding a CD3-binding domain or a CD3-binding polypeptide described herein, wherein the nucleic acid segment is operatively linked to regulatory sequences suitable for expression of the nucleic acid segment in a host cell. A recombinant host cell comprising an expression vector is included in the disclosure.

[0025] The disclosure encompasses an expression vector comprising first and second expression units, wherein the first and second expression units respectively comprise first and second nucleic acid segments encoding the first and second polypeptide chains of a heterodimeric CD3-binding polypeptide, and wherein the first and second nucleic acid segments are operably linked to regulatory sequences suitable for expression of the nucleic acid segments in a host cell. A recombinant host cell comprising an expression vector comprising first and second expression units is part of the disclosure.

[0026] The disclosure further relates to a method for producing a CD3-binding polypeptide, the method comprising: culturing a recombinant host cell comprising an expression vector described herein under conditions whereby the nucleic acid segment is expressed, thereby producing the CD3-binding polypeptide. In some embodiments, a method for producing a heterodimeric CD3-binding protein comprises: culturing a recombinant host cell comprising first and second expression units, wherein the first and second expression units respectively comprise first and second nucleic acid segments encoding the first and second polypeptide chains of a heterodimeric CD3-binding protein, wherein the first and second nucleic acid segments are operably linked to regulatory sequences suitable for expression of the nucleic acid segments in a host cell, and wherein said culturing is under conditions whereby the first and second nucleic acid segments are expressed and the encoded polypeptide chains are produced as the heterodimeric CD3-binding protein. These methods may further comprise recovering the CD3-binding polypeptide or the heterodimeric CD3-binding protein.

[0027] The disclosure encompasses a pharmaceutical composition comprising a CD3-binding polypeptide disclosed herein and a pharmaceutically acceptable carrier, diluent, or excipient. The disclosure also relates to a method for inducing redirected T-cell cytotoxicity (RTCC) against a cell expressing a tumor associated antigen, the method comprising: contacting said tumor associated antigen-expressing cell with a CD3-binding polypeptide, wherein said

contacting is under conditions whereby RTCC against the tumor associated antigen-expressing cell is induced. One aspect of the disclosure includes a method for inhibiting tumor growth in a subject in need thereof, comprising administering a therapeutically effective amount of a CD3-binding polypeptide or a pharmaceutical composition described herein to the subject. The disclosure encompasses a method for treating cancer or an autoimmune disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a CD3-binding polypeptide or a pharmaceutical composition described herein to the subject. Non-limiting examples of cancer that may be treated by methods and CD3-binding polypeptides described herein include prostate cancer, colorectal cancer, renal cell carcinoma, bladder cancer, salivary gland cancer, pancreatic cancer, ovarian cancer, non-small cell lung cancer, breast cancer (e.g., triple negative breast cancer). melanoma, adrenal cancer, mantle cell lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, Non-Hodgkin's lymphoma, acute myeloid leukemia (AML), B-lymphoid leukemia, blastic plasmocytoid dendritic neoplasm (BPDCN), and hairy cell leukemia.

[0028] The disclosure encompasses a CD3-binding domain that binds specifically to human CD3 and that comprises SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, or 60.

[0029] The disclosure also relates to a CD3-binding protein that is a dimer of two identical polypeptides, wherein each polypeptide is any of the CD3-binding polypeptides disclosed herein.

[0030] These and other embodiments and/or other aspects of the disclosure will become evident upon reference to the following detailed description of the disclosure and the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Figure 1 (top panel) is a graph showing the results of a flow cytometry study measuring the binding of CD3-binding domain constructs to Jurkat T-cells. Mean fluorescence intensity (MFI) of bound molecules on live cells is shown on the y-axis. Concentration (nM) of the CD3-binding domain constructs is shown on the x-axis. The table (bottom panel) shows the EC_{50} values obtained from the data in the graph.

[0032] Figure 2 (top panel) is a graph showing the results of a flow cytometry study measuring the binding of CD3-binding domain constructs to a subclone of the Jurkat T-cell line with higher levels of CD3 expression. Mean fluorescence intensity (MFI) of bound molecules on live cells is

shown on the y-axis. Concentration (nM) of the CD3-binding domain constructs is shown on the x-axis. The table (bottom panel) shows the EC_{50} values obtained from the data in the graph.

[0033] Figure 3 is a graph showing the results of a differential scanning fluorimetry study performed with CD3-binding domain constructs. The figure also shows the thermal transition midpoint (Tm) values obtained from the data in the graph.

[0034] Figure 4 is a graph showing the results of a flow cytometry study measuring the binding of CD3-binding domain constructs to a subclone of the Jurkat T-cell line with higher levels of CD3 expression. Mean fluorescence intensity (MFI) of bound molecules on live cells is shown on the y-axis. Concentration (nM) of the CD3-binding domain constructs is shown on the x-axis.

[0035] Figure 5 is a graph showing the results of a flow cytometry study measuring the binding of CD3-binding domain constructs to a subclone of the Jurkat T-cell line with higher levels of CD3 expression. Mean fluorescence intensity (MFI) of bound molecules on live cells is shown on the y-axis. Concentration (nM) of the CD3-binding domain constructs is shown on the x-axis.

[0036] Figure 6 (top panel) is a graph showing the results of a chromium-51 release assay measuring the effectiveness of bispecific anti-PSMA and anti-CD3 constructs at inducing target-dependent T-cell cytotoxicity with human PBMC in 4 hours against C4-2B cells. Percent specific lysis relative to a total lysis control is shown on the y-axis. Concentration (pM) of the CD3-binding domain constructs is shown on the x-axis. The table (bottom panel) shows the EC_{50} values obtained from the data in the graph.

[0037] Figure 7A and **Figure 7B** are graphs showing the results of a flow cytometry study measuring the binding of CD3-binding domain constructs to Cynomolgus T-cells. Mean fluorescence intensity (MFI) of bound molecules on live cells is shown on the y-axis of each graph. Concentration (nM) of the CD3-binding domain constructs is shown on the x-axis of each graph.

[0038] Figure 8A and **Figure 8B** are graphs showing the results of a chromium-51 release assay measuring the effectiveness of CD3-binding domain constructs at inducing target-dependent T-cell cytotoxicity with Cynomolgus PBMC in 4 hours against C4-2B cells. Percent specific lysis relative to a total lysis control is shown on the y-axis of each graph. Concentration (pM) of the CD3-binding domain constructs is shown on the x-axis of each graph.

[0039] Figure 9 is a graph showing the results of a flow cytometry study measuring the binding of bispecific anti-CD37 and anti-CD3 constructs to Cynomolgus T-cells. Mean fluorescence intensity (MFI) of bound molecules on live cells is shown on the y-axis. Concentration (nM) of

the CD3-binding domain constructs is shown on the x-axis. TSC394 DY refers to the TSC394 construct including the E86D and F87Y substitutions.

[0040] Figure 10 (top panel) is a graph showing the results of a chromium-51 release assay measuring the effectiveness of bispecific anti-CD37 and anti-CD3 constructs at inducing target-dependent T-cell cytotoxicity with Cynomolgus PBMC in 4 hours against Ramos cells. Percent specific lysis relative to a total lysis control is shown on the y-axis of each graph. Concentration (pM) of the CD3-binding domain constructs is shown on the x-axis of each graph. The table (bottom panel) shows the EC_{50} values obtained from the data in the graph. TSC394 DY refers to the TSC394 construct including the E86D and F87Y substitutions.

[0041] Figure 11 is a graph showing the results of a study measuring the storage stability of CD3-binding domain constructs at 25°C over the number of days specified on the x-axis. CAS105 is a control construct comprising the DRA222 CD3-binding domain.

[0042] Figure 12 is a graph showing the results of a study measuring the serum stability in human serum of anti-ROR1 x anti-CD3 bispecific molecules over the number of days specified on the x-axis.

[0043] Figure 13 shows an alignment of the amino acid sequences of the DRA222 scFv (SEQ ID NO:85), TSC455 scFv (SEQ ID NO:83), and TSC456 scFv (SEQ ID NO:84). The sequences of these constructs are also shown in Table 14.

[0044] Figure 14 is a graph showing the results of a study measuring serum concentrations of anti-PSMA X anti-CD3 bispecific binding molecules in BALB/c mice as a function of time. Results are expressed as mean serum concentration (µg/mL) over time for each of the treatment groups. Each point shows the mean (+standard deviation) of individual animals.

[0045] Figure 15 is a table showing a comparison of pharmacokinetic parameters of anti-PSMA X anti-CD3 bispecific binding molecules in BALB/c mice.

[0046] Figure 16 is is a graph showing the results of a study measuring serum concentrations of anti-ROR1 X anti-CD3 bispecific binding molecules in NSG mice as a function of time. Results are expressed as mean serum concentration (µg/mL) over time for each of the treatment groups.

[0047] Figure 17A and **Figure 17B** are tables showing a comparison of pharmacokinetic parameters of anti-ROR1 X anti-CD3 bispecific binding molecules in NSG mice. **Figure 17A** shows pharmacokinetic parameter estimates calculated using NCA for IV dosing with sparse sampling and uniform weighting for each treatment group. **Figure 17B** shows pharmacokinetic

parameter estimates determined using a 2 Compartment IV model with 1/Y weighting for each treatment group.

[0048] Figure 18 is a graph showing the results of a study analyzing the effects of anti-ROR1 X anti-CD3 bispecific binding molecules on MDA-MB-231 xenograft tumor growth.

[0049] Figure 19 is a graph showing the results of a study analyzing the effects of anti-ROR1 X anti-CD3 bispecific binding molecules on Kasumi-2 xenograft tumor growth. Results are shown for human T-cell donor #336.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0050] The disclosure provides binding domains that specifically bind to CD3 (cluster of differentiation 3) and binding molecules (e.g. polypeptides and proteins) that specifically bind to CD3. These binding molecules may bind specifically to CD3 and to at least one other target. In some embodiments, a CD3-binding molecule described herein has a favorable manufacturability profile, having one or more of the properties described below. In certain embodiments, CDRs from the Cris7 anti-CD3 antibody have been used to engineer CD3-binding molecules with improved and novel properties. Accordingly, the disclosure relates to humanized anti-CD3 binding domains and proteins that have improved properties (e.g., thermal stability, storage stability, serum half-life, reduced formation of high molecular weight aggregates) compared to other anti-CD3 binding domains and proteins. In some aspects of the disclosure, a CD3-binding molecule is thermally stable. For example, the molecule may have improved thermal stability compared to another CD3-binding molecule (e.g., DRA222). CD3-binding molecules may have a high production yield and a long serum half-life and long storage half-life. Further, CD3-binding molecules described herein may have a low risk of adverse side effects when administered to a subject. For example, CD3-binding molecules may lead to release of low levels of cytokines.

[0051] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components unless otherwise indicated. The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives. As used herein, the terms "include" and "comprise" are used synonymously. In addition, it should be understood that the polypeptides comprising the various combinations of the components (*e.g.*, domains or regions) and substituents described herein,

are disclosed by the present application to the same extent as if each polypeptide was set forth individually. Thus, selection of particular components of individual polypeptides is within the scope of the present disclosure.

[0052] All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. In the event that one or more of the incorporated documents or portions of documents define a term that contradicts that term's definition in the application, the definition that appears in this application controls. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

[0053] As used herein, the term "binding domain" or "binding region" refers to the domain, region, portion, or site of a protein, polypeptide, oligopeptide, or peptide or antibody or binding domain derived from an antibody that possesses the ability to specifically recognize and bind to a target molecule, such as an antigen, ligand, receptor, substrate, or inhibitor (*e.g.*, CD3). Exemplary binding domains include single-chain antibody variable regions (*e.g.*, domain antibodies, sFv, scFv, scFab), receptor ectodomains, and ligands (*e.g.*, cytokines, chemokines). In certain embodiments, the binding domain comprises or consists of an antigen binding site (*e.g.*, comprising a variable heavy chain sequence and variable light chain sequence or three light chain complementary determining regions (CDRs) and three heavy chain CDRs from an antibody placed into alternative framework regions (FRs) (*e.g.*, human FRs optionally comprising one or more amino acid substitutions). A variety of assays are known for identifying binding domains of the present disclosure that specifically bind a particular target, including Western blot, ELISA, phage display library screening, and BIACORE® interaction analysis. As used herein, a CD3-binding polypeptide can have a "first binding domain" and, optionally, a "second binding domain." In certain embodiments, the "first binding domain" is a CD3-binding domain and the format is an antibody or antibody-like protein or domain. In certain embodiments comprising both the first and second binding domains, the second binding domain is a tumor antigen-binding domain. In other embodiments, the second binding domain is a second CD3-binding domain. In yet other embodiments, the second binding domain is a binding domain other than a tumor antigen-binding domain.

[0054] A binding domain or protein "specifically binds" a target if it binds the target with an affinity or K_a (*i.e.*, an equilibrium association constant of a particular binding interaction with units of 1/M) equal to or greater than 10^5 M^{-1}, while not significantly binding other components present in a test sample. Binding domains can be classified as "high affinity" binding domains and "low affinity" binding domains. "High affinity" binding domains refer to those binding domains with a K_a of at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 10^9 M^{-1}, at least 10^{10} M^{-1}, at least 10^{11} M^{-1}, at least 10^{12} M^{-1}, or at least 10^{13} M^{-1}. "Low affinity" binding domains refer to those binding domains with a K_a of up to 10^7 M^{-1}, up to 10^6 M^{-1}, up to 10^5 M^{-1}. Alternatively, affinity can be defined as an equilibrium dissociation constant (K_d) of a particular binding interaction with units of M (*e.g.*, 10^{-5} M to 10^{-13} M). Affinities of binding domain polypeptides and single chain polypeptides according to the present disclosure can be readily determined using conventional techniques (*see, e.g.*, Scatchard et al. (1949) Ann. N.Y. Acad. Sci. 51:660; and U.S. Patent Nos. 5,283,173, 5,468,614, or the equivalent).

[0055] "CD3" is known in the art as a multi-protein complex of six chains (*see, e.g.*, Abbas and Lichtman, 2003; Janeway *et al.*, p. 172 and 178, 1999), which are subunits of the T-cell receptor complex. In mammals, the CD3 subunits of the T-cell receptor complex are a CD3γ chain, a CD3δ chain, two CD3ε chains, and a homodimer of CD3ζ chains. The CD3γ, CD3δ, and CD3ε chains are highly related cell surface proteins of the immunoglobulin superfamily containing a single immunoglobulin domain. The transmembrane regions of the CD3γ, CD3δ, and CD3ε chains are negatively charged, which is a characteristic that allows these chains to associate with the positively charged T-cell receptor chains. The intracellular tails of the CD3γ, CD3δ, and CD3ε chains each contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or ITAM, whereas each CD3ζ chain has three. It is believed the ITAMs are important for the signaling capacity of a TCR complex. CD3 as used in the present disclosure can be from various animal species, including human, monkey, mouse, rat, or other mammals.

[0056] As used herein, a "conservative substitution" is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are well-known in the art (*see, e.g.*, WO 97/09433, page 10, published March 13, 1997; Lehninger, Biochemistry, Second Edition; Worth Publishers, Inc. NY:NY (1975), pp.71-77; Lewin, Genes IV, Oxford University Press, NY and Cell Press, Cambridge, MA (1990), p. 8). In certain embodiments, a conservative substitution includes a leucine to serine substitution.

[0057] As used herein, the term "derivative" refers to a modification of one or more amino acid residues of a peptide by chemical or biological means, either with or without an enzyme, *e.g.*, by glycosylation, alkylation, acylation, ester formation, or amide formation.

[0058] As used herein, a polypeptide or amino acid sequence "derived from" a designated polypeptide or protein refers to the origin of the polypeptide. In certain embodiments, the polypeptide or amino acid sequence which is derived from a particular sequence (sometimes referred to as the "starting" or "parent" or "parental" sequence) has an amino acid sequence that is essentially identical to the starting sequence or a portion thereof, wherein the portion consists of at least 10-20 amino acids, at least 20-30 amino acids, or at least 30-50 amino acids, or at least 50-150 amino acids, or which is otherwise identifiable to one of ordinary skill in the art as having its origin in the starting sequence. For example, a binding domain can be derived from an antibody, e.g., a Fab, F(ab')2, Fab', scFv, single domain antibody (sdAb), etc.

[0059] Polypeptides derived from another polypeptide can have one or more mutations relative to the starting polypeptide, *e.g.*, one or more amino acid residues which have been substituted with another amino acid residue or which has one or more amino acid residue insertions or deletions. The polypeptide can comprise an amino acid sequence which is not naturally occurring. Such variations necessarily have less than 100% sequence identity or similarity with the starting polypeptide. In one embodiment, the variant will have an amino acid sequence from about 60% to less than 100% amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide. In another embodiment, the variant will have an amino acid sequence from about 75% to less thant 100%, from about 80% to less than 100%, from about 85% to less than 100%, from about 90% to less than 100%, from about 95% to less than 100% amino acid sequence identity or similarity with the amino acid sequence of the starting polypeptide.

[0100] As used herein, unless otherwise provided, a position of an amino acid residue in a variable region of an immunoglobulin molecule is numbered using the IMGT criteria (Brochet, X, et al, Nucl. Acids Res. (2008) 36, W503-508), and a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward *et al.*, 1995 *Therap. Immunol.* 2:77-94). The Kabat numbering convention (Kabat, Sequences of Proteins of Immunological Interest, 5th ed. Bethesda, MD: Public Health Service, National Institutes of Health (1991)) is an alternative system used to refer to a position of an amino acid residue in a variable region of an immunoglobulin molecule.

[0060] As used herein, the term "dimer" refers to a biological entity that consists of two subunits associated with each other via one or more forms of intramolecular forces, including covalent bonds (*e.g.*, disulfide bonds) and other interactions (*e.g.*, electrostatic interactions, salt bridges, hydrogen bonding, and hydrophobic interactions), and is stable under appropriate conditions (*e.g.*, under physiological conditions, in an aqueous solution suitable for expressing, purifying, and/or storing recombinant proteins, or under conditions for non-denaturing and/or non-reducing electrophoresis). A "heterodimer" or "heterodimeric protein," as used herein, refers to a dimer formed from two different polypeptides. A heterodimer does not include an antibody formed from four polypeptides (*i.e.*, two light chains and two heavy chains). A "homodimer" or "homodimeric protein," as used herein, refers to a dimer formed from two identical polypeptides.

[0061] In some embodiments, a CD3-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus or in order from carboxyl-terminus to amino-terminus, (i) a second binding domain, (ii) a hinge region, (iii) an immunoglobulin constant region, (iv) a carboxyl-terminus linker (or an amino-terminus linker), and (v) a CD3-binding domain. As used herein and depending on context, a "hinge region" or a "hinge" refers to a polypeptide region between a binding domain (e.g., a CD3-binding domain or a second binding domain) and an immunoglobulin constant region. As used herein and depending on context, a "linker" may refer to (1) a polypeptide region between V_H and V_L regions in a single-chain Fv (scFv) or (2) a polypeptide region between an immunoglobulin constant region and a second binding domain in a CD3-binding polypeptide comprising two binding domains. A polypeptide region between an immunoglobulin constant region and a CD3-binding domain in a CD3-binding polypeptide comprising two binding domains may also be referred to as a "carboxyl-terminus linker" or an "amino-terminus linker." Non-limiting examples of carboxyl-terminus and amino-terminus linkers include flexible linkers comprising glycine-serine repeats, and linkers derived from (a) an interdomain region of a transmembrane protein (*e.g.*, a type I transmembrane protein); (b) a stalk region of a type II C-lectin; or (c) an immunoglobulin hinge. Non-limiting examples of hinges and linkers are provided in Tables 1 and 2. In some embodiments, a "linker" provides a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity to the same target molecule as an antibody that comprises the same light and heavy chain variable regions. In certain embodiments, a linker is comprised of five to about 35 amino acids, for instance, about 15 to about 25 amino acids.

[0062] A "wild-type immunoglobulin hinge region" refers to a naturally occurring upper and middle hinge amino acid sequences interposed between and connecting the CH1 and CH2

domains (for IgG, IgA, and IgD) or interposed between and connecting the CH1 and CH3 domains (for IgE and IgM) found in the heavy chain of an antibody. In certain embodiments, a wild type immunoglobulin hinge region sequence is human, and can comprise a human IgG hinge region.

[0063] An "altered wild-type immunoglobulin hinge region" or "altered immunoglobulin hinge region" refers to (a) a wild type immunoglobulin hinge region with up to 30% amino acid changes (*e.g.*, up to 25%, 20%, 15%, 10%, or 5% amino acid substitutions or deletions), or (b) a portion of a wild type immunoglobulin hinge region that has a length of about 5 amino acids (*e.g.*, about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids) up to about 120 amino acids (for instance, having a length of about 10 to about 40 amino acids or about 15 to about 30 amino acids or about 15 to about 20 amino acids or about 20 to about 25 amino acids), has up to about 30% amino acid changes (*e.g.*, up to about 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% amino acid substitutions or deletions or a combination thereof), and has an IgG core hinge region as disclosed in US 2013/0129723 and US 2013/0095097.

[0064] As used herein, the term "humanized" refers to a process of making an antibody or immunoglobulin binding proteins and polypeptides derived from a non-human species (*e.g.*, mouse or rat) less immunogenic to humans, while still retaining antigen-binding properties of the original antibody, using genetic engineering techniques. In some embodiments, the binding domain(s) of an antibody or immunoglobulin binding proteins and polypeptides (*e.g.*, light and heavy chain variable regions, Fab, scFv) are humanized. Non-human binding domains can be humanized using techniques known as CDR grafting (Jones *et al.*, *Nature* 321:522 (1986)) and variants thereof, including "reshaping" (Verhoeyen, *et al.*, 1988 *Science* 239:1534-1536; Riechmann, *et al.*, 1988 *Nature* 332:323-337; Tempest, *et al.*, *Bio/Technol* 1991 9:266-271), "hyperchimerization" (Queen, *et al.*, 1989 *Proc Natl Acad Sci USA* 86:10029-10033; Co, *et al.*, 1991 *Proc Natl Acad Sci USA* 88:2869-2873; Co, *et al.*, 1992 *J Immunol* 148:1149-1154), and "veneering" (Mark, *et al.*, "Derivation of therapeutically active humanized and veneered anti-CD18 antibodies." In: Metcalf BW, Dalton BJ, eds. Cellular adhesion: molecular definition to therapeutic potential. New York: Plenum Press, 1994: 291-312). If derived from a non-human source, other regions of the antibody or immunoglobulin binding proteins and polypeptides, such as the hinge region and constant region domains, can also be humanized.

[0065] An "immunoglobulin dimerization domain" or "immunoglobulin heterodimerization domain", as used herein, refers to an immunoglobulin domain of a polypeptide chain that preferentially interacts or associates with a different immunoglobulin domain of a second

polypeptide chain, wherein the interaction of the different immunoglobulin heterodimerization domains substantially contributes to or efficiently promotes heterodimerization of the first and second polypeptide chains (*i.e.*, the formation of a dimer between two different polypeptide chains, which is also referred to as a "heterodimer"). The interactions between immunoglobulin heterodimerization domains "substantially contributes to or efficiently promotes" the heterodimerization of first and second polypeptide chains if there is a statistically significant reduction in the dimerization between the first and second polypeptide chains in the absence of the immunoglobulin heterodimerization domain of the first polypeptide chain and/or the immunoglobulin heterodimerization domain of the second polypeptide chain. In certain embodiments, when the first and second polypeptide chains are co-expressed, at least 60%, at least about 60% to about 70%, at least about 70% to about 80%, at least 80% to about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the first and second polypetpide chains form heterodimers with each other. Representative immunoglobulin heterodimerization domains include an immunoglobulin CH1 domain, an immunoglobulin CL domain (*e.g.*, Cκ or Cλ isotypes), or derivatives thereof, including wild type immunoglobulin CH1 and CL domains and altered (or mutated) immunoglobulin CH1 and CL domains, as provided therein.

[0066] An "immunoglobulin constant region" or "constant region" is a term defined herein to refer to a peptide or polypeptide sequence that corresponds to or is derived from part or all of one or more constant region domains. In certain embodiments, the immunoglobulin constant region corresponds to or is derived from part or all of one or more constant region domains, but not all constant region domains of a source antibody. In certain embodiments, the constant region comprises IgG CH2 and CH3 domains, e.g., IgG1 CH2 and CH3 domains. In certain embodiments, the constant region does not comprise a CH1 domain. In certain embodiments, the constant region domains making up the constant region are human. In some embodiments (for example, in certain variations of a CD3-binding polypeptide or protein), the constant region domains of a fusion protein of this disclosure lack or have minimal effector functions of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement activation and complement-dependent cytotoxicity (CDC), while retaining the ability to bind some F_C receptors (such as F_CRn, the neonatal Fc receptor) and retaining a relatively long half life *in vivo*. In other variations, a fusion protein of this disclosure includes constant domains that retain such effector function of one or both of ADCC and CDC. In certain embodiments, a binding domain of this disclosure is fused to a human IgG1 constant region, wherein the IgG1 constant region has one or more of the following amino acids mutated: leucine at position 234 (L234), leucine at position 235 (L235), glycine at position 237 (G237), glutamate at position 318 (E318), lysine at position

320 (K320), lysine at position 322 (K322), or any combination thereof (numbering according to EU). For example, any one or more of these amino acids can be changed to alanine. In a further embodiment, an IgG1 Fc domain has each of L234, L235, G237, E318, K320, and K322 (according to EU numbering) mutated to an alanine (*i.e.*, L234A, L235A, G237A, E318A, K320A, and K322A, respectively), and optionally an N297A mutation as well (*i.e.*, essentially eliminating glycosylation of the CH2 domain).

[0067] "Fc region" or "Fc domain" refers to a polypeptide sequence corresponding to or derived from the portion of a source antibody that is responsible for binding to antibody receptors on cells and the C1q component of complement. Fc stands for "fragment crystalline," the fragment of an antibody that will readily form a protein crystal. Distinct protein fragments, which were originally described by proteolytic digestion, can define the overall general structure of an immunoglobulin protein. As originally defined in the literature, the Fc fragment consists of the disulfide-linked heavy chain hinge regions, CH2, and CH3 domains. However, more recently the term has been applied to a single chain consisting of CH3, CH2, and at least a portion of the hinge sufficient to form a disulfide-linked dimer with a second such chain. For a review of immunoglobulin structure and function, see Putnam, *The Plasma Proteins*, Vol. V (Academic Press, Inc., 1987), pp. 49-140; and Padlan, *Mol. Immunol.* 31:169-217, 1994. As used herein, the term Fc includes variants of naturally occuring sequences.

[0068] In some embodiments, a CD3-binding protein comprises a protein scaffold as generally disclosed in, for example, in US Patent Application Publication Nos. 2003/0133939, 2003/0118592, and 2005/0136049. A CD3-binding protein may comprise, in order from amino-terminus to carboxyl-terminus, a first binding domain, a hinge region, and an immunoglobulin constant constant region. In other embodiments, a CD3-binding protein comprises a protein scaffold as generally disclosed in, for example, in US Patent Application Publication No. 2009/0148447. A CD3-binding protein may comprise, in order from carboxyl-terminus to amino-terminus, an immunoglobulin constant region, a hinge region and a first binding domain.

[0069] CD3-binding polypeptides and proteins disclosed herein may incorporate a multi-specific binding protein scaffold. Multi-specific binding proteins and polypeptides using scaffolds are disclosed, for instance, in PCT Application Publication No. WO 2007/146968, U.S. Patent Application Publication No. 2006/0051844, PCT Application Publication No. WO 2010/040105, PCT Application Publication No. WO 2010/003108, U.S. Patent No. 7,166,707 and U.S. Patent No. 8,409,577, which are each incorporated herein by reference in their entirety. A CD3-binding protein may comprise two binding domains (the domains can be designed to specifically bind

the same or different targets), two hinge regions, and an immunoglobulin constant region. A CD3-binding protein may be a homodimeric protein comprising two identical, disulfide-bonded polypeptides.

[0070] As used herein, the "stalk region" of a type II C-lectin refers to the portion of the extracellular domain of the type II C-lectin that is located between the C-type lectin-like domain (CTLD; *e.g.*, similar to CTLD of natural killer cell receptors) and the transmembrane domain. For example, in the human CD94 molecule (GenBank Accession No. AAC50291.1, PRI November 30, 1995), the extracellular domain corresponds to amino acid residues 34-179, whereas the CTLD corresponds to amino acid residues 61-176. Accordingly, the stalk region of the human CD94 molecule includes amino acid residues 34-60, which is found between the membrane and the CTLD (*see* Boyington *et al.*, *Immunity* 10:75, 1999; for descriptions of other stalk regions, *see also* Beavil *et al.*, *Proc. Nat'l. Acad. Sci. USA* 89:753, 1992; and Figdor *et al.*, *Nature Rev. Immunol.* 2:77, 2002). These type II C-lectins can also have from six to 10 junction amino acids between the stalk region and the transmembrane region or the CTLD. In another example, the 233 amino acid human NKG2A protein (GenBank Accession No. P26715.1, PRI June 15, 2010) has a transmembrane domain ranging from amino acids 71-93 and an extracellular domain ranging from amino acids 94-233. The CTLD is comprised of amino acids 119-231, and the stalk region comprises amino acids 99-116, which is flanked by junctions of five and two amino acids. Other type II C-lectins, as well as their extracellular ligand-bind domains, interdomain or stalk regions, and CTLDs are known in the art (*see, e.g.*, GenBank Accession Nos. NP_001993.2; AAH07037.1, PRI July 15, 2006; NP_001773.1, PRI June 20, 1010; AAL65234.1, PRI January 17, 2002, and CAA04925.1, PRI November 14, 2006, for the sequences of human CD23, CD69, CD72, NKG2A and NKG2D and their descriptions, respectively).

[0071] As used herein, the "interdomain region" of a transmembrane protein (*e.g.*, a type I transmembrane protein) refers to a portion of the extracellular domain of the transmembrane protein that is located between two adjacent domains. Examples of interdomain regions include regions linking adjacent Ig domains of immunoglobulin superfamily members (*e.g.*, an immunoglobulin hinge region from IgG, IgA, IgD, or IgE; the region linking the IgV and IgC2 domains of CD2; or the region linking the IgV and IgC domains of CD80 or CD86). Another example of an interdomain region is the region linking the non-Ig and IgC2 domain of CD22, a type I sialic acid-binding Ig-like lectin.

[0072] A polypeptide region "derived from" a stalk region of a type II C-lectin, or "derived from" a transmembrane protein interdomain region (*e.g.*, an immunoglobulin hinge region), refers to an about five to about 150 amino acid sequence, an about 5 to about 100 amino acid sequence, an about 5 to about 50 amino acid sequence, an about 5 to about 40 amino acid sequence, an about 5 to about 30 amino acid sequence, an about 5 to about 25 amino acid sequence, an about 5 to about 20 amino acid sequence, an about 10 to about 25 amino acid sequence, an about 10 to about 20 amino acid sequence, about 8 to about 20 amino acid sequence, about 9 to about 20 amino acid sequence, about 10 to about 20 amino acid sequence, about 11 to about 20 amino acid sequence, about 12 to about 20 amino acid sequence, about 13 to about 20 amino acid sequence, about 14 to about 20 amino acid sequence, about 15 to about 20 amino acid sequence, or an about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid sequence, wherein all or at least a portion of which includes (i) a wild-type stalk region or interdomain region sequence; (ii) a fragment of the wild-type stalk region or interdomain region sequence; (iii) a polypeptide having at least 80%, 85%, 90%, or 95% amino acid sequence identity with either (i) or (ii); or (iv) either (i) or (ii) in which one, two, three, four, or five amino acids have a deletion, insertion, substitution, or any combination thereof, for instance, the one or more changes are substitutions or the one or more mutations include only one deletion. In some embodiments, a derivative of a stalk region is more resistant to proteolytic cleavage as compared to the wild-type stalk region sequence, such as those derived from about eight to about 20 amino acids of NKG2A, NKG2D, CD23, CD64, CD72, or CD94.

[0073] As used herein, the term "junction amino acids" or "junction amino acid residues" refers to one or more (*e.g.*, about 2-10) amino acid residues between two adjacent regions or domains of a polypeptide, such as between a hinge and an adjacent immunoglobulin constant region or between a hinge and an adjacent binding domain or between a peptide linker and an adjacent immunoglobulin variable domain or an adjacent immunoglobulin constant region. Junction amino acids can result from the construct design of a polypeptide (*e.g.*, amino acid residues resulting from the use of a restriction enzyme site during the construction of a nucleic acid molecule encoding a polypeptide).

[0074] As used herein, the phrase a "linker between CH3 and CH1 or CL" refers to one or more (*e.g.*, about 2-12, about 2-10, about 4-10, about 5-10, about 6-10, about 7-10, about 8-10, about 9-10, about 8-12, about 9-12, or about 10-12) amino acid residues between the C- terminus of a CH3 domain (*e.g.*, a wild type CH3 or a mutated CH3) and the N-terminus of a CH1 domain or CL domain (*e.g.*, Ck).

[0075] As used herein, the term “patient in need” or “subject in need” refers to a patient or a subject at risk of, or suffering from, a disease, disorder or condition that is amenable to treatment or amelioration with a CD3-binding protein or polypeptide or a composition thereof provided herein.

[0076] As used herein, the term "pharmaceutically acceptable" refers to molecular entities and compositions that do not generally produce allergic or other serious adverse reactions when administered using routes well known in the art. Molecular entities and compositions approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans are considered to be “pharmaceutically acceptable.”

[0077] As used herein, the term "promoter" refers to a region of DNA involved in binding RNA polymerase to initiate transcription.

[0078] As used herein, the terms "nucleic acid," "nucleic acid molecule," or "polynucleotide" refer to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the terms encompass nucleic acids containing analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions can be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.* (1991) *Nucleic Acid Res.* 19:5081; Ohtsuka *et al.* (1985) *J. Biol. Chem.* 260:2605-2608; Cassol *et al.* (1992); Rossolini *et al.* (1994) *Mol. Cell. Probes* 8:91-98). The term nucleic acid is used interchangeably with gene, cDNA, and mRNA encoded by a gene. As used herein, the terms "nucleic acid," "nucleic acid molecule," or "polynucleotide" are intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof.

[0079] The term “expression” refers to the biosynthesis of a product encoded by a nucleic acid. For example, in the case of nucleic acid segment encoding a polypeptide of interest, expression involves transcription of the nucleic acid segment into mRNA and the translation of mRNA into one or more polypeptides.

[0080] The terms "expression unit" and "expression cassette" are used interchangeably herein and denote a nucleic acid segment encoding a polypeptide of interest and capable of providing expression of the nucleic acid segment in a host cell. An expression unit typically comprises a transcription promoter, an open reading frame encoding the polypeptide of interest, and a transcription terminator, all in operable configuration. In addition to a transcriptional promoter and terminator, an expression unit can further include other nucleic acid segments such as, *e.g.*, an enhancer or a polyadenylation signal.

[0081] The term "expression vector," as used herein, refers to a nucleic acid molecule, linear or circular, comprising one or more expression units. In addition to one or more expression units, an expression vector can also include additional nucleic acid segments such as, for example, one or more origins of replication or one or more selectable markers. Expression vectors are generally derived from plasmid or viral DNA, or can contain elements of both.

[0082] As used herein, the term "sequence identity" refers to a relationship between two or more polynucleotide sequences or between two or more polypeptide sequences. When a position in one sequence is occupied by the same nucleic acid base or amino acid residue in the corresponding position of the comparator sequence, the sequences are said to be "identical" at that position. The percentage "sequence identity" is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of "identical" positions. The number of "identical" positions is then divided by the total number of positions in the comparison window and multiplied by 100 to yield the percentage of "sequence identity." Percentage of "sequence identity" is determined by comparing two optimally aligned sequences over a comparison window. The comparison window for nucleic acid sequences can be, for instance, at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 or more nucleic acids in length. The comparison windon for polypeptide sequences can be, for instance, at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300 or more amino acids in length. In order to optimally align sequences for comparison, the portion of a polynucleotide or polypeptide sequence in the comparison window can comprise additions or deletions termed gaps while the reference sequence is kept constant. An optimal alignment is that alignment which, even with gaps, produces the greatest possible number of "identical" positions between the reference and comparator sequences. Percentage "sequence identity" between two sequences can be determined using the version of the program "BLAST 2 Sequences" which was available from the National Center for Biotechnology

Information as of September 1, 2004, which program incorporates the programs BLASTN (for nucleotide sequence comparison) and BLASTP (for polypeptide sequence comparison), which programs are based on the algorithm of Karlin and Altschul (Proc. Natl. Acad. Sci. USA 90(12):5873-5877, 1993). When utilizing "BLAST 2 Sequences," parameters that were default parameters as of September 1, 2004, can be used for word size (3), open gap penalty (11), extension gap penalty (1), gap dropoff (50), expect value (10) and any other required parameter including but not limited to matrix option. Two nucleotide or amino acid sequences are considered to have "substantially similar sequence identity" or "substantial sequence identity" if the two sequences have at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity relative to each other.

[0083] As used herein, a "polypeptide" or "polypeptide chain" is a single, linear and contiguous arrangement of covalently linked amino acids. It does not include two polypeptide chains that link together in a non-linear fashion, such as via an interchain disulfide bond (*e.g.*, a half immunoglobulin molecule in which a light chain links with a heavy chain via a disulfide bond). Polypeptides can have or form one or more intrachain disulfide bonds. With regard to polypeptides as described herein, reference to amino acid residues corresponding to those specified by SEQ ID NO includes post-translational modifications of such residues.

[0084] As used herein, "CD3-binding protein" may be used interchangeably with "CD3-binding polypeptide." Such molecules specifically bind to cluster of differentiation 3 protein (CD3) (*e.g.*, human CD3).

[0085] A "protein" is a macromolecule comprising one or more polypeptide chains. A protein can also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents can be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless. A protein may be an antibody or an antigen-binding fragment of an antibody. In some embodiments, a protein may also be an scFv-Fc-scFv molecule, scFv-scFv dimer, or a diabody.

[0086] The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a

polypeptide is located proximal to the carboxyl-terminus of the reference sequence, but is not necessarily at the carboxyl-terminus of the complete polypeptide.

[0087] "T-cell receptor" (TCR) is a molecule found on the surface of T-cells that, along with CD3, is generally responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules. It consists of a disulfide-linked heterodimer of the highly variable α and β chains in most T-cells. In other T-cells, an alternative receptor made up of variable γ and δ chains is expressed. Each chain of the TCR is a member of the immunoglobulin superfamily and possesses one N-terminal immunoglobulin variable domain, one immunoglobulin constant domain, a transmembrane region, and a short cytoplasmic tail at the C-terminal end (*see* Abbas and Lichtman, *Cellular and Molecular Immunology* (5th Ed.), Editor: Saunders, Philadelphia, 2003; Janeway *et al.*, *Immunobiology: The Immune System in Health and Disease*, 4th Ed., Current Biology Publications, p148, 149, and 172, 1999). TCR as used in the present disclosure can be from various animal species, including human, mouse, rat, or other mammals.

[0088] "TCR complex," as used herein, refers to a complex formed by the association of CD3 chains with other TCR chains. For example, a TCR complex can be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRα chain, and a TCRβ chain. Alternatively, a TCR complex can be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRγ chain, and a TCRδ chain.

[0089] "A component of a TCR complex," as used herein, refers to a TCR chain (*i.e.*, TCRα, TCRβ, TCRγ or TCRδ), a CD3 chain (*i.e.*, CD3γ, CD3δ, CD3ε or CD3ζ), or a complex formed by two or more TCR chains or CD3 chains (*e.g.*, a complex of TCRα and TCRβ, a complex of TCRγ and TCRδ, a complex of CD3ε and CD3δ, a complex of CD3γ and CD3ε, or a sub-TCR complex of TCRα, TCRβ, CD3γ, CD3δ, and two CD3ε chains).

[0090] "Antibody-dependent cell-mediated cytotoxicity" and "ADCC," as used herein, refer to a cell-mediated process in which nonspecific cytotoxic cells that express FcγRs (e.g., monocytic cells such as Natural Killer (NK) cells and macrophages) recognize bound antibody (or other protein capable of binding FcγRs) on a target cell and subsequently cause lysis of the target cell. In principle, any effector cell with an activating FcγR can be triggered to mediate ADCC. The primary cells for mediating ADCC are NK cells, which express only FcγRIII, whereas monocytes, depending on their state of activation, localization, or differentiation, can express FcγRI, FcγRII, and FcγRIII. For a review of FcγR expression on hematopoietic cells, see, e.g., Ravetch et al., 1991, Annu. Rev. Immunol., 9:457-92.

[0091] The term "having ADCC activity," as used herein in reference to a polypeptide or protein, means that the polypeptide or protein (for example, one comprising an immunoglobulin hinge region and an immunoglobulin constant region having CH2 and CH3 domains, such as derived from IgG (e.g., IgG1)), is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) through binding of a cytolytic Fc receptor (e.g., FcγRIII) on a cytolytic immune effector cell expressing the Fc receptor (e.g., an NK cell).

[0092] "Complement-dependent cytotoxicity" and "CDC," as used herein, refer to a process in which components in normal serum ("complement"), together with an antibody or other C1q-complement-binding protein bound to a target antigen, exhibit lysis of a target cell expressing the target antigen. Complement consists of a group of serum proteins that act in concert and in an orderly sequence to exert their effect.

[0093] The terms "classical complement pathway" and "classical complement system," as used herein, are synonymous and refer to a particular pathway for the activation of complement. The classical pathway requires antigen-antibody complexes for initiation and involves the activation, in an orderly fashion, of nine major protein components designated C1 through C9. For several steps in the activation process, the product is an enzyme that catalyzes the subsequent step. This cascade provides amplification and activation of large amounts of complement by a relatively small initial signal.

[0094] The term "having CDC activity," as used herein in reference to a polypeptide or protein, means that the polypeptide or protein (for example, one comprising an immunoglobulin hinge region and an immunoglobulin constant region having CH2 and CH3 domains, such as derived from IgG (e.g., IgG1)) is capable of mediating complement-dependent cytotoxicity (CDC) through binding of C1q complement protein and activation of the classical complement system.

[0095] "Redirected T-cell cytotoxicity" and "RTCC," as used herein, refer to a T-cell-mediated process in which a cytotoxic T-cell is recruited to a target cell using a multi-specific protein that is capable of specifically binding both the cytotoxic T-cell and the target cell, and whereby a target-dependent cytotoxic T-cell response is elicited against the target cell. Polypeptides and proteins comprising CD3-binding domains, as disclosed herein, and tumor antigen-binding domains are capable of RTCC.

[0096] As used herein, the term "treatment," "treating," or "ameliorating" refers to either a therapeutic treatment or prophylactic/preventative treatment. A treatment is therapeutic if at least one symptom of disease in an individual receiving treatment improves or a treatment can

delay worsening of a progressive disease in an individual, or prevent onset of additional associated diseases.

[0097] As used herein, the term "therapeutically effective amount (or dose)" or "effective amount (or dose)" of a specific binding molecule or compound refers to that amount of the compound sufficient to result in amelioration of one or more symptoms of the disease being treated in a statistically significant manner or a statistically significant improvement in organ function. When referring to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When referring to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered serially or simultaneously (in the same formuation or concurrently in separate formulations).

[0098] As used herein, the term "transformation," "transfection," and "transduction" refer to the transfer of nucleic acid (i.e., a nucleotide polymer) into a cell. As used herein, the term "genetic transformation" refers to the transfer and incorporation of DNA, especially recombinant DNA, into a cell. The transferred nucleic acid can be introduced into a cell via an expression vector.

[0099] As used herein, the term "variant" or "variants" refers to a nucleic acid or polypeptide differing from a reference nucleic acid or polypeptide, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the reference nucleic acid or polypeptide. For instance, a variant may exhibit at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% sequence identity compared to the active portion or full length reference nucleic acid or polypeptide.

[00100] The terms "light chain variable region" (also referred to as "light chain variable domain" or "VL" or V_L) and "heavy chain variable region" (also referred to as "heavy chain variable domain" or "VH" or V_H) refer to the variable binding region from an antibody light and heavy chain, respectively. The variable binding regions are made up of discrete, well-defined sub-regions known as "complementarity determining regions" (CDRs) and "framework regions" (FRs), generally comprising in order FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 from amino-terminus to carboxyl-terminus. In one embodiment, the FRs are humanized. The term "CL" refers to an "immunoglobulin light chain constant region" or a "light chain constant region," i.e., a constant region from an antibody light chain. The term "CH" refers to an "immunoglobulin heavy chain constant region" or a "heavy chain constant region," which is further divisible, depending on the antibody isotype into CH1, CH2, and CH3 (IgA, IgD, IgG), or CH1, CH2, CH3, and CH4

domains (IgE, IgM). A "Fab" (fragment antigen binding) is the part of an antibody that binds to antigens and includes the variable region and CH1 domain of the heavy chain linked to the light chain via an inter-chain disulfide bond.

[00101] The present disclosure describes binding domains that specifically bind CD3 (e.g., human CD3), as well as polypeptides and proteins comprising these binding domains. In some embodiments, the CD3-binding proteins and polypeptides comprise a second binding domain, which may bind to a tumor antigen (e.g., PSMA, CD19, CD20, CD37, CD38, CD123, Her2, ROR1, RON, glycoprotein A33 antigen (gpA33) or CEA). The polypeptides and proteins comprising binding domains of this disclosure can further comprise immunoglobulin constant regions, linker peptides, hinge regions, immunoglobulin dimerization/heterodimerization domains, junctional amino acids, tags, *etc.* These components of the disclosed polypeptides and proteins are described in further detail below.

[00102] Additionally, the CD3-binding polypeptides and proteins disclosed herein can be in the form of an antibody or a fusion protein of any of a variety of different formats (*e.g.*, the fusion protein can be in the form of a CD3-binding bispecific or multispecific molecule). Non-limiting examples of bispecific molecules include a scFv-Fc-scFv molecule. Some bispecific molecules typically comprise or consist of an anti-tumor antigen scFv linked to an anti-CD3 scFv and typically do not include other sequences such as an immunoglobulin constant region. In other embodiments, a CD3-binding protein is a diabody.

[00103] A CD3-binding protein in accordance with the present disclosure generally includes at least one CD3-binding polypeptide chain comprising (a) a CD3-binding domain as set forth herein. In certain variations, the CD3-binding polypeptide further includes (b) a hinge region carboxyl-terminal to the CD3-binding domain, and (c) an immunoglobulin constant region. In further variations, the ROR1-binding polypeptide further includes (d) a carboxyl-terminus linker carboxyl-terminal to the immunoglobulin constant region, and (e) a second binding domain carboxyl-terminal to the carboxyl-terminus linker.

[00104] In yet other variations, the CD3-binding polypeptide comprises (b) a hinge region amino-terminal to the CD3-binding domain, and (c) an immunoglobulin sub-region amino-terminal to the hinge region. In some variations, the CD3-binding polypeptide comprises (b) a hinge region carboxyl-terminal to the CD3-binding domain, and (c) an immunoglobulin sub-region carboxyl-terminal to the hinge region

[00105] In some embodiments, CD3-binding polypeptides are capable of homodimerization, typically through disulfide bonding, via the immunoglobulin constant region and/or hinge region (*e.g.*, via an immunoglobulin constant region comprising IgG CH2 and CH3 domains and an IgG hinge region). Thus, in certain embodiments of the present disclosure, two identical single chain CD3-binding polypeptides homodimerize to form a dimeric CD3-binding protein.

[00106] In other embodiments, a CD3-binding polypeptide includes a heterodimerization domain that is capable of heterodimerization with a different heterodimerization domain in a second, non-identical polypeptide chain. In certain variations, the second polypeptide chain for heterodimerization includes a second binding domain. Accordingly, in certain embodiments of the present disclosure, two non-identical polypeptide chains, one comprising the CD3-binding domain and the second optionally comprising a second binding domain, dimerize to form a heterodimeric CD3-binding protein. Examples of types of heterodimers include those described in US 2013/0095097 and US 2013/0129723.

[00107] In some embodiments, a CD3-binding domain, protein or polypeptide is conjugated to a drug or a toxic moiety.

[00108] CD3-binding polypeptides, proteins, and their various components used in the present disclosure are further described below.

[00109] As indicated above, the disclosure relates to binding domains that specifically bind CD3 (e.g., human CD3). A CD3-binding domain may comprise amino acid sequences shown in Table 14. In some embodiments, a CD3-binding polypeptide or protein comprises a signal sequence. The disclosure also encompasses CD3-binding domains and proteins comprising or encoded by any of the sequences shown in Table 14, excluding the signal sequences that are part of these sequences. CD3-binding domains and polypeptides, their internal designations, and their sequences are summarized in Table 15. In some cases, CD3-binding domains of the disclosure contain amino acid substitutions. For example, TSC370 has the amino acid sequence of TSC342 with the glycine residue at position 27 according to the IMGT numbering system substituted with tyrosine.

[00110] In certain embodiments, the disclosure relates to a CD3-binding domain that binds specifically to human CD3 and that comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region; wherein the immunoglobulin light chain variable region comprises an amino acid sequence that is (a) at least about 93% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99%

identical to the amino acid sequence in SEQ ID NO:88; or (b) at least about 94% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:89; and wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence that is at least about 82% identical, at least about 85% identical, at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:86. A CD3-binding domain may comprise an amino acid sequence that is at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:83 or SEQ ID NO:84. A CD3-binding domain may comprise or consist of SEQ ID NO:83 or SEQ ID NO:84. In some embodiments, a CD3-binding domain comprises an amino acid sequence that is at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical, at least about 99% identical, or 100% identical to the amino acid sequence in SEQ ID NO:4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, or 60.

[00111] In some embodiments, a CD3-binding domain may comprise an immunoglobulin light chain variable region that comprises an LCDR1 amino acid sequence that differs from SEQ ID NO:94 by at least one amino acid substitution, an LCDR2 amino acid sequence that differs from SEQ ID NO:95 by at least one amino acid substitution, and an LCDR3 amino acid sequence that differs from SEQ ID NO:96 by at least one amino acid substitution, and an immunoglobulin heavy chain variable region that comprises an HCDR1 amino acid sequence that differs from SEQ ID NO:91 by at least one amino acid substitution, an HCDR2 amino acid sequence that differs from SEQ ID NO:92 by at least one amino acid substitution, and an HCDR3 amino acid sequence that differs from SEQ ID NO:93 by at least one amino acid substitution. In other embodiments, a CD3-binding domain may comprise an immunoglobulin light chain variable region that comprises an LCDR1 amino acid sequence that differs from SEQ ID NO:202 by at least one amino acid substitution, an LCDR2 amino acid sequence that differs from SEQ ID NO:203 by at least one amino acid substitution, and an LCDR3 amino acid sequence that differs from SEQ ID NO:204 by at least one amino acid substitution, and an immunoglobulin heavy chain variable region that comprises an HCDR1 amino acid sequence that differs from SEQ ID NO:199 by at least one amino acid substitution, an HCDR2 amino acid sequence that differs from SEQ ID NO:200 by at least one amino acid substitution, and an HCDR3 amino acid

sequence that differs from SEQ ID NO:201 by at least one amino acid substitution. The CDR amino acid sequence of a CD3-binding domain may differ from the recited sequence by at least one amino acid substitution. The at least one amino acid substitution may be a conservative or a non-conservative amino acid substitution. In some embodiments, a LCDR1, LCDR2, LCDR3, HCDR1, HCDR2, and/or HCDR3 differs from an above-listed CDR sequence by 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids. In certain embodiments, a CDR of the present disclosure contains about one or more (*e.g.*, about 2, 3, 4, 5, 6, 7, 8, 9, 10) insertions, about one or more (*e.g.*, about 2, 3, 4, 5, 6, 7, 8, 9, 10) deletions, about one or more (*e.g.*, about 2, 3, 4, 5, 6, 7, 8, 9, 10) amino acid substitutions (*e.g.*, conservative amino acid substitutions or non-conservative amino acid substitutions), or a combination of the above-noted changes, when compared to the CDR sequence of a known monoclonal antibody.

[00112] When describing the amino acid substitutions in this disclosure, a position of an amino acid residue in a variable region of an immunoglobulin molecule is usually numbered using the IMGT criteria (Brochet, X, et al, Nucl. Acids Res. (2008) 36, W503-508). In some embodiments, the amino acid residue at position 52 of the immunoglobulin light chain variable region of a CD3-binding domain is arginine and/or the amino acid residue at position 53 of the immunoglobulin light chain variable region of a CD3-binding domain is tryptophan. The amino acid residue at position 27 of the immunoglobulin heavy chain variable region of a CD3-binding domain may be tyrosine. In some embodiments, a CD3-binding domain comprises one or more of the following: (a) the amino acid residue at position 9 of the immunoglobulin heavy chain variable region is proline; (b) the amino acid residue at position 53 of the immunoglobulin heavy chain variable region is isoleucine; and (c) the amino acid residue at position 21 of the immunoglobulin light chain variable region is methionine. The amino acid residue at position 87 of the immunoglobulin heavy chain variable region of a CD3-binding domain may be tyrosine. The amino acid residue at position 86 of the immunoglobulin heavy chain variable region of a CD3-binding domain may be aspartic acid. In one embodiment, the amino acid residue at position 86 of the immunoglobulin heavy chain variable region of a CD3-binding domain is aspartic acid and the amino acid residue at position 87 of the immunoglobulin heavy chain variable region of a CD3-binding domain is tyrosine.

[00113] In certain embodiments, a CD3-binding domain comprises humanized immunoglobulin VL and/or VH regions. Techniques for humanizing immunoglobulin VL and VH regions are known in the art and are discussed, for example, in U.S. Patent Application Publication No. 2006/0153837. In certain aspects, a CD3-binding domain may comprise an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region that comprise

framework regions and at least one of the immunoglobulin light chain variable region and the immunoglobulin heavy chain variable region may be humanized. In one embodiment, an immunoglobulin light chain variable region comprises framework regions based on the human IGKV3D-20*1 germline amino acid sequence. In another embodiment, an immunoglobulin heavy chain variable region comprises framework regions based on the human IGHV1-69*02 germline amino acid sequence. In some aspects, an immunoglobulin heavy chain variable region comprises framework regions based on the human IGHV1-2*02 (H7), IGHV1-46*02 (H8), IGHV1-3*01(H9), or IGHV1-69*02 (H10) germline amino acid sequence. An immunoglobulin light chain variable region may comprise framework regions based on the human IGKV3-11*01 (L4), IGKV1-33*01 (L5), IGKV1-39*01 (L7), or IGKV3D-20*1 (L8) germline amino acid sequence.

[00114] The disclosure relates to CD3-binding domains that have improved properties compared to the DRA222 CD3-binding domain. DRA222 has a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. DRA222 is described in WO 2013/158856. DRA222 is sometimes referred to as TSC311 or TSC312 in this disclosure. Fc DRA222 has the amino acid sequence of SEQ ID NO:2. The disclosure encompasses a CD3-binding domain (or a protein comprising said domain) that has a thermal stability that is increased at least about 10% when compared to the thermal stability of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. The thermal transition midpoint (Tm) of a CD3-binding domain (or a protein comprising said domain) may be at least about 3°C, at least about 4°C, at least about 5°C, or at least about 6°C increased and up to about 20°C increased when compared to the Tm of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. The thermal transition midpoint of a CD3-binding domain (or a protein comprising said domain) may be at least about 54°C, at least about 55°C, at least about 56°C, or at least about 57°C and up to about 72°C. The thermal stability or the thermal transition midpoint of a CD3-binding domain (or a protein comprising said domain) may be measured by differential scanning calorimetry or differential scanning fluorimetry.

[00115] A CD3-binding domain as disclosed herein (or a protein comprising said domain) may have storage stability that is increased at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% and up to about 100% when compared to the storage stability of a CD3-binding domain comprising a light chain variable region

comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87. Storage stability may be measured after a CD3-binding domain (or a protein comprising said domain) is stored in PBS at about 25°C. In one embodiment, a CD3-binding domain (or a protein comprising said domain) is stable in storage in PBS at about 25°C for at least about 6 days, at least about 10 days, or at least about 13 days and up to about 90 days.

[00116] In some aspects, a CD3-binding domain as disclosed herein (or a protein comprising said domain) has a level of high molecular weight aggregates produced during recombinant expression that are at least about 5%, at least about 10%, at least about 20% decreased, at least about 30% decreased and up to about 50% decreased when compared to the level of high molecular weight aggregates produced during recombinant expression of a CD3-binding domain comprising a light chain variable region comprising SEQ ID NO:90 and a heavy chain variable region comprising SEQ ID NO:87.

[00117] The disclosure also relates to a CD3-binding domain that binds to human CD3 with an EC50 of about 10 nM or lower. A CD3-binding domain of the disclosure may bind specifically to both human CD3 and cynomolgus CD3. For example, a CD3-binding domain may bind to cynomolgus CD3 with an EC50 of about 30 nM or lower. Binding to cynomolgus CD3 allows the anti-CD3 therapeutic to be tested in non-human primates.

[00118] The disclosure encompasses a CD3-binding domain that binds specifically to human CD3 and that comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region, wherein the immunoglobulin light chain variable region comprises an LCDR1 amino acid sequence of SEQ ID NO:94, an LCDR2 amino acid sequence of SEQ ID NO:95, and an LCDR3 amino acid sequence of SEQ ID NO:96 and wherein the immunoglobulin heavy chain variable region comprises an HCDR1 amino acid sequence of SEQ ID NO:91, an HCDR2 amino acid sequence of SEQ ID NO:92, and an HCDR3 amino acid sequence of SEQ ID NO:93, and wherein the CD3-binding domain has any one or more of the properties described herein. For example, (i) the thermal transition midpoint of the CD3-binding domain (or a protein comprising the CD3-binding domain) is at least about 54°C, at least about 55°C, at least about 56°C, or at least about 57°C and up to about 72°C; (ii) the CD3-binding domain (or a protein comprising the CD3-binding domain) is stable in storage in PBS at about 25°C for at least about 6 days, at least about 10 days, or at least about 13 days and up to about 90 days; (iii) the CD3-binding domain (or a protein comprising the CD3-binding domain) binds to human CD3 with an EC50 of about 10 nM or lower; and (iv) the CD3-binding domain (or a protein comprising the CD3-binding domain) binds to cynomolgus CD3 with an EC50 of about 30 nM or lower.

[00119] In some embodiments, a CD3-binding polypeptide when bound to a CD3 protein on a T cell does not induce or induces a minimally detectable cytokine release from said T cell. In certain aspects, a CD3-binding protein or polypeptide exhibits reduced cytokine release in a patient as compared to the cytokine released when anti-CD3 antibody OKT3 is administered to a patient. A CD3-binding polypeptide may induce T-cell activation or T-cell proliferation.

[00120] In certain embodiments, a CD3-binding protein can comprise one or more additional binding domains (*e.g.*, second binding domain) that bind a target other than CD3. These other binding domains can comprise, for example, a particular cytokine or a molecule that targets the binding domain polypeptide to a particular cell type, a toxin, an additional cell receptor, an antibody, *etc.*

[00121] In certain embodiments, a CD3-binding polypeptide used in the methods and compositions described herein is a bispecific single chain molecule comprising a CD3-binding domain and a second binding domain. In some embodiments, a CD3- and/or a second binding domain is derived from an antibody and comprises a variable heavy chain (VH) and a variable light chain (VL). These binding domains and variable chains may be arranged in any order that still retains some binding to the target(s). For example, the variable domains may be arranged in the order such as VH SBD-VL SBD-VH CD3-VL CD3; VL SBD-VH SBD-VH CD3-VL CD3; VH SBD-VL SBD-VL CD3-VH CD3; VL SBD-VH SBD-VL CD3-VH CD3; VH CD3-VL CD3-VH SBD-VL SBD; VL CD3-VH CD3-VL SBD-VH SBD; VH CD3-VL CD3-VL SBD-VH SBD; or VL CD3-VH CD3-VH SBD-VL SBD (where SBD refers to "second binding domain"). In certain aspects, the pairs of VH regions and VL regions in the binding domain binding to CD3 are in the format of a single chain antibody (scFv). The VH and VL regions may be arranged in the order VH-VL or VL-VH. In certain embodiments, the scFv may bind more effectively to CD3 in the VL-VH orientation than in the VH-VL orientation, or vice versa. The VH-region may be positioned N-terminally to a linker sequence. The VL region may be positioned C-terminally to the linker sequence. The domain arrangement in the CD3 binding domain of the bispecific single chain molecule may be VH-VL, with said CD3 binding domain located C-terminally to the second binding domain. In some cases, a bispecific molecule may comprise an scFv binding to a second binding domain linked to an scFv binding to CD3. These scFvs may be linked with a short peptide. In some embodiments, bispecific single chain molecules do not comprise a hinge region or a constant region (see, for example, US 2013/0295121, US 2013/0129730, US 2011/0293619, US 7,635,472, WO 2010/037836, WO 2004/106381 and WO 2011/121110; each incorporated herein by reference in its entirety).

[00122] In some embodiments, a binding domain is a single-chain Fv fragment (scFv) that comprises V_H and V_L regions specific for a target of interest. In certain embodiments, the V_H and V_L regions are human or humanized. In some variations, a binding domain is a single-chain Fv (scFv) comprising immunoglobulin V_L and V_H regions joined by a peptide linker. The use of peptide linkers for joining V_L and V_H regions is well-known in the art, and a large number of publications exist within this particular field. A linker may comprise the amino acid sequence QRHNNSSLNTGTQMAGHSPNS (SEQ ID NO:148). In some embodiments, a peptide linker is a 15mer consisting of three repeats of a Gly-Gly-Gly-Gly-Ser amino acid sequence ($(Gly_4Ser)_3$) (SEQ ID NO:193). Other linkers have been used, and phage display technology, as well as selective infective phage technology, has been used to diversify and select appropriate linker sequences (Tang *et al.*, *J. Biol. Chem.* 271, 15682-15686, 1996; Hennecke *et al.*, *Protein Eng.* 11, 405-410, 1998). In certain embodiments, the V_L and V_H regions are joined by a peptide linker having an amino acid sequence comprising the formula $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:194). In some embodiments, a Gly_4Ser sequence may be repeated between 6 and 10 times. Other suitable linkers can be obtained by optimizing a simple linker (*e.g.*, $(Gly_4Ser)_n$ (SEQ ID NO:194)) through random mutagenesis. In some embodiments, the heavy chain variable region of an scFv is amino-terminal to the light chain variable region of the scFv. In other embodiments, the light chain variable region of an scFv is amino-terminal to the heavy chain variable region of the scFv.

[00123] In some embodiments, a CD3-binding polypeptide comprises, in order from amino-terminus to carboxyl-terminus (or in order from carboxyl-terminus to amino-terminus), (i) a second binding domain, (ii) a hinge region, (iii) an immunoglobulin constant region, (iv) a carboxyl-terminus linker (or an amino-terminus linker), and (v) a CD3-binding domain. As used herein in the context of a polypeptide construct comprising a first binding domain and a second binding domain, a "hinge region" or a "hinge" refers to a polypeptide region between the first binding domain and the Fc region. A "carboxyl-terminus linker" or "an amino-terminus linker" refers to a polypeptide region between the Fc region and the second binding domain. In some embodiments, a carboxyl-terminus (or an amino-terminus linker) linker comprises or consists of SEQ ID NO:196. In certain embodiments, a hinge is a wild-type human immunoglobulin hinge region. In certain other embodiments, one or more amino acid residues can be added at the amino- or carboxyl-terminus of a wild type immunoglobulin hinge region as part of a fusion protein construct design. For example, additional junction amino acid residues at the hinge amino-terminus can be "RT," "RSS," "TG," or "T," or at the hinge carboxyl-terminus can be "SG",

or a hinge deletion can be combined with an addition, such as ΔP with "SG" added at the carboxyl-terminus.

[00124] In certain embodiments, a hinge, a carboxyl-terminus linker, or an amino-terminus linker is an altered immunoglobulin hinge in which one or more cysteine residues in a wild type immunoglobulin hinge region is substituted with one or more other amino acid residues (*e.g.*, serine or alanine).

[00125] Exemplary altered immunoglobulin hinges, carboxyl-terminus linkers, and amino-terminus linkers include an immunoglobulin human IgG1 hinge region having one, two or three cysteine residues found in a wild type human IgG1 hinge substituted by one, two or three different amino acid residues (*e.g.*, serine or alanine). An altered immunoglobulin hinge can additionally have a proline substituted with another amino acid (*e.g.*, serine or alanine). For example, the above-described altered human IgG1 hinge can additionally have a proline located carboxyl-terminal to the three cysteines of wild type human IgG1 hinge region substituted by another amino acid residue (*e.g.*, serine, alanine). In one embodiment, the prolines of the core hinge region are not substituted.

[00126] In certain embodiments, a hinge, a carboxyl-terminus linker, or an amino-terminus linker polypeptide comprises or is a sequence that is at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a wild type immunoglobulin hinge region, such as a wild type human IgG1 hinge, a wild type human IgG2 hinge, or a wild type human IgG4 hinge.

[00127] In further embodiments, a hinge, a carboxyl-terminus linker, or an amino-terminus linker present in a CD3-binding polypeptide can be a hinge that is not based on or derived from an immunoglobulin hinge (*i.e.*, not a wild-type immunoglobulin hinge or an altered immunoglobulin hinge). Examples for such hinges and carboxyl-terminus linkers include peptides of about five to about 150 amino acids derived from an interdomain region of a transmembrane protein or stalk region of a type II C-lectin, for instance, peptides of about eight to 25 amino acids and peptides of about seven to 18 amino acids.

[00128] In certain embodiments, interdomain or stalk region hinges, carboxyl-terminus linkers, and amino-terminus linkers have seven to 18 amino acids and can form an α-helical coiled coil structure. In certain embodiments, interdomain or stalk region hinges, carboxyl-terminus

linkers, or amino-terminus linkers contain 0, 1, 2, 3, or 4 cysteines. Exemplary interdomain or stalk region hinges, carboxyl-terminus linkers, and amino-terminus linkers are peptide fragments of the interdomain or stalk regions, such as ten to 150 amino acid fragments from the stalk regions of CD69, CD72, CD94, NKG2A and NKG2D. A hinge, a carboxyl-terminus linker, or an amino-terminus linker may also be a flexible linker sequence comprising (Gly_4Ser) repeats. In some embodiments, a hinge is a 15mer consisting of three repeats of a Gly-Gly-Gly-Gly-Ser amino acid sequence (($Gly_4Ser)_3$) (SEQ ID NO:193). In certain embodiments, a hinge has an amino acid sequence comprising the formula $(Gly_4Ser)_n$, wherein n = 1-5 (SEQ ID NO:194). In some embodiments, a Gly_4Ser sequence may be repeated between 6 and 10 times. Other suitable hinges can be obtained by optimizing a simple linker (*e.g.*, $(Gly_4Ser)_n$ (SEQ ID NO:194)) through random mutagenesis.

[00129] In certain embodiments, hinge, carboxyl-terminus linker, and amino-terminal linker sequences have about 5 to 150 amino acids, 5 to 10 amino acids, 10 to 20 amino acids, 20 to 30 amino acids, 30 to 40 amino acids, 40 to 50 amino acids, 50 to 60 amino acids, 5 to 60 amino acids, 5 to 40 amino acids, 8 to 20 amino acids, or 10 to 15 amino acids. The hinge or linker can be primarily flexible, but can also provide more rigid characteristics or can contain primarily α-helical structure with minimal β-sheet structure. The lengths or the sequences of the hinges and linkers can affect the binding affinities of the binding domains to which the hinges are directly or indirectly (via another region or domain, such as an heterodimerization domain) connected as well as one or more activities of the Fc region portions to which the hinges or linkers are directly or indirectly connected.

[00130] In certain embodiments, hinge, carboxyl-terminus linker, and amino-terminal linker sequences are stable in plasma and serum and are resistant to proteolytic cleavage. The first lysine in the IgG1 upper hinge region can be mutated to minimize proteolytic cleavage, for instance, the lysine can be substituted with methionine, threonine, alanine or glycine, or is deleted.

[00131] In some embodiments of the disclosure, the CD3-binding polypeptide is capable of forming a heterodimer with a second polypeptide chain and comprises a hinge region (a) immediately amino-terminal to an immunoglobulin constant region (*e.g.*, amino-terminal to a CH2 domain wherein the immungobloubolin constant region includes CH2 and CH3 domains, or amino-terminal to a CH3 domain wherein the immunoglobulin sub-regions includes CH3 and CH4 domains), (b) interposed between and connecting a binding domain (*e.g.*, scFv) and a immunoglobulin heterodimerization domain, (c) interposed between and connecting a

immunoglobulin heterodimerization domain and an immunoglobulin constant region (*e.g.*, wherein the immunoglobulin constant region includes CH2 and CH3 domains or CH3 and CH4 domains), (d) interposed between and connecting an immunoglobulin constant region and a binding domain, (e) at the amino-terminus of a polypeptide chain, or (f) at the carboxyl-terminus of a polypeptide chain. A polypeptide chain comprising a hinge region as described herein will be capable of associating with a different polypeptide chain to form a heterodimeric protein provided herein, and the heterodimer formed will contain a binding domain that retains its target specificity or its specific target binding affinity.

[00132] In certain embodiments, a hinge present in a polypeptide that forms a heterodimer with another polypeptide chain can be an immunoglobulin hinge, such as a wild-type immunoglobulin hinge region or an altered immunoglobulin hinge region thereof. In certain embodiments, a hinge of one polypeptide chain of a heterodimeric protein is identical to a corresponding hinge of the other polypeptide chain of the heterodimer. In certain other embodiments, a hinge of one chain is different from that of the other chain (in their length or sequence). The different hinges in the different chains allow different manipulation of the binding affinities of the binding domains to which the hinges are connected, so that the heterodimer is able to preferentially bind to the target of one binding domain over the target of the other binding domain. For example, in certain embodiments, a heterodimeric protein has a CD3-binding domain in one chain and a second binding domain in another chain. Having two different hinges in the two chains may allow the heterodimer to bind to the second target first, and then to a CD3 component second. Thus, the heterodimer may recruit $CD3^+$ T-cells to the second target-expressing cells (*e.g.*, tumor or cancer cells), which in turn may damage or destroy the second target-expressing cells.

[00133] Some exemplary hinge, carboxyl-terminus linker, and amino-terminus linker sequences suitable for use in accordance with the present disclosure are shown in the Tables 1 and 2 below. Additional exemplary hinge and linker regions are set forth in SEQ ID NOs: 241-244, 601, 78, 763-791, 228, 379-434, 618-749 of US 2013/0129723 (said sequences incorporated by reference herein).

Table 1. Exemplary hinges and linkers

Hinge Region	Amino Acid Sequence	SEQ ID NO
sss(s)-hIgG1 hinge	EPKSSDKTHTSPPSS	SEQ ID NO:121
csc(s)-hIgG1 hinge	EPKSCDKTHTSPPCS	SEQ ID NO:122
ssc(s)-hIgG1 hinge	EPKSSDKTHTSPPCS	SEQ ID NO:123
scc(s)-hIgG1 hinge	EPKSSDKTHTCPPCS	SEQ ID NO:124

Hinge Region	Amino Acid Sequence	SEQ ID NO
css(s)-hIgG1 hinge	EPKSCDKTHTSPPSS	SEQ ID NO:125
scs(s)-hIgG1 hinge	EPKSSDKTHTCPPSS	SEQ ID NO:126
ccc(s)-hIgG1 hinge	EPKSCDKTHTSPPCS	SEQ ID NO:127
ccc(p)-hIgG1 hinge	EPKSCDKTHTSPPCP	SEQ ID NO:128
sss(p)-hIgG1 hinge	EPKSSDKTHTSPPSP	SEQ ID NO:129
csc(p)-hIgG1 hinge	EPKSCDKTHTSPPCP	SEQ ID NO:130
ssc(p)-hIgG1 hinge	EPKSSDKTHTSPPCP	SEQ ID NO:131
scc(p)-hIgG1 hinge	EPKSSDKTHTCPPCP	SEQ ID NO:132
css(p)-hIgG1 hinge	EPKSCDKTHTSPPSP	SEQ ID NO:133
scs(p)-hIgG1 hinge	EPKSSDKTHTCPPSP	SEQ ID NO:134
Scppcp	SCPPCP	SEQ ID NO:135
STD1	NYGGGGSGGGGSGGGGSGNS	SEQ ID NO:136
STD2	NYGGGGSGGGGSGGGGSGNY GGGGSGGGGSGGGGSGNS	SEQ ID NO:137
H1	NS	SEQ ID NO:138
H2	GGGGSGNS	SEQ ID NO:139
H3	NYGGGGSGNS	SEQ ID NO:140
H4	GGGGSGGGGSGNS	SEQ ID NO:141
H5	NYGGGGSGGGGSGNS	SEQ ID NO:142
H6	GGGGSGGGGSGGGGSGNS	SEQ ID NO:143
H7	GCPPCPNS	SEQ ID NO:144
$(G_4S)_3$	GGGGSGGGGSGGGGS	SEQ ID NO:145
H105	SGGGGSGGGGSGGGGS	SEQ ID NO:146
$(G_4S)_4$	GGGGSGGGGSGGGGSGGGGS	SEQ ID NO:147
H75 (NKG2A quadruple mutant)	QRHNNSSLNTGTQMAGHSPNS	SEQ ID NO:148
H83 (NKG2A derived)	SSLNTGTQMAGHSPNS	SEQ ID NO:149
H106 (NKG2A derived)	QRHNNSSLNTGTQMAGHS	SEQ ID NO:150
H81 (NKG2D derived)	EVQIPLTESYSPNS	SEQ ID NO:151
H91 (NKG2D derived)	NSLANQEVQIPLTESYSPNS	SEQ ID NO:152
H94	SGGGGSGGGGSGGGGSPNS	SEQ ID NO:153
H111	SGGGGSGGGGSGGGGSPGS	SEQ ID NO:196

Table 2. Exemplary hinges and linkers (derived from H7 hinge, stalk region of a type II C-lectin, or interdomain region of a type I transmembrane protein)

Hinge Region	Amino Acid Sequence	Molecule and/or hinge from which derived	SEQ ID NO:
H16	LSVKADFLTPSIGNS	CD80	SEQ ID NO:154
H17	LSVKADFLTPSISCPPCPNS	CD80 + H7	SEQ ID NO:155
H18	LSVLANFSQPEIGNS	CD86	SEQ ID NO:156
H19	LSVLANFSQPEISCPPCPNS	CD86 + H7	SEQ ID NO:157
H20	LKIQERVSKPKISNS	CD2	SEQ ID NO:158
H21	LKIQERVSKPKISCPPCPNS	CD2 + H7	SEQ ID NO:159
H22	LNVSERPFPPHIQNS	CD22	SEQ ID NO:160
H23	LDVSERPFPPHIQSCPPCPNS	CD22 + H7	SEQ ID NO:161
H24	REQLAEVTLSLKANS	CD80	SEQ ID NO:162
H25	REQLAEVTLSLKACPPCPNS	CD80 + H7	SEQ ID NO:163
H26	RIHQMNSELSVLANS	CD86	SEQ ID NO:164
H27	RIHQMNSELSVLACPPCPNS	CD86 + H7	SEQ ID NO:165
H28	DTKGKNVLEKIFSNS	CD2	SEQ ID NO:166
H30	LPPETQESQEVTLNS	CD22	SEQ ID NO:167
H32	RIHLNVSERPFPPNS	CD22	SEQ ID NO:168
H33	RIHLNVSERPFPPCPPCPNS	CD22 + H7	SEQ ID NO:169
H36	GCPPCPGGGGSNS	H7	SEQ ID NO:170
H40	GCPPCPANS	H7	SEQ ID NO:171
H41	GCPPCPANS	H7	SEQ ID NO:172
H42	GCPPCPNS	H7	SEQ ID NO:173
H44	GGGASCPPCPGNS	H7	SEQ ID NO:174
H45	GGGASCPPCAGNS	H7	SEQ ID NO:175
H46	GGGASCPPCANS	H7	SEQ ID NO:176
H47	LSVKADFLTPSIGNS	CD80	SEQ ID NO:177
H48	ADFLTPSIGNS	CD80	SEQ ID NO:178
H50	LSVLANFSQPEIGNS	CD86	SEQ ID NO:179
H51	LSVLANFSQPEIGNS	CD86	SEQ ID NO:180
H52	SQPEIVPISNS	CD86	SEQ ID NO:181
H53	SQPEIVPISCPPCPNS	CD86 + H7	SEQ ID NO:182
H54	SVLANFSQPEISCPPCPNS	CD86 + H7	SEQ ID NO:183
H55	RIHQMNSELSVLANS	CD86	SEQ ID NO:184
H56	QMNSELSVLANS	CD86	SEQ ID NO:185
H57	VSERPFPPNS	CD22	SEQ ID NO:186
H58	KPFFTCGSADTCPNS	CD72	SEQ ID NO:187

Hinge Region	Amino Acid Sequence	Molecule and/or hinge from which derived	SEQ ID NO:
H59	KPFFTCGSADTCPNS	CD72	SEQ ID NO:188
H60	QYNCPGQYTFSMPNS	CD69	SEQ ID NO:189
H61	EPAFTPGPNIELQKDSDCPNS	CD94	SEQ ID NO:190
H62	QRHNNSSLNTRTQKARHCPNS	NKG2A	SEQ ID NO:191
H63	NSLFNQEVQIPLTESYCPNS	NKG2D	SEQ ID NO:192

[00134] In certain embodiments, a CD3-binding polypeptide or protein of the disclosure can comprise an "immunoglobulin dimerization domain" or "immunoglobulin heterodimerization domain."

[00135] An "immunoglobulin dimerization domain" or "immunoglobulin heterodimerization domain," as used herein, refers to an immunoglobulin domain of a polypeptide chain that preferentially interacts or associates with a different immunoglobulin domain of another polypeptide chain, wherein the interaction of the different immunoglobulin heterodimerization domains substantially contributes to or efficiently promotes heterodimerization of the first and second polypeptide chains (*i.e.*, the formation of a dimer between two different polypeptide chains, which is also referred to as a "heterodimer" or "heterodimeric protein"). The interactions between immunoglobulin heterodimerization domains "substantially contributes to or efficiently promotes" the heterodimerization of first and second polypeptide chains if there is a statistically significant reduction in the dimerization between the first and second polypeptide chains in the absence of the immunoglobulin heterodimerization domain of the first polypeptide chain and/or the immunoglobulin heterodimerization domain of the second polypeptide chain. In certain embodiments, when the first and second polypeptide chains are co-expressed, at least 60%, at least about 60% to about 70%, at least about 70% to about 80%, at least 80% to about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the first and second polypetpide chains form heterodimers with each other. Representative immunoglobulin heterodimerization domains include an immunoglobulin CH1 domain, an immunoglobulin CL1 domain (*e.g.*, Cκ or Cλ isotypes), or derivatives thereof, including wild-type immunoglobulin CH1 and CL domains and altered (or mutated) immunoglobulin CH1 and CL domains, such as provided herein.

[00136] Dimerization/heterodimerization domains can be used where it is desired to form heterodimers from two non-identical polypeptide chains, where one or both polypeptide chains comprise a binding domain. In certain embodiments, one polypeptide chain member of certain

heterodimers described herein does not contain a binding domain. As indicated above, a heterodimeric protein of the present disclosure comprises an immunoglobulin heterodimerization domain in each polypeptide chain. The immunoglobulin heterodimerization domains in the polypeptide chains of a heterodimer are different from each other and thus can be differentially modified to facilitate heterodimerization of both chains and to minimize homodimerization of either chain. Immunoglobulin heterodimerization domains provided herein allow for efficient heterodimerization between different polypeptides and facilitate purification of the resulting heterodimeric protein.

[00137] As provided herein, immunoglobulin heterodimerization domains useful for promoting heterodimerization of two different single chain polypeptides (*e.g.*, one short and one long) according to the present disclosure include immunoglobulin CH1 and CL domains, for instance, human CH1 and CL domains. In certain embodiments, an immunoglobulin heterodimerization domain is a wild-type CH1 domain, such as a wild type IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 domain. In further embodiments, an immunoglobulin heterodimerization domain is a wild-type human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 domain as set forth in SEQ ID NOS:114, 186-192 and 194, respectively, of US 2013/0129723 (said sequences incorporated by reference herein). In certain embodiments, an immunoglobulin heterodimerization domain is a wild-type human IgG1 CH1 domain as set forth in SEQ ID NO:114 of US 2013/0129723 (said sequence incorporated by reference herein).

[00138] In further embodiments, an immunoglobulin heterodimerization domain is an altered immunoglobulin CH1 domain, such as an altered IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 IgD, IgE, or IgM CH1 domain. In certain embodiments, an immunoglobulin heterodimerization domain is an altered human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM CH1 domain. In still further embodiments, a cysteine residue of a wild-type CH1 domain (*e.g.*, a human CH1) involved in forming a disulfide bond with a wild type immunoglobulin CL domain (*e.g.*, a human CL) is deleted or substituted in the altered immunoglobulin CH1 domain such that a disulfide bond is not formed between the altered CH1 domain and the wild-type CL domain.

[00139] In certain embodiments, an immunoglobulin heterodimerization domain is a wild-type CL domain, such as a wild type Cκ domain or a wild type Cλ domain. In certain embodiments, an immunoglobulin heterodimerization domain is a wild type human Cκ or human Cλ domain as set forth in SEQ ID NOS:112 and 113, respectively, of US 2013/0129723 (said sequences incorporated by reference herein). In further embodiments, an immunoglobulin

heterodimerization domain is an altered immunoglobulin CL domain, such as an altered Cκ or Cλ domain, for instance, an altered human Cκ or human Cλ domain.

[00140] In certain embodiments, a cysteine residue of a wild-type CL domain (*e.g.*, a human CL) involved in forming a disulfide bond with a wild type immunoglobulin CH1 domain (*e.g.*, a human CH1) is deleted or substituted in the altered immunoglobulin CL domain. Such altered CL domains can further comprise an amino acid deletion at their amino-termini. An exemplary Cκ domain is set forth in SEQ ID NO:141 of US 2013/0129723 (said sequence incorporated by reference herein), in which the first arginine and the last cysteine of the wild type human Ck domain are both deleted. In certain embodiments, only the last cysteine of the wild type human Ck domain is deleted in the altered Ck domain because the first arginine deleted from the wild type human Ck domain can be provided by a linker that has an arginine at its carboxyl-terminus and links the amino-terminus of the altered Ck domain with another domain (*e.g.*, an immunoglobulin sub-region, such as a sub-region comprising immunoglobulin CH2 and CH3 domains). An exemplary Cλ domain is set forth in SEQ ID NO:140 of US 2013/0129723 (said sequence incorporated by reference herein), in which the first arginine of a wild type human Cλ domain is deleted and the cysteine involved in forming a disulfide bond with a cysteine in a CH1 domain is substituted by a serine.

[00141] In further embodiments, an immunoglobulin heterodimerization domain is an altered Cκ domain that contains one or more amino acid substitutions, as compared to a wild type Cκ domain, at positions that may be involved in forming the interchain-hydrogen bond network at a Cκ-Cκ interface. For example, in certain embodiments, an immunoglobulin heterodimerization domain is an altered human Cκ domain having one or more amino acids at positions N29, N30, Q52, V55, T56, S68 or T70 that are substituted with a different amino acid. The numbering of the amino acids is based on their positions in the altered human Cκ sequence as set forth in SEQ ID NO:141 of US 2013/0129723 (said sequence incorporated by reference herein). In certain embodiments, an immunoglobulin heterodimerization domain is an altered human Cκ domain having one, two, three or four amino acid substitutions at positions N29, N30, V55, or T70. The amino acid used as a substitute at the above-noted positions can be an alanine, or an amino acid residue with a bulk side chain moiety such as arginine, tryptophan, tyrosine, glutamate, glutamine, or lysine. Additional amino acid residues that can be used to substitute amino acid residues of the wild type human Ck sequence at the above noted positions (*e.g.*, N30) include aspartate, methionine, serine and phenyalanine. Exemplary altered human Cκ domains are set forth in SEQ ID NOS:142-178 of US 2013/0129723 (said sequences

incorporated by reference herein). Altered human Cκ domains are those that facilitate heterodimerization with a CH1 domain, but minimize homodimerization with another Cκ domain. Representative altered human Cκ domains are set forth in SEQ ID NOS:160 (N29W V55A T70A), 161 (N29Y V55A T70A), 202 (T70E N29A N30A V55A), 167 (N30R V55A T70A), 168 (N30K V55A T70A), 170 (N30E V55A T70A), 172 (V55R N29A N30A), 175 (N29W N30Y V55A T70E), 176 (N29Y N30Y V55A T70E), 177 (N30E V55A T70E), 178 (N30Y V55A T70E), 838 (N30D V55A T70E), 839 (N30M V55A T70E), 840 (N30S V55A T70E), and 841 (N30F V55A T70E) of US 2013/0129723 (said sequences incorporated by reference herein).

[00142] In certain embodiments, in addition to or alternative to the mutations in Ck domains described herein, both the immunoglobulin heterodimerization domains (*i.e.*, immunoglobulin CH1 and CL domains) of a polypeptide heterodimer have mutations so that the resulting immunoglobulin heterodimerization domains form salt bridges (*i.e.*, ionic interactions) between the amino acid residues at the mutated sites. For example, the immunoglobulin heterodimerization domains of a polypeptide heterodimer can be a mutated CH1 domain in combination with a mutated Ck domain. In the mutated CH1 domain, valine at position 68 (V68) of the wild type human CH1 domain is substituted by an amino acid residue having a negative charge (*e.g.*, aspartate or glutamate), whereas leucine at position 29 (L29) of a mutated human Ck domain in which the first arginine and the last cysteine have been deleted is substituted by an amino acid residue having a positive charge (*e.g.*, lysine, arginine or histidine). The charge-charge interaction between the amino acid residue having a negative charge of the resulting mutated CH1 domain and the amino acid residue having a positive charge of the resulting mutated Ck domain forms a salt bridge, which stabilizes the heterodimeric interface between the mutated CH1 and Ck domains. Alternatively, V68 of the wild type CH1 can be substituted by an amino acid residue having a positive charge, whereas L29 of a mutated human Ck domain in which the first arginine and the last cysteine have been deleted can be substituted by an amino acid residue having a negative charge. Exemplary mutated CH1 sequences in which V68 is substituted by an amino acid with either a negative or positive charge are set forth in SEQ ID NOS:844 and 845 of US 2013/0129723 (said sequences incorporated by reference herein). Exemplary mutated Ck sequences in which L29 is substituted by an amino acid with either a negative or positive charge are set forth in SEQ ID NOS:842 and 843 of US 2013/0129723 (said sequences incorporated by reference herein).

[00143] Positions other than V68 of human CH1 domain and L29 of human Ck domain can be substituted with amino acids having opposite charges to produce ionic interactions between the

amino acids in addition or alternative to the mutations in V68 of CH1 domain and L29 of Ck domain. Such positions can be identified by any suitable method, including random mutagenesis, analysis of the crystal structure of the CH1-Ck pair to identify amino acid residues at the CH1-Ck interface, and further identifying suitable positions among the amino acid residues at the CH1-Ck interface using a set of criteria (*e.g.*, propensity to engage in ionic interactions, proximity to a potential partner residue, etc.).

[00144] In certain embodiments, polypeptide heterodimers of the present disclosure contain only one pair of immunoglobulin heterodimerization domains. For example, a first chain of a polypeptide heterodimer can comprise a CH1 domain as an immunoglobulin heterodimerization domain, while a second chain can comprise a CL domain (*e.g.*, a Cκ or Cλ) as an immunoglobulin heterodimerization domain. Alternatively, a first chain can comprise a CL domain (*e.g.*, a Cκ or Cλ) as an immunoglobulin heterodimerization domain, while a second chain can comprise a CH1 domain as an immunoglobulin heterodimerization domain. As set forth herein, the immunoglobulin heterodimerization domains of the first and second chains are capable of associating to form a heterodimeric protein of this disclosure.

[00145] In certain other embodiments, heterodimeric proteins of the present disclosure can have two pairs of immunoglobulin heterodimerization domains. For example, a first chain of a heterodimer can comprise two CH1 domains, while a second chain can have two CL domains that associate with the two CH1 domains in the first chain. Alternatively, a first chain can comprise two CL domains, while a second chain can have two CH1 domains that associate with the two CL domains in the first chain. In certain embodiments, a first polypeptide chain comprises a CH1 domain and a CL domain, while a second polypeptide chain comprises a CL domain and a CH1 domain that associate with the CH1 domain and the CL domain, respectively, of the first polypeptide chain.

[00146] In the embodiments where a heterodimeric protein comprises only one heterodimerization pair (*i.e.*, one immunoglobulin heterodimerization domain in each chain), the immunoglobulin heterodimerization domain of each chain can be located amino-terminal to the immunoglobulin constant region of that chain. Alternatively, the immunoglobulin heterodimerization domain in each chain can be located carboxyl-terminal to the immunoglobulin constant region of that chain.

[00147] In the embodiments where a heterodimeric protein comprises two heterodimerization pairs (*i.e.*, two immunoglobulin heterodimerization domains in each chain), both immunoglobulin heterodimerization domains in each chain can be located amino-terminal to the immunoglobulin

constant region of that chain. Alternatively, both immunoglobulin heterodimerization domains in each chain can be located carboxyl-terminal to the immunoglobulin constant region of that chain. In further embodiments, one immunoglobulin heterodimerization domain in each chain can be located amino-terminal to the immunoglobulin constant region of that chain, while the other immunoglobulin heterodimerization domain of each chain can be located carboxyl-terminal to the immunoglobulin constant region of that chain. In other words, in those embodiments, the immunoglobulin constant region is interposed between the two immunoglobulin heterodimerization domains of each chain.

[00148] As indicated herein, in certain embodiments, CD3-binding polypeptides of the present disclosure comprise an immunoglobulin constant region (also referred to as a constant region) in a polypeptide chain. The inclusion of an immunoglobulin constant region slows clearance of the homodimeric and heterodimeric proteins formed from two CD3-binding polypeptide chains from circulation after administration to a subject. By mutations or other alterations, an immunoglobulin constant region further enables relatively easy modulation of dimeric polypeptide effector functions (*e.g.*, ADCC, ADCP, CDC, complement fixation, and binding to Fc receptors), which can either be increased or decreased depending on the disease being treated, as known in the art and described herein. In certain embodiments, an immunoglobulin constant region of one or both of the polypeptide chains of the polypeptide homodimers and heterodimers of the present disclosure will be capable of mediating one or more of these effector functions In other embodiments, one or more of these effector functions are reduced or absent in an immunoglobulin constant region of one or both of the polypeptide chains of the polypeptide homodimers and heterodimers of the present disclosure, as compared to a corresponding wild-type immunoglobulin constant region. For example, for dimeric CD3-binding polypeptides designed to elicit RTCC, such as, *e.g.*, via the inclusion of a second binding domain, an immunoglobulin constant region may have reduced or no effector function relative to a corresponding wild-type immunoglobulin constant region.

[00149] An immunoglobulin constant region present in CD3-binding polypeptides of the present disclosure can comprise or is derived from part or all of: a CH2 domain, a CH3 domain, a CH4 domain, or any combination thereof. For example, an immunoglobulin constant region can comprise a CH2 domain, a CH3 domain, both CH2 and CH3 domains, both CH3 and CH4 domains, two CH3 domains, a CH4 domain, two CH4 domains, and a CH2 domain and part of a CH3 domain.

[00150] A CH2 domain that can form an immunoglobulin constant region of a CD3-binding polypeptide of the present disclosure can be a wild type immunoglobulin CH2 domain or an altered immunoglobulin CH2 domain thereof from certain immunoglobulin classes or subclasses (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD) and from various species (including human, mouse, rat, and other mammals).

[00151] In certain embodiments, a CH2 domain is a wild type human immunoglobulin CH2 domain, such as wild type CH2 domains of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, or IgD, as set forth in SEQ ID NOS:115, 199-201 and 195-197, respectively, of US 2013/0129723 (said sequences incorporated by reference herein). In certain embodiments, the CH2 domain is a wild type human IgG1 CH2 domain as set forth in SEQ ID NO:115 of US 2013/0129723 (said sequence incorporated by reference herein).

[00152] In certain embodiments, a CH2 domain is an altered immunoglobulin CH2 region (*e.g.*, an altered human IgG1 CH2 domain) that comprises an amino acid substitution at the asparagine of position 297 (*e.g.*, asparagine to alanine). Such an amino acid substitution reduces or eliminates glycosylation at this site and abrogates efficient Fc binding to FcγR and C1q. The sequence of an altered human IgG1 CH2 domain with an Asn to Ala substitution at position 297 is set forth in SEQ ID NO:324 of US 2013/0129723 (said sequence incorporated by reference herein).

[00153] In certain embodiments, a CH2 domain is an altered immunoglobulin CH2 region (*e.g.*, an altered human IgG1 CH2 domain) that comprises at least one substitution or deletion at positions 234 to 238. For example, an immunoglobulin CH2 region can comprise a substitution at position 234, 235, 236, 237 or 238, positions 234 and 235, positions 234 and 236, positions 234 and 237, positions 234 and 238, positions 234-236, positions 234, 235 and 237, positions 234, 236 and 238, positions 234, 235, 237, and 238, positions 236-238, or any other combination of two, three, four, or five amino acids at positions 234-238. In addition or alternatively, an altered CH2 region can comprise one or more (*e.g.*, two, three, four or five) amino acid deletions at positions 234-238, for instance, at one of position 236 or position 237 while the other position is substituted. The above-noted mutation(s) decrease or eliminate the antibody-dependent cell-mediated cytotoxicity (ADCC) activity or Fc receptor-binding capability of a polypeptide heterodimer that comprises the altered CH2 domain. In certain embodiments, the amino acid residues at one or more of positions 234-238 has been replaced with one or more alanine residues. In further embodiments, only one of the amino acid residues at

positions 234-238 have been deleted while one or more of the remaining amino acids at positions 234-238 can be substituted with another amino acid (*e.g.*, alanine or serine).

[00154] In certain other embodiments, a CH2 domain is an altered immunoglobulin CH2 region (*e.g.*, an altered human IgG1 CH2 domain) that comprises one or more amino acid substitutions at positions 253, 310, 318, 320, 322, and 331. For example, an immunoglobulin CH2 region can comprise a substitution at position 253, 310, 318, 320, 322, or 331, positions 318 and 320, positions 318 and 322, positions 318, 320 and 322, or any other combination of two, three, four, five or six amino acids at positions 253, 310, 318, 320, 322, and 331. The above-noted mutation(s) decrease or eliminate the complement-dependent cytotoxicity (CDC) of a polypeptide heterodimer that comprises the altered CH2 domain.

[00155] In certain other embodiments, in addition to the amino acid substitution at position 297, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) can further comprise one or more (*e.g.*, two, three, four, or five) additional substitutions at positions 234-238. For example, an immunoglobulin CH2 region can comprise a substitution at positions 234 and 297, positions 234, 235, and 297, positions 234, 236 and 297, positions 234-236 and 297, positions 234, 235, 237 and 297, positions 234, 236, 238 and 297, positions 234, 235, 237, 238 and 297, positions 236-238 and 297, or any combination of two, three, four, or five amino acids at positions 234-238 in addition to position 297. In addition or alternatively, an altered CH2 region can comprise one or more (*e.g.*, two, three, four or five) amino acid deletions at positions 234-238, such as at position 236 or position 237. The additional mutation(s) decreases or eliminates the antibody-dependent cell-mediated cytotoxicity (ADCC) activity or Fc receptor-binding capability of a polypeptide heterodimer that comprises the altered CH2 domain. In certain embodiments, the amino acid residues at one or more of positions 234-238 have been replaced with one or more alanine residues. In further embodiments, only one of the amino acid residues at positions 234-238 has been deleted while one or more of the remaining amino acids at positions 234-238 can be substituted with another amino acid (*e.g.*, alanine or serine).

[00156] In certain embodiments, in addition to one or more (*e.g.*, 2, 3, 4, or 5) amino acid substitutions at positions 234-238, a mutated CH2 region (*e.g.*, an altered human IgG1 CH2 domain) in a fusion protein of the present disclosure can contain one or more (*e.g.*, 2, 3, 4, 5, or 6) additional amino acid substitutions (*e.g.*, substituted with alanine) at one or more positions involved in complement fixation (*e.g.*, at positions I253, H310, E318, K320, K322, or P331). Examples of mutated immunoglobulin CH2 regions include human IgG1, IgG2, IgG4 and mouse IgG2a CH2 regions with alanine substitutions at positions 234, 235, 237 (if present), 318, 320

and 322. An exemplary mutated immunoglobulin CH2 region is mouse IGHG2c CH2 region with alanine substitutions at L234, L235, G237, E318, K320, and K322.

[00157] In still further embodiments, in addition to the amino acid substitution at position 297 and the additional deletion(s) or substitution(s) at positions 234-238, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) can further comprise one or more (*e.g.*, two, three, four, five, or six) additional substitutions at positions 253, 310, 318, 320, 322, and 331. For example, an immunoglobulin CH2 region can comprise a (1) substitution at position 297, (2) one or more substitutions or deletions or a combination thereof at positions 234-238, and one or more (*e.g.*, 2, 3, 4, 5, or 6) amino acid substitutions at positions I253, H310, E318, K320, K322, and P331, such as one, two, three substitutions at positions E318, K320 and K322. The amino acids at the above-noted positions can be substituted by alanine or serine.

[00158] In certain embodiments, an immunoglobulin CH2 region polypeptide comprises: (i) an amino acid substitution at the asparagines of position 297 and one amino acid substitution at position 234, 235, 236 or 237; (ii) an amino acid substitution at the asparagine of position 297 and amino acid substitutions at two of positions 234-237; (iii) an amino acid substitution at the asparagine of position 297 and amino acid substitutions at three of positions 234-237; (iv) an amino acid substitution at the asparagine of position 297, amino acid substitutions at positions 234, 235 and 237, and an amino acid deletion at position 236; (v) amino acid substitutions at three of positions 234-237 and amino acid substitutions at positions 318, 320 and 322; or (vi) amino acid substitutions at three of positions 234-237, an amino acid deletion at position 236, and amino acid substitutions at positions 318, 320 and 322.

[00159] Exemplary altered immunoglobulin CH2 regions with amino acid substitutions at the asparagine of position 297 include: human IgG1 CH2 region with alanine substitutions at L234, L235, G237 and N297 and a deletion at G236 (SEQ ID NO:325 of US 2013/0129723, said sequence incorporated by reference herein), human IgG2 CH2 region with alanine substitutions at V234, G236, and N297 (SEQ ID NO:326 of US 2013/0129723, said sequence incorporated by reference herein), human IgG4 CH2 region with alanine substitutions at F234, L235, G237 and N297 and a deletion of G236 (SEQ ID NO:322 of US 2013/0129723, said sequence incorporated by reference herein), human IgG4 CH2 region with alanine substitutions at F234 and N297 (SEQ ID NO:343 of US 2013/0129723, said sequence incorporated by reference herein), human IgG4 CH2 region with alanine substitutions at L235 and N297 (SEQ ID NO:344 of US 2013/0129723, said sequence incorporated by reference herein), human IgG4 CH2 region with alanine substitutions at G236 and N297 (SEQ ID NO:345 of US 2013/0129723, said

sequence incorporated by reference herein), and human IgG4 CH2 region with alanine substitutions at G237 and N297 (SEQ ID NO:346 of US 2013/0129723, said sequence incorporated by reference herein).

[00160] In certain embodiments, in addition to the amino acid substitutions described above, an altered CH2 region (*e.g.*, an altered human IgG1 CH2 domain) can contain one or more additional amino acid substitutions at one or more positions other than the above-noted positions. Such amino acid substitutions can be conservative or non-conservative amino acid substitutions. For example, in certain embodiments, P233 can be changed to E233 in an altered IgG2 CH2 region (*see, e.g.*, SEQ ID NO:326 of US 2013/0129723, said sequence incorporated by reference herein). In addition or alternatively, in certain embodiments, the altered CH2 region can contain one or more amino acid insertions, deletions, or both. The insertion(s), deletion(s) or substitution(s) can be anywhere in an immunoglobulin CH2 region, such as at the N- or C-terminus of a wild type immunoglobulin CH2 region resulting from linking the CH2 region with another region (*e.g.*, a binding domain or an immunoglobulin heterodimerization domain) via a hinge.

[00161] In certain embodiments, an altered CH2 region in a polypeptide of the present disclosure comprises or is a sequence that is at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a wild type immunoglobulin CH2 region, such as the CH2 region of wild type human IgG1, IgG2, or IgG4, or mouse IgG2a (*e.g.*, IGHG2c).

[00162] An altered immunoglobulin CH2 region in a CD3-binding polypeptide of the present disclosure can be derived from a CH2 region of various immunoglobulin isotypes, such as IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, and IgD, from various species (including human, mouse, rat, and other mammals). In certain embodiments, an altered immunoglobulin CH2 region in a fusion protein of the present disclosure can be derived from a CH2 region of human IgG1, IgG2 or IgG4, or mouse IgG2a (*e.g.*, IGHG2c), whose sequences are set forth in SEQ ID NOS:115, 199, 201, and 320 of US 2013/0129723 (said sequences incorporated by reference herein).

[00163] In certain embodiments, an altered CH2 domain is a human IgG1 CH2 domain with alanine substitutions at positions 235, 318, 320, and 322 (*i.e.*, a human IgG1 CH2 domain with L235A, E318A, K320A and K322A substitutions) (SEQ ID NO:595 of US 2013/0129723, said sequence incorporated by reference herein), and optionally an N297 mutation (*e.g.*, to alanine). In certain other embodiments, an altered CH2 domain is a human IgG1 CH2 domain with alanine substitutions at positions 234, 235, 237, 318, 320 and 322 (*i.e.*, a human IgG1 CH2

domain with L234A, L235A, G237A, E318A, K320A and K322A substitutions) (SEQ ID NO:596 of US 2013/0129723, said sequence incorporated by reference herein), and optionally an N297 mutation (*e.g.*, to alanine).

[00164] In certain embodiments, an altered CH2 domain is an altered human IgG1 CH2 domain with mutations known in the art that enhance immunological activities such as ADCC, ADCP, CDC, complement fixation, Fc receptor binding, or any combination thereof.

[00165] The CH3 domain that can form an immunoglobulin constant region of a CD3-binding polypeptide of the present disclosure can be a wild type immunoglobulin CH3 domain or an altered immunoglobulin CH3 domain thereof from certain immunoglobulin classes or subclasses (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, IgM) of various species (including human, mouse, rat, and other mammals). In certain embodiments, a CH3 domain is a wild type human immunoglobulin CH3 domain, such as wild type CH3 domains of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM as set forth in SEQ ID NOS:116, 208-210, 204-207, and 212, respectively of US 2013/0129723 (said sequences incorporated by reference herein). In certain embodiments, the CH3 domain is a wild type human IgG1 CH3 domain as set forth in SEQ ID NO:116 of US 2013/0129723 (said sequence incorporated by reference herein). In certain embodiments, a CH3 domain is an altered human immunoglobulin CH3 domain, such as an altered CH3 domain based on or derived from a wild-type CH3 domain of human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgD, IgE, or IgM antibodies. For example, an altered CH3 domain can be a human IgG1 CH3 domain with one or two mutations at positions H433 and N434 (positions are numbered according to EU numbering). The mutations in such positions can be involved in complement fixation. In certain other embodiments, an altered CH3 domain can be a human IgG1 CH3 domain but with one or two amino acid substitutions at position F405 or Y407. The amino acids at such positions are involved in interacting with another CH3 domain. In certain embodiments, an altered CH3 domain can be an altered human IgG1 CH3 domain with its last lysine deleted. The sequence of this altered CH3 domain is set forth in SEQ ID NO:761 of US 2013/0129723 (said sequence incorporated by reference herein).

[00166] In certain embodiments, CD3-binding polypeptides forming a polypeptide heterodimer comprise a CH3 pair that comprises so called "knobs-into-holes" mutations (*see*, Marvin and Zhu, Acta Pharmacologica Sinica 26:649-58, 2005; Ridgway *et al.*, Protein Engineering 9:617-21, 1966). More specifically, mutations can be introduced into each of the two CH3 domains of each polypeptide chain so that the steric complementarity required for CH3/CH3 association obligates these two CH3 domains to pair with each other. For example, a CH3 domain in one

single chain polypeptide of a polypeptide heterodimer can contain a T366W mutation (a "knob" mutation, which substitutes a small amino acid with a larger one), and a CH3 domain in the other single chain polypeptide of the polypeptide heterodimer can contain a Y407A mutation (a "hole" mutation, which substitutes a large amino acid with a smaller one). Other exemplary knobs-into-holes mutations include (1) a T366Y mutation in one CH3 domain and a Y407T in the other CH3 domain, and (2) a T366W mutation in one CH3 domain and T366S, L368A and Y407V mutations in the other CH3 domain.

[00167] The CH4 domain that can form an immunoglobulin constant region of CD3-binding polypeptides of the present disclosure can be a wild type immunoglobulin CH4 domain or an altered immunoglobulin CH4 domain thereof from IgE or IgM molecules. In certain embodiments, the CH4 domain is a wild type human immunoglobulin CH4 domain, such as wild type CH4 domains of human IgE and IgM molecules as set forth in SEQ ID NOS:213 and 214, respectively, of US 2013/0129723 (said sequences incorporated by reference herein). In certain embodiments, a CH4 domain is an altered human immunoglobulin CH4 domain, such as an altered CH4 domain based on or derived from a CH4 domain of human IgE or IgM molecules, which have mutations that increase or decrease an immunological activity known to be associated with an IgE or IgM Fc region.

[00168] In certain embodiments, an immunoglobulin constant region of CD3-binding polypeptides of the present disclosure comprises a combination of CH2, CH3 or CH4 domains (*i.e.*, more than one constant region domain selected from CH2, CH3 and CH4). For example, the immunoglobulin constant region can comprise CH2 and CH3 domains or CH3 and CH4 domains. In certain other embodiments, the immunoglobulin constant region can comprise two CH3 domains and no CH2 or CH4 domains (*i.e.*, only two or more CH3). The multiple constant region domains that form an immunoglobulin constant region can be based on or derived from the same immunoglobulin molecule, or the same class or subclass immunoglobulin molecules. In certain embodiments, the immunoglobulin constant region is an IgG CH2CH3 (*e.g.*, IgG1 CH2CH3, IgG2 CH2CH3, and IgG4 CH2CH3) and can be a human (*e.g.*, human IgG1, IgG2, and IgG4) CH2CH3. For example, in certain embodiments, the immunoglobulin constant region comprises (1) wild type human IgG1 CH2 and CH3 domains, (2) human IgG1 CH2 with N297A substitution (*i.e.*, CH2(N297A)) and wild type human IgG1 CH3, or (3) human IgG1 CH2(N297A) and an altered human IgG1 CH3 with the last lysine deleted.

[00169] Alternatively, the multiple constant region domains can be based on or derived from different immunoglobulin molecules, or different classes or subclasses immunoglobulin

molecules. For example, in certain embodiments, an immunoglobulin constant region comprises both human IgM CH3 domain and human IgG1 CH3 domain. The multiple constant region domains that form an immunoglobulin constant region can be directly linked together or can be linked to each other via one or more (*e.g.*, about 2-10) amino acids.

[00170] Exemplary immunoglobulin constant regions are set forth in SEQ ID NOS:305-309, 321, 323, 341, 342, and 762 of US 2013/0129723 (said sequences incorporated by reference herein).

[00171] In certain embodiments, the immunoglobulin constant regions of both CD3-binding polypeptides of a polypeptide homodimer or heterodimer are identical to each other. In certain other embodiments, the immunoglobulin constant region of one polypeptide chain of a heterodimeric protein is different from the immunoglobulin constant region of the other polypeptide chain of the heterodimer. For example, one immunoglobulin constant region of a heterodimeric protein can contain a CH3 domain with a "knob" mutation, whereas the other immunoglobulin constant region of the heterodimeric protein can contain a CH3 domain with a "hole" mutation.

[00172] The disclosure relates to CD3-binding proteins and polypeptides that may comprise any of the sequences shown in Table 14. Amino acid sequences for polypeptide constructs may or may not include signal sequences. CD3-binding proteins may comprise any of the CD3-binding domains described above. In some aspects, CD3-binding proteins comprise humanized V_H or V_L amino acid sequences, or both.

[00173] Examples of bispecific CD3-binding polypeptides are provided in Tables 12 and 13. Such examples include anti-PSMA x anti-CD3 binding molecules (SEQ ID NOs:62, 64, 66, and 68), anti-CD37 x anti-CD3 binding molecules (SEQ ID NOs:72, 74, 76, 78, 80, and 82), anti-ROR1 x anti-CD3 binding molecules (SEQ ID NOs:100, 104, 108, 112, 116, and 120), and anti-CD123 x anti-CD3 binding molecules (SEQ ID NOs:197 and 198).

[00174] CD3-binding molecules may be made using scaffolding as generally disclosed in US 2013/0129723 and US 2013/0095097, which are each incorporated herein by reference in their entirety. The CD3-binding proteins may comprise two non-identical polypeptide chains, each polypeptide chain comprising an immunoglobulin heterodimerization domain. The interfacing immunoglobulin heterodimerization domains are different. In one embodiment, the immunoglobulin heterodimerization domain comprises a CH1 domain or a derivative thereof. In another embodiment, the immunoglobulin heterodimerization domain comprises a CL domain or

a derivative thereof. In one embodiment, the CL domain is a Cκ or Cλ isotype or a derivative thereof.

[00175] The disclosure also includes nucleic acids (*e.g.*, DNA or RNA) encoding CD3-binding domains, proteins and polypeptides described herein, or one or more polypeptide chains of a homodimeric or heterodimeric CD3-binding protein as described herein. Nucleic acids of the disclosure include nucleic acids having a region that is substantially identical to a polynucleotide as listed in Table 14, *infra*. In certain embodiments, a nucleic acid in accordance with the present disclosure has at least 80%, typically at least about 90%, and more typically at least about 95% or at least about 98% identity to a polypeptide-encoding polynucleotide as listed in Table 14. Nucleic acids of the disclosure also include complementary nucleic acids. In some instances, the sequences will be fully complementary (no mismatches) when aligned. In other instances, there can be up to about a 20% mismatch in the sequences. In some embodiments of the disclosure are provided nucleic acids encoding both first and second polypeptide chains of a heterodimeric CD3-binding protein of the disclosure. The nucleic acid sequences provided herein can be exploited using codon optimization, degenerate sequence, silent mutations, and other DNA techniques to optimize expression in a particular host, and the present disclosure encompasses such sequence modifications.

[00176] The disclosure relates to an isolated nucleic acid molecule encoding CD3-binding domains, proteins and polypeptides (or portions thereof) described herein, wherein said nucleic acid molecule comprises a nucleotide sequence set forth in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, or 59.

[00177] Polynucleotide molecules comprising a desired polynucleotide sequence are propagated by placing the molecule in a vector. Viral and non-viral vectors are used, including plasmids. The choice of plasmid will depend on the type of cell in which propagation is desired and the purpose of propagation. Certain vectors are useful for amplifying and making large amounts of the desired DNA sequence. Other vectors are suitable for expression in cells in culture. Still other vectors are suitable for transfer and expression in cells in a whole animal or person. The choice of appropriate vector is well within the skill of the art. Many such vectors are available commercially. The partial or full-length polynucleotide is inserted into a vector typically by means of DNA ligase attachment to a cleaved restriction enzyme site in the vector. Alternatively, the desired nucleotide sequence can be inserted by homologous recombination *in vivo*. Typically this is accomplished by attaching regions of homology to the vector on the flanks of the desired nucleotide sequence. Regions of homology are added by ligation of

oligonucleotides, or by polymerase chain reaction using primers comprising both the region of homology and a portion of the desired nucleotide sequence, for example.

[00178] For expression, an expression cassette or system may be employed. To express a nucleic acid encoding a polypeptide disclosed herein, a nucleic acid molecule encoding the polypeptide, operably linked to regulatory sequences that control transcriptional expression in an expression vector, is introduced into a host cell. In addition to transcriptional regulatory sequences, such as promoters and enhancers, expression vectors can include translational regulatory sequences and a marker gene which is suitable for selection of cells that carry the expression vector. The gene product encoded by a polynucleotide of the disclosure is expressed in any convenient expression system, including, for example, bacterial, yeast, insect, amphibian and mammalian systems. In the expression vector, the polypeptide-encoding polynucleotide is linked to a regulatory sequence as appropriate to obtain the desired expression properties. These can include promoters, enhancers, terminators, operators, repressors, and inducers. The promoters can be regulated (*e.g.*, the promoter from the steroid inducible pIND vector (Invitrogen)) or constitutive (*e.g.*, promoters from CMV, SV40, Elongation Factor, or LTR sequences). These are linked to the desired nucleotide sequence using the techniques described above for linkage to vectors. Any techniques known in the art can be used. Accordingly, the expression vector will generally provide a transcriptional and translational initiation region, which can be inducible or constitutive, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region.

[00179] An expression cassette ("expression unit") can be introduced into a variety of vectors, *e.g.*, plasmid, BAC, YAC, bacteriophage such as lambda, P1, M13, *etc.*, plant or animal viral vectors (*e.g.*, retroviral-based vectors, adenovirus vectors), and the like, where the vectors are normally characterized by the ability to provide selection of cells comprising the expression vectors. The vectors can provide for extrachromosomal maintenance, particularly as plasmids or viruses, or for integration into the host chromosome. Where extrachromosomal maintenance is desired, an origin sequence is provided for the replication of the plasmid, which can be low- or high copy-number. A wide variety of markers are available for selection, particularly those which protect against toxins, more particularly against antibiotics. The particular marker that is chosen is selected in accordance with the nature of the host, where, in some cases, complementation can be employed with auxotrophic hosts. Introduction of the DNA construct can use any convenient method, including, *e.g.*, conjugation, bacterial transformation, calcium-

precipitated DNA, electroporation, fusion, transfection, infection with viral vectors, biolistics, and the like. The disclosure relates to an expression vector comprising a nucleic acid segment, wherein said nucleic acid segment may comprise a nucleotide sequence set forth in SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, or 59.

[00180] Accordingly, proteins for use within the present disclosure can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells (including cultured cells of multicellular organisms), particularly cultured mammalian cells. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2001), and Ausubel *et al.*, *Short Protocols in Molecular Biology* (4th ed., John Wiley & Sons, 1999).

[00181] For example, for recombinant expression of a homodimeric CD3-binding protein comprising two identical CD3-binding polypeptides as described herein, an expression vector will generally include a nucleic acid segment encoding the CD3-binding polypeptide, operably linked to a promoter. For recombinant expression of a heterodimeric CD3-binding protein, comprising different first and second polypeptide chains, the first and second polypeptide chains can be co-expressed from separate vectors in the host cell for expression of the entire heterodimeric protein. Alternatively, for the expression of heterodimeric CD3-binding proteins, the first and second polypeptide chains are co-expressed from separate expression units in the same vector in the host cell for expression of the entire heterodimeric protein. The expression vector(s) are transferred to a host cell by conventional techniques, and the transfected cells are then cultured by conventional techniques to produce the encoded polypeptide(s) to produce the corresponding CD3-binding protein.

[00182] To direct a recombinant protein into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence) is provided in the expression vector. The secretory signal sequence can be that of the native form of the recombinant protein, or can be derived from another secreted protein or synthesized *de novo*. The secretory signal sequence is operably linked to the polypeptide-encoding DNA sequence, *i.e.*, the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized polypeptide into the secretory pathway of the host cell. Secretory signal sequences are commonly

positioned 5' to the DNA sequence encoding the polypeptide of interest, although certain signal sequences can be positioned elsewhere in the DNA sequence of interest (*see, e.g.*, Welch *et al.*, U.S. Patent No. 5,037,743; Holland *et al.*, U.S. Patent No. 5,143,830). In certain variations, a secretory signal sequence for use in accordance with the present disclosure has the amino acid sequence MEAPAQLLFLLLLWLPDTTG (SEQ ID NO:195).

[00183] Cultured mammalian cells are suitable hosts for production of recombinant proteins for use within the present disclosure. Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler *et al.*, *Cell* 14:725, 1978; Corsaro and Pearson, *Somatic Cell Genetics* 7:603, 1981: Graham and Van der Eb, *Virology* 52:456, 1973), electroporation (Neumann *et al.*, *EMBO J.* 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel *et al.*, *supra*), and liposome-mediated transfection (Hawley-Nelson *et al.*, *Focus* 15:73, 1993; Ciccarone *et al.*, *Focus* 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson *et al.*, U.S. Patent No. 4,713,339; Hagen *et al.*, U.S. Patent No. 4,784,950; Palmiter *et al.*, U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Examples of suitable mammalian host cells include African green monkey kidney cells (Vero; ATCC CRL 1587), human embryonic kidney cells (293-HEK; ATCC CRL 1573), baby hamster kidney cells (BHK-21, BHK-570; ATCC CRL 8544, ATCC CRL 10314), canine kidney cells (MDCK; ATCC CCL 34), Chinese hamster ovary cells (CHO-K1; ATCC CCL61; CHO DG44; CHO DXB11 (Hyclone, Logan, UT); *see also, e.g.*, Chasin *et al., Som. Cell. Molec. Genet.* 12:555, 1986)), rat pituitary cells (GH1; ATCC CCL82), HeLa S3 cells (ATCC CCL2.2), rat hepatoma cells (H-4-II-E; ATCC CRL 1548) SV40-transformed monkey kidney cells (COS-1; ATCC CRL 1650) and murine embryonic cells (NIH-3T3; ATCC CRL 1658). Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Manassas, Virginia. Strong transcription promoters can be used, such as promoters from SV-40 or cytomegalovirus. *See, e.g.*, U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patents Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter.

[00184] Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants." Cells that have been cultured in the presence of the selective agent and are able to pass the gene of interest to their progeny are referred to as "stable transfectants." Exemplary selectable markers include a gene encoding resistance to the antibiotic neomycin, which allows selection to be

carried out in the presence of a neomycin-type drug, such as G-418 or the like; the gpt gene for xanthine-guanine phosphoribosyl transferase, which permits host cell growth in the presence of mycophenolic acid/xanthine; and markers that provide resistance to zeocin, bleomycin, blastocidin, and hygromycin (*see, e.g.*, Gatignol *et al., Mol. Gen. Genet.* 207:342, 1987; Drocourt *et al., Nucl. Acids Res.* 18:4009, 1990). Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (*e.g.*, hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

[00185] Other higher eukaryotic cells can also be used as hosts, including insect cells, plant cells and avian cells. The use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar *et al.*, *J. Biosci. (Bangalore)* 11:47-58, 1987. Transformation of insect cells and production of foreign polypeptides therein is disclosed by Guarino *et al.*, US 5,162,222 and WO 94/06463.

[00186] Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). *See* King and Possee, *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London); O'Reilly *et al.*, *Baculovirus Expression Vectors: A Laboratory Manual* (Oxford University Press., New York 1994); and *Baculovirus Expression Protocols. Methods in Molecular Biology* (Richardson ed., Humana Press, Totowa, NJ, 1995). Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow *et al.* (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (BAC-TO-BAC kit; Life Technologies, Gaithersburg, MD). The transfer vector (*e.g.*, PFASTBAC1; Life Technologies) contains a Tn7 transposon to move the DNA encoding the protein of interest into a baculovirus genome maintained in *E. coli* as a large plasmid called a "bacmid." *See* Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning *et al.*, *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995. In addition, transfer vectors can include an in-frame fusion with DNA encoding a polypeptide extension or affinity tag as disclosed above. Using techniques known in the art, a transfer vector containing a protein-encoding DNA sequence is transformed into *E. coli* host cells, and the cells are

screened for bacmids which contain an interrupted lacZ gene indicative of recombinant baculovirus. The bacmid DNA containing the recombinant baculovirus genome is isolated, using common techniques, and used to transfect *Spodoptera frugiperda* cells, such as Sf9 cells. Recombinant virus that expresses the protein or interest is subsequently produced. Recombinant viral stocks are made by methods commonly used in the art.

[00187] For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (*e.g.*, Sf9 or Sf21 cells) or *Trichoplusia ni* (*e.g.*, HIGH FIVE cells; Invitrogen, Carlsbad, CA). *See generally* Glick and Pasternak, *Molecular Biotechnology, Principles & Applications of Recombinant DNA* (ASM Press, Washington, D.C., 1994). *See also* U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10^5 cells to a density of 1-2 x 10^6 cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (*see, e.g.*, King and Possee, *supra*; O'Reilly *et al.*, *supra*; Richardson, *supra*).

[00188] Fungal cells, including yeast cells, can also be used within the present disclosure. Yeast species of in this regard include, e.g., *Saccharomyces cerevisiae*, *Pichia pastoris*, and *Pichia methanolica*. Methods for transforming *S. cerevisiae* cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki *et al.*, U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch *et al.*, U.S. Patent No. 5,037,743; and Murray *et al.*, U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (*e.g.*, leucine). An exemplary vector system for use in *Saccharomyces cerevisiae* is the *POT1* vector system disclosed by Kawasaki *et al.* (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (*see, e.g.*, Kawasaki, U.S. Patent No. 4,599,311; Kingsman *et al.*, U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. *See also* U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936; and 4,661,454. Transformation systems for other yeasts, including *Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii*, and *Candida*

maltosa are known in the art. *See, e.g.*, Gleeson *et al.*, *J. Gen. Microbiol.* 132:3459-3465, 1986; Cregg, U.S. Patent No. 4,882,279; and Raymond *et al.*, *Yeast* 14:11-23, 1998. *Aspergillus* cells can be utilized according to the methods of McKnight *et al.*, U.S. Patent No. 4,935,349. Methods for transforming *Acremonium chrysogenum* are disclosed by Sumino *et al.*, U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in *Pichia methanolica* is disclosed in U.S. Patents Nos. 5,716,808; 5,736,383; 5,854,039; and 5,888,768.

[00189] Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus*, and other genera are also useful host cells within the present disclosure. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well-known in the art (*see, e.g.*, Sambrook and Russell, *supra*). When expressing a recombinant protein in bacteria such as *E. coli*, the protein can be retained in the cytoplasm, typically as insoluble granules, or can be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured protein can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the alternative, the protein can be recovered from the cytoplasm in soluble form and isolated without the use of denaturants. The protein is recovered from the cell as an aqueous extract in, for example, phosphate buffered saline. To capture the protein of interest, the extract is applied directly to a chromatographic medium, such as an immobilized antibody or heparin-Sepharose column. Secreted proteins can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding. Antibodies, including single-chain antibodies, can be produced in bacterial host cells according to known methods. *See, e.g.*, Bird *et al.*, *Science* 242:423-426, 1988; Huston *et al.*, *Proc. Natl. Acad. Sci. USA* 85:5879-5883, 1988; and Pantoliano *et al.*, *Biochem.* 30:10117-10125, 1991.

[00190] Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media can also contain such components as

growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

[00191] CD3-binding proteins may be purified by conventional protein purification methods, typically by a combination of chromatographic techniques. *See generally Affinity Chromatography: Principles & Methods* (Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988); Scopes, *Protein Purification: Principles and Practice* (Springer-Verlag, New York 1994). Proteins comprising an immunoglobulin Fc region can be purified by affinity chromatography on immobilized protein A or protein G. Additional purification steps, such as gel filtration, can be used to obtain the desired level of purity or to provide for desalting, buffer exchange, and the like.

[00192] CD3-binding molecules disclosed herein may be used in a method for treating a subject (for example, a human or a non-human primate) or for manufacture of a medicament for treating a subject. Generally, such methods include administering to a subject in need of such treatment a CD3-binding protein as described herein.

[00193] CD3-binding molecules disclosed herein may be used in a method for treating a subject (for example, a human or a non-human primate) or for manufacture of a medicament for treating a subject. Generally, such methods include administering to a subject in need of such treatment a CD3-binding protein as described herein. In some embodiments, a CD3-binding protein comprises at least one effector function selected from antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), such that the CD3-binding protein induces ADCC and/or CDC against CD3-expressing cells in the subject.

[00194] In some aspects, the present disclosure provides methods for treating a subject with a disorder characterized by over-expression of CD3. In one case, a monospecific CD3 binding polypeptide is administered to a patient suffering from an autoimmune disease (e.g., rheumatoid arthritis). In certain variations, a CD3-binding protein provided herein could be used for the modulation of T-cell function and fate, thereby providing therapeutic treatment of T cell mediated disease, including autoimmune or inflammatory diseases in which T-cells are significant contributors. Because some CD3-binding proteins of the present disclosure do not activate T-cells and/or do not induce cytokine release, they are advantageous over other molecules directed against the TCR complex (e.g., anti-CD3 antibodies) for having no or reduced side

effects such as cytokine release syndrome and acute toxicity. In another case, a CD3-binding polypeptide is administered to a subject about to undergo an organ transplant.

[00195] In another aspect, the present disclosure provides a method for treating a disorder characterized by overexpression of a tumor antigen, such as cancer. Examples of tumor antigens that may be recognized by bispecific CD3-binding proteins include PSMA, CD19, CD20, CD37, CD38, CD123, Her2, ROR1, RON, glycoprotein A33 antigen (gpA33) and CEA. Generally, such methods include administering to a subject in need of such treatment a therapeutically effective amount of a CD3-binding protein comprising a second binding domain that binds a tumor antigen as described herein. In some embodiments, the CD3 binding protein induces redirected T-cell cytotoxicity (RTCC) against tumor antigen-expressing cells in the subject. Exemplary cancers amenable to treatment in accordance with the present disclosure include, for example, prostate cancer, colorectal cancer, renal cell carcinoma, bladder cancer, salivary gland cancer, pancreatic cancer, ovarian cancer, non-small cell lung cancer, melanoma, breast cancer (e.g., triple negative breast cancer), adrenal cancer, mantle cell lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, Non-Hodgkin's lymphoma, acute myeloid leukemia (AML), B-lymphoid leukemia, blastic plasmocytoid dendritic neoplasm (BPDCN), and hairy cell leukemia.

[00196] The disclosure also provides methods for treating cancer or an autoimmune disorder comprising administering a therapeutically effective amount of the compositions or CD3-binding polypeptides described herein to a patient in need thereof.

[00197] In some embodiments, the disclosure provides a method of treating a patient with a cancer, comprising administering to the patient a CD3-binding polypeptide comprising a CD3-binding domain that binds specifically to human CD3 and that comprises an immunoglobulin light chain variable region and an immunoglobulin heavy chain variable region; wherein the immunoglobulin light chain variable region comprises an amino acid sequence that is (a) at least about 93% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:88; or (b) at least about 94% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:89; and wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence that is at least about 82% identical, at least about 85% identical, at least about 87% identical, at least about 90% identical, at least about 92% identical, at least about 95% identical, at least about 97% identical, at least about 98% identical or at least about 99% identical to the amino acid sequence in SEQ ID NO:86.

[00198] In some embodiments, for treatment methods and uses described herein, a CD3-binding protein is delivered in a manner consistent with conventional methodologies associated with management of the disease or disorder for which treatment is sought. In accordance with the disclosure herein, a therapeutically effective amount of the CD3-binding protein is administered to a subject in need of such treatment for a time and under conditions sufficient to prevent or treat the disease or disorder.

[00199] Subjects for administration of CD3-binding proteins as described herein include patients at high risk for developing a particular disorder as well as patients presenting with an existing such disorder. Typically, the subject has been diagnosed as having the disorder for which treatment is sought. Further, subjects can be monitored during the course of treatment for any change in the disorder (*e.g.*, for an increase or decrease in clinical symptoms of the disorder). Also, in some variations, the subject does not suffer from another disorder requiring treatment that involves targeting CD3-expressing cells.

[00200] In prophylactic applications, pharmaceutical compositions or medicants are administered to a patient susceptible to, or otherwise at risk of, a particular disorder in an amount sufficient to eliminate or reduce the risk or delay the onset of the disorder. In therapeutic applications, compositions or medicants are administered to a patient suspected of, or already suffering from such a disorder in an amount sufficient to cure, or at least partially arrest, the symptoms of the disorder and its complications. An amount adequate to accomplish this is referred to as a therapeutically effective dose or amount. In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient response has been achieved. Typically, the response is monitored and repeated dosages are given if the desired response starts to fade.

[00201] To identify subject patients for treatment according to the methods of the disclosure, accepted screening methods can be employed to determine risk factors associated with specific disorders or to determine the status of an existing disorder identified in a subject. Such methods can include, for example, determining whether an individual has relatives who have been diagnosed with a particular disorder. Screening methods can also include, for example, conventional work-ups to determine familial status for a particular disorder known to have a heritable component. For example, various cancers are also known to have certain inheritable components. Inheritable components of cancers include, for example, mutations in multiple genes that are transforming (*e.g.*, Ras, Raf, EGFR, cMet, and others), the presence or absence of certain HLA and killer inhibitory receptor (KIR) molecules, or mechanisms by which cancer

cells are able to modulate immune suppression of cells like NK cells and T-cells, either directly or indirectly (*see, e.g.*, Ljunggren and Malmberg, *Nature Rev. Immunol.* 7:329-339, 2007; Boyton and Altmann, *Clin. Exp. Immunol.* 149:1-8, 2007). Toward this end, nucleotide probes can be routinely employed to identify individuals carrying genetic markers associated with a particular disorder of interest. In addition, a wide variety of immunological methods are known in the art that are useful to identify markers for specific disorder. For example, various ELISA immunoassay methods are available and well-known in the art that employ monoclonal antibody probes to detect antigens associated with specific tumors. Screening can be implemented as indicated by known patient symptomology, age factors, related risk factors, etc. These methods allow the clinician to routinely select patients in need of the methods described herein for treatment. In accordance with these methods, targeting pathological, tumor antigen-expressing cells can be implemented as an independent treatment program or as a follow-up, adjunct, or coordinate treatment regimen to other treatments.

[00202] For administration, a CD3-binding protein may be formulated as a pharmaceutical composition. A pharmaceutical composition may comprise: (i) a CD3-binding polypeptide; and (ii) a pharmaceutically acceptable carrier, diluent or excipient. A pharmaceutical composition comprising a CD3-binding protein can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic molecule is combined in a mixture with a pharmaceutically acceptable carrier, diluent or excipient. A carrier is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers, diluents or excipients are well-known to those in the art. (*See, e.g.*, Gennaro (ed.), *Remington's Pharmaceutical Sciences* (Mack Publishing Company, 19th ed. 1995).) Formulations can further include one or more excipients, preservatives, solubilizers, buffering agents, albumin to prevent protein loss on vial surfaces, *etc.*

[00203] A pharmaceutical composition may be formulated in a dosage form selected from the group consisting of: an oral unit dosage form, an intravenous unit dosage form, an intranasal unit dosage form, a suppository unit dosage form, an intradermal unit dosage form, an intramuscular unit dosage form, an intraperitoneal unit dosage form, a subcutaneous unit dosage form, an epidural unit dosage form, a sublingual unit dosage form, and an intracerebral unit dosage form. The oral unit dosage form may be selected from the group consisting of: tablets, pills, pellets, capsules, powders, lozenges, granules, solutions, suspensions, emulsions, syrups, elixirs, sustained-release formulations, aerosols, and sprays.

[00204] A pharmaceutical composition comprising a CD3-binding protein therapeutic may be administered to a subject in a therapeutically effective amount. According to the methods of the present disclosure, a CD3-binding protein can be administered to subjects by a variety of administration modes, including, for example, by intramuscular, subcutaneous, intravenous, intra-atrial, intra-articular, parenteral, intranasal, intrapulmonary, transdermal, intrapleural, intrathecal, and oral routes of administration. For prevention and treatment purposes, an antagonist can be administered to a subject in a single bolus delivery, via continuous delivery (*e.g.*, continuous transdermal delivery) over an extended time period, or in a repeated administration protocol (*e.g.*, on an hourly, daily, weekly, or monthly basis).

[00205] Determination of effective dosages in this context is typically based on animal model studies followed up by human clinical trials and is guided by determining effective dosages and administration protocols that significantly reduce the occurrence or severity of the subject disorder in model subjects. Effective doses of the compositions of the present disclosure vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, whether treatment is prophylactic or therapeutic, as well as the specific activity of the composition itself and its ability to elicit the desired response in the individual. Usually, the patient is a human, but in some diseases, the patient can be a nonhuman mammal. Typically, dosage regimens are adjusted to provide an optimum therapeutic response, *i.e.*, to optimize safety and efficacy. Accordingly, a therapeutically effective amount is also one in which any undesired collateral effects are outweighed by the beneficial effects of administering a CD3-binding protein as described herein. For administration of a CD3-binding protein, a dosage may range from about 0.1 µg to 100 mg/kg or 1 µg/kg to about 50 mg/kg, and more usually 10 µg to 5 mg/kg of the subject's body weight. In more specific embodiments, an effective amount of the agent is between about 1 µg/kg and about 20 mg/kg, between about 10 µg/kg and about 10 mg/kg, or between about 0.1 mg/kg and about 5 mg/kg. Dosages within this range can be achieved by single or multiple administrations, including, *e.g.*, multiple administrations per day or daily, weekly, bi-weekly, or monthly administrations. For example, in certain variations, a regimen consists of an initial administration followed by multiple, subsequent administrations at weekly or bi-weekly intervals. Another regimen consists of an initial administration followed by multiple, subsequent administrations at monthly or bi-monthly intervals. Alternatively, administrations can be on an irregular basis as indicated by monitoring clinical symptoms of the disorder.

[00206] Dosage of the pharmaceutical composition can be varied by the attending clinician to maintain a desired concentration at a target site. For example, if an intravenous mode of delivery is selected, local concentration of the agent in the bloodstream at the target tissue can be between about 0.01-50 nanomoles of the composition per liter, sometimes between about 1.0 nanomole per liter and 10, 15, or 25 nanomoles per liter depending on the subject's status and projected measured response. Higher or lower concentrations can be selected based on the mode of delivery, *e.g.*, trans-epidermal delivery versus delivery to a mucosal surface. Dosage should also be adjusted based on the release rate of the administered formulation, *e.g.*, nasal spray versus powder, sustained release oral or injected particles, transdermal formulations, *etc.* To achieve the same serum concentration level, for example, slow-release particles with a release rate of 5 nanomolar (under standard conditions) would be administered at about twice the dosage of particles with a release rate of 10 nanomolar.

[00207] The anti-CD3 therapeutic (e.g., CD3-binding protein) may also be administered at a daily dosage of from about 0.001 to about 10 milligrams (mg) per kilogram (mpk) of body weight, preferably given as a single daily dose or in divided doses about two to six times a day. For administration to a human adult patient, the therapeutically effective amount may be administered in doses in the range of 0.2 mg to 800 mg per dose, including but not limited to 0.2 mg per dose, 0.5 mg per dose, 1 mg per dose, 5 mg per dose, 10 mg per dose, 25 mg per dose, 100 mg per dose, 200 mg per dose, and 400 mg per dose, and multiple, usually consecutive daily doses may be administered in a course of treatment. The anti-CD3 therapeutic can be administered at different times of the day. In one embodiment the optimal therapeutic dose can be administered in the evening. In another embodiment the optimal therapeutic dose can be administered in the morning. The total daily dosage of the anti-CD3 therapeutic thus can in one embodiment range from about 1 mg to about 2 g, and often ranges from about 100 mg to about 1.5 g, and most often ranges from about 200 mg to about 1200 mg. In the case of a typical 70 kg adult human, the total daily dose of the anti-CD3 therapeutic can range from about 2 mg to about 1200 mg and will often range, as noted above, from about 0.2 mg to about 800 mg.

[00208] With particular regard to treatment of solid tumors, protocols for assessing endpoints and anti-tumor activity are well-known in the art. While each protocol may define tumor response assessments differently, the RECIST (Response evaluation Criteria in solid tumors) criteria is currently considered to be the recommended guidelines for assessment of tumor response by the National Cancer Institute (*see* Therasse *et al.*, *J. Natl. Cancer Inst.* 92:205-216, 2000). According to the RECIST criteria tumor response means a reduction or elimination of all

measurable lesions or metastases. Disease is generally considered measurable if it comprises lesions that can be accurately measured in at least one dimension as ≥ 20mm with conventional techniques or ≥ 10mm with spiral CT scan with clearly defined margins by medical photograph or X-ray, computerized axial tomography (CT), magnetic resonance imaging (MRI), or clinical examination (if lesions are superficial). Non-measurable disease means the disease comprises of lesions < 20mm with conventional techniques or < 10mm with spiral CT scan, and truly non-measurable lesions (too small to accurately measure). Non-measureable disease includes pleural effusions, ascites, and disease documented by indirect evidence.

[00209] The criteria for objective status are required for protocols to assess solid tumor response. Representative criteria include the following: (1) Complete Response (CR), defined as complete disappearance of all measurable disease; no new lesions; no disease related symptoms; no evidence of non-measurable disease; (2) Partial Response (PR) defined as 30% decrease in the sum of the longest diameter of target lesions (3) Progressive Disease (PD), defined as 20% increase in the sum of the longest diameter of target lesions or appearance of any new lesion; (4) Stable or No Response, defined as not qualifying for CR, PR, or Progressive Disease. (*See* Therasse *et al.*, *supra*.)

[00210] Additional endpoints that are accepted within the oncology art include overall survival (OS), disease-free survival (DFS), objective response rate (ORR), time to progression (TTP), and progression-free survival (PFS) (*see Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*, April 2005, Center for Drug Evaluation and Research, FDA, Rockville, MD.)

[00211] Pharmaceutical compositions can be supplied as a kit comprising a container that comprises the pharmaceutical composition as described herein. A pharmaceutical composition can be provided, for example, in the form of an injectable solution for single or multiple doses, or as a sterile powder that will be reconstituted before injection. Alternatively, such a kit can include a dry-powder disperser, liquid aerosol generator, or nebulizer for administration of a pharmaceutical composition. Such a kit can further comprise written information on indications and usage of the pharmaceutical composition.

[00212] The disclosure will be further clarified by the following examples, which are intended to be purely exemplary of the disclosure and in no way limiting.

EXAMPLES

Example 1. Generation of stabilized CD3-binding molecules

[00213] To improve thermal stability of the CD3-binding molecule DRA222, an engineered variant of the humanized Cris7 antibody, the Cris7 variable domains were re-humanized using alternate human germline framework sequences. The DRA222 variable heavy chain domain is SEQ ID NO:87, and the DRA222 variable light chain domain is SEQ ID NO:90. Fc DRA222 is sometimes referred to as TSC311 or TSC312 (amino acid sequence is SEQ ID NO:2; nucleic acid sequence is SEQ ID NO:1). See, Reinherz, E. L. et al. (eds.), Leukocyte typing II., Springer Verlag, New York, (1986) for description of parent Cris7 antibody. Additional changes were also made to improve affinity and thermal stability.

Methods

[00214] The following methods were used to obtain results shown in this example:

[00215] Differential Scanning Calorimetry (DSC). Thermograms for recombinant proteins purified by standard purification techniques were obtained on a GE VP-Capillary DSC instrument equipped with an autosampler. Approximately 550 µL of each sample (typically 0.5 mg/mL) in PBS was injected into the sample capillary, using PBS as a control in the second capillary. Analysis was conducted at temperatures from 25°C to 130°C, with a heating rate of 1°C per min. Feedback was set to low, and a sampling time of 8 ms was used. Data analysis was conducted using Origin. Sample thermogram was corrected for heat capacity of the buffer by subtracting a previous buffer/buffer scan using formulation vehicle, and normalized based on sample concentration and baseline corrected.

[00216] Differential Scanning Fluorimetry (DSF). In a high throughput format, thermograms for recombinant proteins purified by standard purification techniques were also obtained by DSF assay run on a Real Time PCR machine (Bio-Rad iCycler iQ5). Approximately 40 µL of each sample in a concentration of 0.8 mg/mL in PBS was mixed with 5 µL of pre-diluted SYPRO Orange Dye (Catalogue # S-6650, Life Technologies). A melting curve protocol was set up as ramping the temperature up from 25°C to 90°C, 0.2°C per step. Fluorescent signals were collected through the TexasRed Fluorescent Dye filter set, which is 575/30X Excitation Filter and 620/30M Emission Filter. The collected fluorescent intensity data was exported to data analysis software Prism 6 (GraphPad Software, Inc.). Protein thermal Tm value was calculated as the temperature when second derivatives of fluorescent intensity against temperature – d(RUF)/dT2=0.

[00217] Flow cytometry on human Jurkat T-cells. Binding studies were performed by standard flow cytometry-based staining procedures using the $CD3^+$ Jurkat T-cell line. All

labeling and washes were performed in U-bottom 96-well plates in saline buffer with 3% BSA and 2mM EDTA. Jurkat cells were plated at 200,000 cells per well and incubated with a range of 0.1 nM to 200 nM concentrations of test molecules in 50 µL volume/well, for 30 minutes on ice. Cells were washed three times then incubated for another 30 minutes on ice with fluorescently-labeled minimum cross reactive secondary polyclonal antibody, $F(ab')^2$ goat anti-human IgG, (Jackson ImmunoResearch Laboratories) and the viability dye 7-AAD. The cells were then washed twice, and the samples acquired in a BD LSRII flow cytometer. The sample files were analyzed using FlowJo software; the mean fluorescence intensity (MFI) of the live population of Jurkat cells in each well was calculated after gating on live cells (forward vs. side scatter, then 7-AAD^- cells).

[00218] Homology modeling, Spatial Aggregation Propensity analysis. Homology models were constructed within Accelrys Discovery Studio 4.0 for variable domains using the Annotate Antibody Sequence, Identify Framework Templates, Model Antibody Framework, and Model Antibody Loops protocols. Spatial Aggregation Propensity analysis was also conducted within Accelrys Discovery Studio 4.0 using the Calculate Aggregation Scores protocol.

[00219] Chromium release assays with Human T-cells. Target positive tumor cell lines (MDA-MB-231, Kasumi-2, C4-2B and Ramos cell lines) were all cultured according to the provided protocols. Peripheral blood mononuclear cells (PBMC) were isolated from human blood using standard ficoll gradients. The isolated cells were washed in saline buffer. T-cells were additionally isolated using a Pan T-cell Isolation Kit (catalogue#130-096-535, Miltenyi Biotec, Bergisch Gladbach, Germany) using the manufacturer's protocol. Isolated T-cells were aliquoted and stored long term in Liquid Nitrogen. The pre-prepared T-cells were thawed one day before the assay into warm RPMI media with 10% human serum. During the assay, concentrations of bispecific molecules with final concentration ranging from 200 pM to 0.01 pM were added to the pre-prepared T-cells (approximately 100,000 per well). A total lysis control was generated by including 0.04% NP-40 as the treatment.

[00220] Approximately 2.5×10^6 target cells were treated with 0.125 mCi of ^{51}Cr and incubated for 90 minutes in a 37°C, 5% CO_2 humidified incubator. After incubation, cells were washed 4 times with diluted assay media (RPMI with 1% human serum) and re-suspended in 12.5 mL of the complete assay media (RPMI with 10% human serum). From this suspension, 50 µL was dispensed per well into 96 well U-bottom plates (approximately 10,000 cells per well) to bring the total volume to 200mL per well, and the T-cell to target cell ratio to 10:1. A zero lysis control was generated by target cells only, omitting the T-cells.

[00221] Plates were incubated for 4 hours (and occasionally also for 24 hours) at 37°C, 5% CO_2 in a humidified incubator, after which they were centrifuged at 1000 rpm for 3 minutes, and 25 µL of supernatant was transferred from each well to the corresponding well of a 96-well Luma sample plate. Sample plates were allowed to air dry in a chemical safety hood for 18 hours, and then radioactivity was read on a TopCount microplate scintillation counter (PerkinElmer) using a standard protocol.

[00222] Percent specific lysis was calculated using the formula: ((signal in drug treated sample – background signal from samples with Target Cell only)/(signal in total lysis wells - background signal from samples with Target Cell only))×100.

[00223] Flow Cytometry on Cynomolgus T-cells. Cynomolgus macaque peripheral blood collected in heparin tubes was shipped overnight from a vendor (Charles River laboratories). When received, peripheral blood cells (PBMC) were isolated using density separation tubes (CPT tubes, Beckton Dickinson). Blood was diluted 1 to 1.5 in saline buffer prior to transfer into CPT tubes. CPT tubes were centrifuged and the separated PBMC population was collected and washed with saline buffer containing 0.2% BSA and 5nM EDTA. Remaining red blood cells in the preparation were lysed using Ammonium-Chloride-Potassium red blood lysis buffer. Cells were washed an additional time to remove remaining platelets.

[00224] PBMC labeling and washing steps were performed in U-bottom 96-well plates in saline buffer with 0.2% BSA and 2mM EDTA. PBMC were plated at 200,000 cells per well and incubated with a range of 0.1 nM to 300 nM concentrations of test molecules in 50 µL volume/well, for 30 minutes on ice. Cells were washed three times, then incubated for another 30 min on ice with fluorescently-labeled antibodies to non-human primate CD2 and CD16 (Biolegend), anti-idiotypic antibodies to either anti-PSMA or anti-CD37 binding domains, and the viability dye 7-AAD. The samples were washed twice, fixed for 20 minutes on ice with 1% formaldehyde solution in saline, washed again, and acquired in a BD LSRII flow cytometer. The sample files were analyzed using FlowJo software; the mean fluorescence intensity (MFI) of test molecule binding on T-cells in each well was calculated after gating on live T-cells (forward vs. side scatter, 7-AAD$^-$, CD2$^+$ CD16$^-$ cells).

[00225] Chromium Release assays with Cynomolgus PBMC. C4-2B and Ramos cell lines were both cultured according to the provided protocols. Peripheral blood mononuclear cells (PBMC) were isolated from cynomolgus macaque peripheral blood using BD VACUTAINER® CPT™ Cell Preparation Tube with Sodium Heparin (Cat#362753). The isolated cells were washed in saline buffer. Concentrations of bispecific molecules with final concentration ranging

from 10000 pM to 0.0128 pM were added to isolated PBMC (approximately 100,000). A total lysis control was generated by including 0.04% NP-40 as the treatment.

[00226] Approximately 5×10^6 target C4-2B or Ramos cells were treated with 0.25 mCi of ^{51}Cr and incubated for 75 minutes at 37°C. After incubation, cells were washed 4 times with the cell culture media (RPMI with 10% FBS, 1% NEAA, 1% sodium pyruvate, Na Glutamine and 20 mM HEPES) and re-suspended in 25 mL of media. From this suspension, 50 µL was dispensed per well into 96 well U-bottom plates (approximately 10,000 cells/well) to bring the T-cell to target cell ratio to 10:1.

[00227] Plates were incubated for 4 hours at 37°C, 5% CO_2 in a humidified incubator, after which they were centrifuged at 225 x G for 3 minutes, and 25 µL of supernatant was transferred from each well to the corresponding well of a 96-well Luma sample plate. Sample plates were allowed to air dry in a chemical safety hood for 18 hours, and then radioactivity was read on a Topcount scintillation counter using a standard protocol.

Results

[00228] Step 1: Generation of Initial Humanized CD3-Binding Constructs

[00229] The Cris7 variable domains were re-humanized using four human variable heavy germline sequences (IGHV1-2*02 (H7), IGHV1-46*02 (H8), IGHV1-3*01(H9) and IGHV1-69*02 (H10)) and 2 human variable light chain germline sequences (IGKV3-11*01 (L4) and IGKV1-33*01 (L5)) based on sequence homology. A total of 12 single chain variable fragment (scFv) constructs were generated in the Fc anti-CD3 scFv format using the H75 linker (QRHNNSSLNTGTQMAGHSPNS; SEQ ID NO:148) (Table 3). Sequences of the 12 constructs and the control molecule Fc DRA222 (TSC311 or TSC312) are provided in Table 14.

Table 3. Variable Domain Composition of Initial Constructs

Heavy chain	Light chain		
	L1 (original light chain)	**L4**	**L5**
H7	H7L1 (TSC313)	H7L4 (TSC314)	H7L5 (TSC315)
H8	H8L1 (TSC316)	H8L4 (TSC317)	H8L5 (TSC318)
H9	H9L1 (TSC319)	H9L4 (TSC320)	H9L5 (TSC321)
H10	H10L1 (TSC322)	H10L4 (TSC323)	H10L5 (TSC324)

[00230] All 12 constructs were expressed transiently in HEK293 cells, purified and tested for binding to Jurkat T-cells and evaluated for thermal stability. Constructs containing the L4 light chain or H9 heavy chain had lower levels of protein expression (see final yield column in Table 4) and/or higher levels of high molecular weight aggregates (see analytical SEC column in Table 4) and were eliminated in the subsequent optimization step. While most of the other

constructs had some improvement in thermal stability of the scFv over the original humanized domains (TSC312) as measured by the midpoint of thermal denaturation (Tm) using Differential Scanning Calorimetry (DSC) (Table 5), the level of binding saturation observed on Jurkat T-cells was reduced by varying levels (Figure 1). The most stable construct, TSC324, had a nearly 50% reduction in observed median fluorescence intensity at saturation and an two-fold increase in the EC50 of binding (3.6 nM) when compared to the original humanized construct (TSC312, also known as DRA222).

Table 4. Expression and Purity of Transiently Expressed Material

Molecule	Database Name	1st step titer (µg/ml)	Final yield (mg)	Analytical SEC - Main Peak (%)	Analytical SEC - Recovery %
Fc DRA222	TSC312	43.8	4.12	92.6	100.3
Fc H7L1	TSC313	35.2	2.66	95.3	90.2
Fc H7L4	TSC314	57.8	5.78	58.8	96.0
Fc H7L5	TSC315	52.6	6.99	90.6	93.3
Fc H8L1	TSC316	39.9	3.73	93.4	99.5
Fc H8L4	TSC317	52.9	4.95	66.5	97.6
Fc H8L5	TSC318	48.1	4.83	92.1	96.2
Fc DRA222	TSC312	16.1	1.41	95.4	97.8
Fc H9L1	TSC319	8.0	0.71	80.0	85.8
Fc H9L4	TSC320	43.1	3.60	69.3	102.5
Fc H9L5	TSC321	31.1	2.66	92.6	98.6
Fc H10L1	TSC322	45.6	3.94	73.2	56.7
Fc H10L4	TSC323	50.6	4.58	67.3	106.7
Fc H10L5	TSC324	33.1	2.85	90.7	104.0

Table 5. Thermal Stability as Measured by Differential Scanning Calorimetry

Molecules	Tm of anti-CD3 scFv (°C)	Improvement in Tm (over DRA222)
TSC312 (DRA222)	53.02	
TSC313 (H7L1)	54.47	1.45
TSC315 (H7L5)	54.99	1.97
TSC316 (H8L1)	53.70	0.68

TSC318 (H8L5)	55.16	2.14
TSC312 (H7L1)	52.88	-0.14
TSC321 (H9L5)	53.10	0.08
TSC324 (H10L5)	55.83	2.81

[00231] Step 2: Initial optimization to restore binding to CD3

[00232] The goal of the next step was to improve binding to CD3 while maintaining improved thermal stability over DRA222. Three additional light chain sequences were introduced at this step. The first light chain was based on the L5 sequence containing two amino acid reverted to the parental murine residues at positions 52 and 53 (LL to RW), and this light chain was named L6. Two additional germline light chains were also used (IGKV1-39*01 (L7) and IGKV3D-20*1 (L8) containing the same two amino acids reverted at position 52 and 53. The 3 new light chains (L6, L7 and L8) were combined with 3 heavy chains (H7, H8 and H10) in the Fc anti-CD3 scFv format to give the following scFv combinations (Table 6):

Table 6. Variable Domain Composition of Second Round Constructs

Heavy chain	**Light chain**		
	L6	**L7**	**L8**
H7	H7L6 (TSC334)	H7L7 (TSC335)	H7L8 (TSC336)
H8	H8L6 (TSC337)	H8L7 (TSC338)	H8L8 (TSC339)
H10	H10L6 (TSC340)	H10L7 (TSC341)	H10L8 (TSC342)

[00233] These 9 constructs were expressed transiently in HEK293 cells and examined for protein quality, expression, binding and thermal stability. The sequences of these 9 constructs are found in Table 14. The H10 series of molecules (TSC340, TSC341, TSC342) had the best binding of all the new constructs (Figure 2), and achieved comparable levels of binding saturation on Jurkat T-cells as TSC312. However, the EC50 measured for binding was still two-fold higher than the original molecule, TSC312. The H10 series of molecules also had significant improvement in thermal stability as measured by increase in Tm over TSC312 using Differential Scanning Fluorimetry (DSF) (Figure 3). Of these three molecules, TSC342 was picked as the lead molecule for further optimization due to its improvement in thermal stability.

[00234] The parent murine sequence was then examined for potential hotspots to mutate to improve binding. Three residues were chosen for reversion and back-mutated independently: G27Y(TSC370), M53I(TSC371) and I21M(TSC372). Binding studies of these three constructs on Jurkat T-cells revealed that the G27Y mutation on the heavy chain restored binding to CD3 to comparable levels as the original construct TSC312 (Figure 4). The stability of these three constructs was also evaluated by DSC. While the G27Y mutation did not improve Tm, surprisingly, both of the remaining mutations, M53I on the heavy chain and I21M on the light chain independently improved Tm by 3-4°C (Table 7).

Table 7. Thermal Stability of Mutants Designed to Improve Binding

Mutations	Constructs	Tm (°C)	ΔTm (°C)
No mutation	TSC312	52.8	-
TSC342 G27Y	TSC370	53.6	0.8
TSC342 M53I	TSC371	55.97	3.17
TSC342 I21M	TSC372	56.55	3.75

[00235] Step 3: Final optimization step to improve thermal stability

[00236] The homology model of TSC370 was examined using Spatial Aggregation Propensity to identify hotspots for potential aggregation. One mutation, A9P on the heavy chain, was identified to reduce a potential aggregation hotspot in the homology model. This mutation was introduced into the TSC370 backbone to produce TSC390. This mutation alone had a mild effect on improving Tm (0.25°C). A9P mutation was combined with the M53I and I21M mutations described above to generate the following Fc anti-CD3 constructs (Table 8):

Table 8. Rationale behind Mutation Set of Fourth Round Constructs

Constructs	G27Y (improved affinity)	A9P (improved stability)	M53I (improved stability)	I21M (improved stability)
TSC390	X	X		
TSC391	X	X	X	
TSC392	X	X		X
TSC393	X		X	X
TSC394	X	X	X	X

Table 9. Thermal Stability of Fourth Round Constructs Assessed by DSC

Mutations	Name	Tm	ΔTm
No mutation	TSC312	52.8	-
TSC370_A9P	TSC390	53.05	0.25
TSC370_A9P_ M53I	TSC391	56.57	3.77
TSC370_A9P_ I21M	TSC392	59.15	6.35
TSC370_ M53I_ I21M	TSC393	58.29	5.49
TSC370_A9P_ M53I_ I21M	TSC394	59.3	6.5

[00237] Combining two or more of these mutations seemed to have beneficial effect on thermal stability as shown by a substantial increase in Tm from DSC analysis (Table 9). Surprisingly, the A9P mutation was also synergistic with the other mutations, providing anywhere from a 1 to 2.6 C increase in stability compared to the matched constructs not featuring the A9P mutation. More importantly, the stabilizing mutations did not affect the binding to CD3 (Figure 5).

[00238] Bispecific molecules targeting PSMA and CD3 were also built using these new anti-CD3 scFv molecules to study the effect, if any, of the changes to the anti-CD3 scFv on redirected T-cell cytotoxicity (RTCC) activity. The original humanized construct (DRA222) is highly efficient at redirecting T-cell cytotoxicity (see, e.g., US 2014/0161800). The new constructs were tested for their ability to show similar activity. Four different anti-PSMA x anti-CD3 constructs were made using TSC391, TSC392, TSC393 and TSC394 and these were named as TSC408, TSC409, TSC410 and TSC411 respectively. All the four constructs had similar RTCC activity as a molecule built with the parental DRA222 scFv (TSC249) (Figure 6), verifying that cytotoxic activity as well as binding was comparable with human T-cells.

[00239] Step 4: Optimization step to restore Cynomolgus cross-reactivity and activity

[00240] The original humanized construct (DRA222) was previously shown to also bind cynomolgus monkey T-cells and redirect their cytotoxic activity towards target cells when used in a bispecific format. TSC408, TSC409, TSC410 and TSC411 were all evaluated for binding and cytotoxic activity with cynomolgus T-cells. Unexpectedly, TSC408, TSC409, TSC410 and TSC411 all had reduced binding to cynomolgus monkey T-cells (Figures 7A and 7B) and significant reduction in RTCC activity using cynomolgus T-cells as effector cells when compared to an anti-PSMA x anti-CD3 bispecific molecule containing DRA222 (Figures 8A and 8B). This

was not anticipated as the binding and activity with human T-cells was directly comparable to constructs containing DRA222.

[00241] Two approaches were used to attempt to restore binding to cynomolgus CD3. One approach was to combine the light chain from TSC394 with the heavy chain from DRA222 or to combine the heavy chain from TSC394 with the light chain from DRA222 to see if framework residues specific to one framework were contributing to binding. The second approach was to back mutate residues at positions 86 and 87 on the light chain of TSC394. Residues at these two positions interact with light chain CDRs that could influence binding to cynomolgus CD3. These variants were incorporated into anti-CD37 x anti-CD3 bispecific molecules (Table 10). Some of the variants, especially TSC455, TSC456 and TSC452 displayed improved binding to cynomolgus T-cells when compared to anti-CD37 x TSC394 (TSC445), as reflected by higher levels of binding at saturating concentrations (Figure 9). A cynomolgus RTCC assay was also performed that showed TSC456 and TSC452 had comparable activity to CAS105 (Figure 10). In addition, these molecules had superior thermal stability compared to CAS105 (Table 11) as shown by a higher Tm1 when analyzed by DSC. Alignments of the DRA222 scFv, TSC455 scFv, and TSC456 scFv are shown in Figure 13.

Table 10. Fifth Round of Optimized Constructs

Anti-CD3 Constructs	Description of anti-CD37 X anti-CD3 bispecific molecules
CAS105	anti-CD37 x DRA222
TSC445	anti-CD37 x TSC394
TSC452	anti-CD37 x (TSC394VL+ DRA222 VH)
TSC453	anti-CD37 x (TSC394VH + DRA222 VL)
TSC454	anti-CD37 x TSC394 E86D
TSC455	anti-CD37 x TSC394 F87Y
TSC456	anti-CD37 x TSC394 E86D F87Y

Table 11. Stability of Bispecific Constructs

Anti-CD3 Constructs	Description of anti-CD37 X anti-CD3 bispecific molecules	Tm 1
CAS105	Anti-CD37 x DRA222	53.04
TSC445	anti-CD37 x TSC394	55.45

TSC452	anti-CD37 x (TSC394VL+ DRA222 VH)	55.37
TSC453	Anti-CD37 x (TSC394VH + DRA222 VL)	56.54
TSC454	Anti-CD37 x TSC394 E86D	57.94
TSC455	Anti-CD37 x TSC394 F87Y	56.73
TSC456	Anti-CD37x TSC394 E86D F87Y	55.45

Example 2. Impacts of Improved Thermal Stability on Storage Stability

[00242] In principle, proteins with improved thermodynamic stability should also be more resistant to aggregation upon storage, and should have enhanced storage stability compared to less stable proteins. To determine whether or not the increases seen in Tm correlated with improved storage stability, the proteins listed in Table 10 were evaluated for storage stability in PBS at 25°C over two weeks.

[00243] Each protein was buffer exchanged into PBS using preparative size exclusion chromatography and the protein concentration was adjusted to 1 mg/mL. For every protein to be assessed, four vials each containing approximately 120 µL were prepared. One vial was used at each stability time point. Purity was determined by analyzing 25 µL (or 25 µg) on an analytical size exclusion HPLC column equilibrated in PBS and measuring the absorbance at 280 nm. Triplicate injections were performed for each construct at each time point. Following completion of the SEC method, the chromatograph was integrated using the Agilent ChemStation software. The percent purity of each protein was calculated by dividing the peak area of the intact molecule by the total peak area, then multiplying by 100.

(peak area of intact molecule) / (total peak area) x 100 = %Purity

[00244] The reported purity was an average of the values obtained from three injections from the same vial. Purity was typically determined at T=0, 3, 7 and 14 days. Purity values were plotted on a graph as a function of time and a linear regression analysis was performed. The slope of the regression line represented the rate at purity was decreasing for each protein. The rate of purity decline was used to estimate the number of days of storage that would cause a 2% decrease in purity. The stability of different variants was compared by ranking them by the highest to lowest number of days estimated to cause a 2% decline. To mitigate inter-assay variability, storage stability values were not compared across different experiments, constructs within the same experimental group were only ranked against each other.

[00245] All new molecules displayed superior solution stability in PBS at 25°C compared to CAS105 (Figure 11). The time to the formation of aggregate was also calculated for each construct (Table 12).

Table 12. Relative Storage Stability at 25°C

Anti-CD3 Construct	Description of anti-CD37 X anti-CD3 bispecific molecules	# of days to drop 2%
CAS105	Anti-CD37 x DRA222	4
TSC445	Anti-CD37 x TSC394	8
TSC450	Anti-CD37 x TSC313	12
TSC451	Anti-CD37 x TSC316	12
TSC452	Anti-CD37 x (TSC394VL+H4)	7
TSC453	Anti-CD37 x (TSC394VH+L1)	8
TSC454	Anti-CD37 x TSC394 E462D	7
TSC455	Anti-CD37 x TSC394 F463Y	10
TSC456	Anti-CD37 x TSC394 DY	10

[00246] This data showed that almost all constructs had a two-fold or greater increase in storage stability at 25ºC when compared to the construct containing the original anti-CD3 scFv (DRA222).

Example 3. Impacts of Improved Thermal Stability on Serum Stability

[00247] Similar to storage stability, molecules with higher thermodynamic stability are also frequently more resistant to proteolysis, which can improve stability in human serum. This can in turn improve overall serum pharmacokinetics and the overall exposure of a therapeutic.

[00248] To test if the improvements in thermodynamic stability impacted the overall serum stability, one of the stabilized anti-CD3 scFv molecules (TSC394 F463Y) was evaluated for serum stability in the context of an anti-ROR1 x anti-CD3 bispecific molecule (ROR193). A similar bispecific molecule was also evaluated simultaneously which contained the original anti-CD3 scFv, DRA222 (ROR133). The parent rabbit anti-ROR1 antibody R11 used to generate the ROR1-binding domains is described in, for example, U.S. Patent Application Publication No. 2013/0251642 and Yang et al., PLoS ONE 6(6): e21018 (2011).

[00249] Human serum donated by a random healthy donor was collected in a Red/Grey Vacutanor (BD# 367988), and was prepared according to vendor suggested protocol. Test articles were spiked into 50 µL serum at a concentration of 1 µM in sterile PCR tubes, and were incubated in a humidified 37°C tissue culture incubator for up to 21 days. Specific time points were 21, 14, 7, 3 and 0 days. Samples were incubated in a reverse chronological order starting as "assay day 21", and all samples were assessed simultaneously using a chromium release

RTCC assay at the end of incubation on "experiment day 0" following the protocol listed above in Example 1. EC50 values were fit from titration curves conducted with samples at each time points and were normalized against the EC50 value measured for each construct at day 0.

[00250] Plotting the EC50 values over time showed a dramatic difference for the observed serum stability of ROR133 vs ROR193 (Figure 12), with a 2.5 fold loss in observed EC50 over 21 days for ROR133 but minimal change in EC50 for ROR193. This demonstrates that a moderate change in thermodynamic stability can have a noticeable impact on serum stability.

Example 4. Impacts of Improved Thermodynamic Stability on Protein Expression and Quality

[00251] Previously, it has also been shown that improvements in thermodynamic stability can result in improvements in protein expression and overall protein quality, as measured by the production of high molecular weight aggregates during protein production.

[00252] To test whether or not the improved thermodynamic stability of the new anti-CD3 scFv regions translated into improved protein expression or protein quality, one of the anti-CD3 domains (TSC394DY) was compared to DRA222 in the context of five different pairs of anti-ROR1 x anti-CD3 bispecific molecules, each featuring the same anti-ROR1 scFv (Table 13).

Table 13. Relative Expression and Protein Quality

BD pair	Construct ID	CD3 binding domain	Expression (ug/mL)	% improvement	SEC (post-ProA)	% HMW aggregate	% reduction aggregate
A	ROR134	DRA222	26		78	22	
	ROR189	TSC394DY	37	42%	89	11	50%
B	ROR154	DRA222	16		91	9	
	ROR185	TSC394DY	26	63%	94	6	33%
C	ROR179	DRA222	14		83	17	
	ROR186	TSC394DY	27	93%	88	12	29%
D	ROR181	DRA222	25		81	19	
	ROR191	TSC394DY	33	32%	90	10	47%
E	ROR182	DRA222	16		90	10	
	ROR192	TSC394DY	21	31%	92	8	20%

[00253] With each molecule pair, a higher titer of overall protein expression was seen – from 31% to 93% higher – with the construct featuring the stabilized anti-CD3 scFv (TSC394DY). Also, within each molecule pair, the construct featuring the stabilized anti-CD3 scFv had a lower level of high molecular weight aggregates after protein A purification (anywhere from a 20% to 50% reduction in aggregate levels). This confirms that inclusion of a stabilized anti-CD3 scFv

can result in improved protein expression and improved protein quality when compared to the original anti-CD3 scFv.

Example 5. Effects of Stabilized Anti-CD3 Binding Domains on Stability and Pharmacokinetics of Anti-PSMA X Anti-CD3 Binding Molecules

[00254] To test the effects of a stabilized anti-CD3 scFv on stability and pharmacokinetics of a bispecific binding molecule, the PSMA-binding domain of TSC266 (an anti-PSMA X anti-CD3 bispecific molecule comprising the DRA222 CD3 binding domain) was transferred into a bispecific molecule utilizing the TSC456 anti-CD3 scFv. This new bispecific molecule is referred to as TSC471. BALB/c mice were dosed intravenously with TSC266 and TSC471 at approximately 10 mg/kg. TSC266 was diluted into PBS, while TSC471 was diluted into formulation buffer, which was used for all dilutions (5mM succinate, 6.5% sucrose, 0.02% Tween80, pH 4.8). Serum was collected from 3 animals at 10 time points (n = 30 total). The time points were 15 min and 2, 6, 24, 48, 72, 96, 168, 336, and 504 hr post-administration of the bispecific molecules. Terminal bleeds were used to collect larger volumes. Serum concentrations were determined using ELISA methods capturing the anti-PSMA binding domain and detecting the anti-CD3 binding domain. Serum concentrations over time were used to determine pharmacokinetic (PK) parameter estimates by non-compartmental analysis (NCA) and compartmental analysis. Serum samples from late time points were also tested for anti-drug antibodies using a standard bridging ELISA with the respective bispecific molecules +/- biotin.

[00255] More specifically, the following ELISA methods were used. Concentrations of anti-PSMA X anti-CD3 bispecifics were determined using 96-well plates coated with a mouse monoclonal antibody (mAb 1H5) to capture the anti-PSMA portion of each construct. The other ends of constructs were detected using a biotin conjugated mouse monoclonal antibody targeting the anti-CD3-binding domain (mAb 5H5), so only intact protein would be measured with this ELISA method. To quantify bound immune complexes from serum samples and assay controls, polymerized horseradish peroxidase (poly HRP) and a fluorogenic peroxidase substrate were used, with results measured on a fluorescent plate reader. Standard curves used to calculate serum concentrations consisted of various known concentrations of the appropriate PSMA bispecific construct spiked into ELISA diluent. SOFTMAX® Pro software was used to calculate serum concentrations using a 4-parameter logistic equation, as well as precision and accuracy for standards and test samples.

[00256] Results of these studies are shown in Figures 14 and 15. By non compartmental analysis (NCA) using Phoenix-64 WinNonLin Software, TSC471 had about a 2-fold

improvement in half-life, with a 3-4 fold reduction in clearance parameter, over TSC266. The Fc of TSC471 maintained functional characteristics of TSC266 (no ADCC or CDC activity, equivalent FcRn binding) with improved stability. The Fc of TSC471 comprises a stability improved version of the CH2 domain. The mutations are the same in the '234-236' region of the molecule as in the TSC266 Fc, but the TSC471 Fc has a reduced number of mutations in the CDC region, maintaining only the K322A mutation, rather than all three found in the null Fc CH2. The anti-CD3 scFv of TSC471 maintained binding and activity on human and cynomolgus T-cells. The linker used in TSC471 had enhanced resistance to CHO proteases and other PTMs and does not contain an N-linked glycosylation site.

Example 6. Effects of Stabilized Anti-CD3 Binding Domains on Pharmacokinetics of Anti-ROR1 X Anti-CD3 Binding Molecules

[00257] The pharmacokinetics of anti-ROR1 x anti-CD3 bispecific molecules containing either the less stable DRA222 CD3 binding domain or the more stable TSC456 CD3 binding domain were compared. The following constructs were evaluated. The sequences of the constructs are provided in Table 14.

Construct	Anti-ROR1	Anti-CD3
ROR206 (CHO line: ROR206a)	Binding domain A	DRA222
ROR207 (CHO line: ROR207a)	Binding domain A	TSC456
ROR208 (CHO line: ROR208a)	Binding domain B	DRA222
ROR209 (CHO line: ROR209a)	Binding domain B	TSC456

[00258] NSG mice were dosed intravenously with the anti-ROR1 X anti-CD3 bispecifics at approximately 10 mg/kg. All bispecifics were diluted into PBS. Serum was collected from 3 animals at 10 time points (n = 30 for each construct) post-administration as well as at one time point pre-dose. The time points were 15 min and 2, 6, 24, 48, 72, 96, 168, 336, and 504 hr post-administration of the bispecific molecules. Terminal bleeds were used to collect larger volumes. Serum concentrations were determined using ELISA methods to detect the intact molecule. Serum concentrations over time were used to determine PK parameter estimates by non-compartmental analysis (NCA) and compartmental analysis.

[00259] More specifically, the following ELISA methods were used. Concentrations of anti-ROR1 X anti-CD3 bispecifics were determined using 96-well plates coated with ROR1 ECD-AFH (ROR177) to capture the anti-ROR1 portion of each construct. The other end of ROR constructs was detected using a biotin conjugated mouse monoclonal antibody targeting the anti-CD3-binding-domain (mAb 5H5), so only intact protein would be measured with this ELISA method. To quantify bound immune complexes from serum samples and assay controls, polymerized horseradish peroxidase (poly HRP) and a fluorogenic peroxidase substrate were used, with results measured on a fluorescent plate reader. Standard curves used to calculate serum concentrations consisted of various known concentrations of the appropriate ROR construct spiked into ELISA diluent. SOFTMAX® Pro software was used to calculate serum concentrations using a 4-parameter logistic equation, as well as precision and accuracy for standards and test samples.

[00260] Results of these studies are shown in Figures 16, 17A and 17B. By NCA and compartmental analysis, ROR209a had the longest half-life. ROR207a had the lowest clearance and volume estimates by both analysis methods. Both anti-ROR1 bispecifics with the DRA222 CD3 binding domain had shorter half-life and faster clearance parameters. Notably, constructs with the improved anti-CD3 binding domain (TSC456) had better pharmacokinetics than those with the less stable anti-CD3 binding domain (DRA222).

Example 7. Effects of Stabilized Anti-CD3 Binding Domains on *In Vivo* Efficacy of Anti-ROR1 X Anti-CD3 Binding Molecules

[00261] MDA-MB-231 cells were co-mixed with donor T-cells and matrigel and implanted into the flank of NOD/SCID mice on day 0 of the study. Each group contained N=5 animals, with T-cells from one donor. Figure 18 shows an example graph which shows minimal impact of T-cells on tumor growth by the donor T-cells. Animals were treated with PBS or with 30 µg or 3 µg of ROR208 (DRA222 anti-CD3 binding domain) or ROR209 (TSC456 anti-CD3 binding domain). The dose was administered on day 0, 4, and 8. Tumor growth was measured with calipers over time of study.

[00262] Significant inhibition of tumor growth was seen after treatment with both ROR bispecifics. No significant difference of tumor growth was seen with T-cells from the donor (Figure 18) compared to tumor only. There were no significant differences between animals treated with ROR208 compared to ROR209 at any dose level, indicating the stability improved anti-CD3 binding domain had the same potency as the non-stable anti-CD3 binding domain.

Example 8. Effects of Stabilized Anti-CD3 Binding Domains on *In Vivo* Efficacy of Anti-ROR1 X Anti-CD3 Binding Molecules

[00263] Kasumi-2 cells were co-mixed with donor T-cells and matrigel and implanted into the flank of NOD/SCID mice on day 0 of the study. Each group contained N=10 animals, with T-cells from one donor. Animals were treated with PBS or with 30 µg, 3 µg or 0.3 µg of ROR243 (TSC456 anti-CD3 binding domain) as shown in Figure 19. The dose was administered on day 0, 4, and 8. The route for administration was intravenous (IV), with exception of one group, where the dose was administered subcutaneously (SC). Figure 19 shows results of the assay. Tumor growth was measured with calipers over time of study.

[00264] No inhibition of tumor growth was seen in the presence of T-cells in the absence of ROR243 or with ROR243 treatment in the absence of T-cells. Significant inhibition of tumor growth was seen at 0.3 µg per dose, with dose dependent titration. No difference in route of administration was seen.

Table 14. Binding Domain and Polypeptide Sequences and Components

DNA sequence of Fc DRA222 (TSC311 or TSC312):

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atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt ggagtctggg     840
ggcggagtgg tgcagcctgg gcggtcactg aggctgtcct gcaaggcttc tggctacacc     900
tttactagat ctacgatgca ctgggtaagg caggcccctg gacaaggtct ggaatggatt     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacaggttc    1020
acaatcagcg cagacaaatc caagagcaca gccttcctgc agatggacag cctgaggccc    1080
gaggacaccg gcgtctattt ctgtgcacgg ccccaagtcc actatgatta caacgggttt    1140
ccttactggg gccaagggac tcccgtcact gtctctagcg gtggcggagg gtctgggggt    1200
ggcggatccg gaggtggtgg ctctgcacaa gacatccaga tgacccagtc tccaagcagc    1260
ctgtctgcaa gcgtgggggа cagggtcacc atgacctgca gtgccagctc aagtgtaagt    1320
tacatgaact ggtaccagca gaagccgggc aaggccccca aaagatggat ttatgactca    1380
tccaaactgg cttctggagt ccctgctcgc ttcagtggca gtgggtctgg gaccgactat    1440
accctcacaa tcagcagcct gcagcccgaa gatttcgcca cttattactg ccagcagtgg    1500
agtcgtaacc cacccacgtt cggaggggggg accaagctac aaattacatc ctccagctaa    1560
```

(SEQ ID NO:1)

Signal sequence is residue 1 to 60. Fc region is residue 61 - 753. Linker is 754 to 816. Anti-CD3 scFv is 817 to 1560.

Mature protein sequence of Fc DRA222 (TSC311 or TSC312)

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF      60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT     120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP     180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN     240
TGTQMAGHSP NSQVQLVESG GGVVQPGRSL RLSCKASGYT FTRSTMHWVR QAPGQGLEWI     300
GYINPSSAYT NYNQKFKDRF TISADKSKST AFLQMDSLRP EDTGVYFCAR PQVHYDYNGF     360
```

```
PYWGQGTPVT VSSGGGGSGG GGSGGGGSAQ DIQMTQSPSS LSASVGDRVT MTCSASSSVS       420
YMNWYQQKPG KAPKRWIYDS SKLASGVPAR FSGSGSGTDY TLTISSLQPE DFATYYCQQW       480
SRNPPTFGGG TKLQITSSS                                                   499
```

(SEQ ID NO:2)

DNA sequence of Fc H7L1 (TSC313):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
accectgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc       900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc      1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct      1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccaagcagcc tgtctgcaag cgtgggggac agggtcacca tgacctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccagcag aagccgggca aggccccaa aagatggatt       1380
tatgactcat ccaaactggc ttctggagtc cctgctcgct tcagtggcag tgggtctggg      1440
accgactata ccctcacaat cagcagcctg cagcccgaag atttcgccac ttattactgc      1500
cagcagtgga gtcgtaaccc acccacgttc ggaggggggа ccaagctaca aattacatcc      1560
tccagctaa                                                              1569
```

(SEQ ID NO:3)

Signal sequence is residue 1 to 60. Fc region is residue 61 - 753. Linker is 754 to 816. Anti-CD3 scFv is 817 to 1569.

Mature protein sequence of Fc H7L1 (TSC313):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PARFSGSGSG TDYTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKLQITS SS                                                502
```

(SEQ ID NO:4)

DNA sequence of Fc H7L4 (TSC314):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
accectgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
```

```
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc     1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct     1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacacagtct     1260
ccagccaccc tgtctttgtc tccaggggaa agagccaccc tctcctgcag tgccagctca     1320
agtgtaagtt acatgaactg gtaccaacag aaacctggcc aggctcccag gctcctcatc     1380
tatgactcat ccaaactggc ttctggcatc ccagccaggt tcagtggcag tgggtctggg     1440
acagacttca ctctcaccat cagcagccta gagcctgaag attttgcagt ttattactgt     1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:5)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H7L4 (TSC314):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF       60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT      120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP      180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN      240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM      300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF      360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS      420
SVSYMNWYQQ KPGQAPRLLI YDSSKLASGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC      480
QQWSRNPPTF GGGTKVEIKR SSS                                              503
```

(SEQ ID NO:6)

DNA sequence of Fc H7L5 (TSC315):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg      120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg      180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc      420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc     1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct     1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gctcctgatc     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg     1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:7)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H7L5 (TSC315):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKLLI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:8)

DNA sequence of Fc H8L1 (TSC316):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc        420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc       900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccaagcagcc tgtctgcaag cgtgggggac agggtcacca tgacctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccagcag aagccgggca aggccccaa aagatggatt       1380
tatgactcat ccaaactggc ttctggagtc cctgctcgct tcagtggcag tgggtctggg      1440
accgactata ccctcacaat cagcagcctg cagcccgaag atttcgccac ttattactgc      1500
cagcagtgga gtcgtaaccc acccacgttc ggaggggga ccaagctaca aattacatcc       1560
tccagctaa                                                              1569
```

(SEQ ID NO:9)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L1 (TSC316):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PARFSGSGSG TDYTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKLQITS SS                                                502
```

(SEQ ID NO:10)

DNA sequence of Fc H8L4 (TSC317):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
accccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg     840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc     900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc    1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct    1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt    1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga    1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacacagtct    1260
ccagccaccc tgtctttgtc tccaggggaa agagccaccc tctcctgcag tgccagctca    1320
agtgtaagtt acatgaactg gtaccaacag aaacctggcc aggctcccag gctcctcatc    1380
tatgactcat ccaaactggc ttctggcatc ccagccaggt tcagtggcag tgggtctggg    1440
acagacttca ctctcaccat cagcagccta gagcctgaag attttgcagt ttattactgt    1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg    1560
tcctccagct aa                                                       1572
```

(SEQ ID NO:11)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L4 (TSC317):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF      60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT     120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP     180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN     240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM     300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF     360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS     420
SVSYMNWYQQ KPGQAPRLLI YDSSKLASGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC     480
QQWSRNPPTF GGGTKVEIKR SSS                                             503
```

(SEQ ID NO:12)

DNA sequence of Fc H8L5 (TSC318):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
accccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg     840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc     900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg     960
```

```
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagccctaa gctcctgatc       1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg      1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                         1572
```

(SEQ ID NO:13)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L5 (TSC318):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKLLI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:14)

DNA sequence of Fc H9L1 (TSC319):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagcttgt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcttc tggctacacc       900
tttactagat ctacgatgca ttgggtgcgc caggcccccg gacaaaggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc      1020
accattacca gggacacatc cgcgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaagacacgg ctgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccaagcagcc tgtctgcaag cgtgggggac agggtcacca tgacctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccagcag aagccgggca aggcccccaa aagatggatt      1380
tatgactcat ccaaactggc ttctggagtc cctgctcgct tcagtggcag tgggtctggg      1440
accgactata ccctcacaat cagcagcctg cagcccgaag atttcgccac ttattactgc      1500
cagcagtgga gtcgtaaccc acccacgttc ggaggggggа ccaagctaca aattacatcc      1560
tccagctaa                                                             1569
```

(SEQ ID NO:15)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H9L1 (TSC319):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQRLEWM       300
GYINPSSAYT NYNQKFKDRV TITRDTSAST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PARFSGSGSG TDYTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKLQITS SS                                                502
```

(SEQ ID NO:16)

DNA sequence of Fc H9L4 (TSC320):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagcttgt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcttc tggctacacc       900
tttactagat ctacgatgca ttgggtgcgc caggccccg gacaaaggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc      1020
accattacca gggacacatc cgcgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaagacacgg ctgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacacagtct      1260
ccagccaccc tgtctttgtc tccaggggaa agagccaccc tctcctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccaacag aaacctggcc aggctcccag gctcctcatc      1380
tatgactcat ccaaactggc ttctggcatc ccagccaggt tcagtggcag tgggtctggg      1440
acagacttca ctctcaccat cagcagccta gagcctgaag attttgcagt ttattactgt      1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                          1572
```

(SEQ ID NO:17)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H9L4 (TSC320):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQRLEWM       300
GYINPSSAYT NYNQKFKDRV TITRDTSAST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS       420
SVSYMNWYQQ KPGQAPRLLI YDSSKLASGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:18)

DNA sequence of Fc H9L5 (TSC321):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
```

```
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc        420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagcttgt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcttc tggctacacc       900
tttactagat ctacgatgca ttgggtgcgc caggccccg gacaaaggct tgagtggatg        960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc      1020
accattacca gggacacatc cgcgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaagacacgg ctgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagccctaa gctcctgatc       1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg      1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                         1572
```

(SEQ ID NO:19)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H9L5 (TSC321):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQRLEWM       300
GYINPSSAYT NYNQKFKDRV TITRDTSAST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKLLI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:20)

DNA sequence of Fc H10L1 (TSC322):

```
atggaagcac cagcgcagct tctcttcctc ctgctacttct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc        420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg       840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc       900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
```

```
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccaagcagcc tgtctgcaag cgtgggggac agggtcacca tgacctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccagcag aagccgggca aggcccccaa aagatggatt      1380
tatgactcat ccaaactggc ttctggagtc cctgctcgct tcagtggcag tgggtctggg      1440
accgactata ccctcacaat cagcagcctg cagcccgaag atttcgccac ttattactgc      1500
cagcagtgga gtcgtaaccc acccacgttc ggaggggggа ccaagctaca aattacatcc      1560
tccagctaa                                                              1569
```

(SEQ ID NO:21)

Signal sequence is residue 1 to 60

Mature protein sequence of FC H10L1 (TSC322):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PARFSGSGSG TDYTLTISSL QPEDFATYYC       480
QQWSRNPPTF GGGTKLQITS SS                                                502
```

(SEQ ID NO:22)

DNA sequence of Fc H10L4 (TSC323):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg       840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc       900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacacagtct      1260
ccagccaccc tgtctttgtc tccagggggaa agagccaccc tctcctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccaacag aaacctggcc aggctcccag gctcctcatc      1380
tatgactcat ccaaactggc ttctggcatc ccagccaggt tcagtggcag tgggtctggg      1440
acagacttca ctctcaccat cagcagccta gagcctgaag attttgcagt ttattactgt      1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                          1572
```

(SEQ ID NO:23)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H10L4 (TSC323):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
```

```
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP   180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN   240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM   300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF   360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS   420
SVSYMNWYQQ KPGQAPRLLI YDSSKLASGI PARFSGSGSG TDFTLTISSL EPEDFAVYYC   480
QQWSRNPPTF GGGTKVEIKR SSS                                           503
```

(SEQ ID NO:24)

DNA sequence of Fc H10L5 (TSC324):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt    60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg   120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg   180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc   240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag   300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat   360
ggcaaggcat acgcgtgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc   420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg   480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc   540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct   600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc   660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac   720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat   780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg   840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc   900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg   960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc  1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct  1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt  1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga  1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct  1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca  1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gctcctgatc  1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg  1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt  1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg  1560
tcctccagct aa                                                      1572
```

(SEQ ID NO:25)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H10L5 (TSC324):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF    60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT   120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP   180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN   240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM   300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF   360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS   420
SVSYMNWYQQ KPGKAPKLLI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC   480
QQWSRNPPTF GGGTKVEIKR SSS                                           503
```

(SEQ ID NO:26)

DNA sequence of Fc H7L6 (TSC334):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt    60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg   120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg   180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc   240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag   300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat   360
```

```
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagcccccat cgagaaaacc      420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc     1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct     1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg     1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:27)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H7L6 (TSC334):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF       60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT      120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP      180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN      240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM      300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF      360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS      420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC      480
QQWSRNPPTF GGGTKVEIKR SSS*                                              504
```

(SEQ ID NO:28)

DNA sequence of Fc H7L7 (TSC335):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg      120
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg      180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc     1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct     1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacgcagtct     1260
ccagccaccc tgtctttgtc tccagggaa agagccaccc tctcctgcag tgccagctca      1320
agtgtaagtt acatgaactg gtaccagcag aaacctggcc tggcgcccag gagatggatt     1380
```

```
tatgactcat ccaaactggc ttctggcatc ccagacaggt tcagtggcag tgggtctggg      1440
acagacttca ctctcaccat cagcagactg gagcctgaag attttgcagt gtattactgt      1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                          1572
```

(SEQ ID NO:29)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H7L7 (TSC335):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS       420
SVSYMNWYQQ KPGLAPRRWI YDSSKLASGI PDRFSGSGSG TDFTLTISRL EPEDFAVYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                          504
```

(SEQ ID NO:30)

DNA sequence of Fc H7L8 (TSC336):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccca cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg       840
gctgaggtga agaagcctgg ggcctcagtg aaggtctcct gcaaggcttc tggatacacc       900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagggtc      1020
accatgacca gggacacgtc catcagcaca gcctacatgg agctgagcag gctgagatct      1080
gacgacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt      1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg      1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                          1572
```

(SEQ ID NO:31)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H7L8 (TSC336):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TMTRDTSIST AYMELSRLRS DDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS       420
```

```
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC   480
QQWSRNPPTF GGGTKVEIKR SSS*                                          504
```

(SEQ ID NO:32)

DNA sequence of Fc H8L6 (TSC337):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt    60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg   120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg   180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc   240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag   300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat   360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc   420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg   480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc   540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct   600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc   660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac   720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat   780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg   840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc   900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg   960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc  1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct  1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt  1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga  1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct  1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca  1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagccсctaa gagatggatt  1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg  1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt  1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg  1560
tcctccagct aa                                                      1572
```

(SEQ ID NO:33)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L6 (TSC337):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF    60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT   120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP   180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN   240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM   300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF   360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS   420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC   480
QQWSRNPPTF GGGTKVEIKR SSS*                                          504
```

(SEQ ID NO:34)

DNA sequence of Fc H8L7 (TSC338):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt    60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg   120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg   180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc   240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag   300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat   360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc   420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg   480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc   540
```

```
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacgcagtct     1260
ccagccaccc tgtctttgtc tccaggggaa agagccaccc tctcctgcag tgccagctca     1320
agtgtaagtt acatgaactg gtaccagcag aaacctggcc tggcgcccag gagatggatt     1380
tatgactcat ccaaactggc ttctggcatc ccagacaggt tcagtggcag tgggtctggg     1440
acagacttca ctctcaccat cagcagactg gagcctgaag attttgcagt gtattactgt     1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:35)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L7 (TSC338):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF       60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT      120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP      180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN      240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM      300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF      360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS      420
SVSYMNWYQQ KPGLAPRRWI YDSSKLASGI PDRFSGSGSG TDFTLTISRL EPEDFAVYYC      480
QQWSRNPPTF GGGTKVEIKR SSS                                              503
```

(SEQ ID NO:36)

DNA sequence of Fc H8L8 (TSC339):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg      120
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg      180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tgcagctggt gcagtctggg      840
gctgaggtga agaagcctgg ggcctcagtg aaggtttcct gcaaggcatc tggatacacc      900
ttcaccagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
accatgacca gggacacgtc cacgagcaca gtctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgctaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagccccta gagatggatt      1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg     1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc     1500
```

caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg 1560
tcctccagct aa 1572

(SEQ ID NO:37)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H8L8 (TSC339):

EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF 60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT 120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN 240
TGTQMAGHSP NSQVQLVQSG AEVKKPGASV KVSCKASGYT FTRSTMHWVR QAPGQGLEWM 300
GYINPSSAYT NYNQKFKDRV TMTRDTSTST VYMELSSLRS EDTAVYYCAR PQVHYDYNGF 360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS 420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC 480
QQWSRNPPTF GGGTKVEIKR SSS 504

(SEQ ID NO:38)

DNA sequence of Fc H10L6 (TSC340):

atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt 60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg 120
ggtgcaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc 420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc 540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc 660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac 720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat 780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg 840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc 900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg 960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc 1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct 1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt 1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga 1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct 1260
ccatcctccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca 1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt 1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagtggcag tggatctggg 1440
acagatttca ctctcaccat cagcagtctg caacctgaag attttgcaac ttactactgt 1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg 1560
tcctccagct aa 1572

(SEQ ID NO:39)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H10L6 (TSC340):

EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF 60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT 120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN 240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM 300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF 360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSSLSASVGD RVTITCSASS 420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC 480
QQWSRNPPTF GGGTKVEIKR SSS 503

(SEQ ID NO:40)

DNA sequence of Fc H10L7 (TSC341):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg     840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc     900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc    1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct    1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt    1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga    1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg aaattgtgtt gacgcagtct    1260
ccagccaccc tgtctttgtc tccaggggaa agagccaccc tctcctgcag tgccagctca    1320
agtgtaagtt acatgaactg gtaccagcag aaacctggcc tggcgcccag gagatggatt    1380
tatgactcat ccaaactggc ttctggcatc ccagacaggt tcagtggcag tgggtctggg    1440
acagacttca ctctcaccat cagcagactg gagcctgaag attttgcagt gtattactgt    1500
cagcagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg    1560
tcctccagct aa                                                       1572
```

(SEQ ID NO:41)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H10L7 (TSC341):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF      60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT     120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP     180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN     240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM     300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF     360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSEIVLTQS PATLSLSPGE RATLSCSASS     420
SVSYMNWYQQ KPGLAPRRWI YDSSKLASGI PDRFSGSGSG TDFTLTISRL EPEDFAVYYC     480
QQWSRNPPTF GGGTKVEIKR SSS                                             503
```

(SEQ ID NO:42)

DNA sequence of Fc H10L8 (TSC342):

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
```

```
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg      840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc      900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg     1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:43)

Signal sequence is residue 1 to 60

Mature protein sequence of Fc H10L8 (TSC342):

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF       60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT      120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP      180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN      240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM      300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF      360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS      420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC      480
QQWSRNPPTF GGGTKVEIKR SSS                                              503
```

(SEQ ID NO:44)

DNA sequence of TSC370:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg      120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg      180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg      840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc      900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg     1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
```

```
tcctccagct aa                                                          1572
```

(SEQ ID NO:45)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC370:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:46)

DNA sequence of TSC371:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg       840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc       900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggata       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagccсctaa gagatggatt      1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg      1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                          1572
```

(SEQ ID NO:47)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC371:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWI       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:48)

DNA sequence of TSC372:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg     840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggaggcacc     900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc    1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct    1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt    1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga    1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct    1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tgacttgcag tgccagctca    1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt    1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg    1440
acagaattca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc    1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg    1560
tcctccagct aa                                                       1572
```

(SEQ ID NO:49)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC372:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF      60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT     120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP     180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN     240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGGT FSRSTMHWVR QAPGQGLEWM     300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF     360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTMTCSASS     420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC     480
QQWSRNPPTF GGGTKVEIKR SSS                                             503
```

(SEQ ID NO:50)

DNA sequence of TSC390:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccccа aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccсat cgagaaaacc     420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
```

```
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg      840
cctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc      900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg     1440
acagagttca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:51)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC390:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF       60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT      120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP      180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN      240
TGTQMAGHSP NSQVQLVQSG PEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWM      300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF      360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS      420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC      480
QQWSRNPPTF GGGTKVEIKR SSS                                              503
```

(SEQ ID NO:52)

DNA sequence of TSC391:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt       60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg      120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg      180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc      240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag      300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat      360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc       420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg      480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc      540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct      600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc      660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac      720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat      780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg      840
cctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc      900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggata      960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc     1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct     1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt     1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga     1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct     1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tcacttgcag tgccagctca     1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt     1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg     1440
acagagttca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc     1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg     1560
tcctccagct aa                                                        1572
```

(SEQ ID NO:53)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC391:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG PEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWI       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTITCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:54)

DNA sequence of TSC392:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg       120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg       180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc       240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag       300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat       360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc        420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg       480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc       540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct       600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc       660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac       720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat       780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg       840
cctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc       900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggatg       960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc      1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tgacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt      1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg      1440
acagagttca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                         1572
```

(SEQ ID NO:55)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC392:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG PEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWM       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:56)

DNA sequence of TSC393:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc      420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg     840
gctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc     900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggata     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc    1020
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct    1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt    1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga    1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct    1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tgacttgcag tgccagctca    1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt    1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg    1440
acagagttca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc    1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg    1560
tcctccagct aa                                                       1572
```

(SEQ ID NO:57)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC393:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF      60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT     120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP     180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN     240
TGTQMAGHSP NSQVQLVQSG AEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWI     300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF     360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTMTCSASS     420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC     480
QQWSRNPPTF GGGTKVEIKR SSS                                             503
```

(SEQ ID NO:58)

DNA sequence of TSC394:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt      60
gagcccaaat cttctgacaa aactcacaca tgcccaccgt gcccagcacc tgaagccgcg     120
ggtgcaccgt cagtcttcct cttccccca aaacccaagg acaccctcat gatctcccgg     180
acccctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc     240
aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag     300
tacaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat     360
ggcaaggcat acgcatgcgc ggtctccaac aaagccctcc cagccccat cgagaaaacc      420
atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg     480
gatgagctga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatccaagc     540
gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct     600
cccgtgctgg actccgacgg ctccttcttc ctctacagca agctcaccgt ggacaagagc     660
aggtggcagc aggggaacgt cttctcatgc tccgtgatgc atgaggctct gcacaaccac     720
tacacgcaga agagcctctc cctgtctccg ggtcagaggc acaacaattc ttccctgaat     780
acaggaactc agatggcagg tcattctccg aattctcagg tccagctggt gcaatctggg     840
cctgaggtga agaagcctgg gtcctcggtg aaggtctcct gcaaggcttc tggatatacc     900
ttcagcagat ctacgatgca ctgggtgcga caggcccctg gacaagggct tgagtggata     960
ggatacatta atcctagcag tgcttatact aattacaatc agaaattcaa ggacagagtc    1020
```

```
acgattaccg cggacaaatc cacgagcaca gcctacatgg agctgagcag cctgagatct      1080
gaggacacgg ccgtgtatta ctgtgcgaga ccccaagtcc actatgatta caacgggttt      1140
ccttactggg gccaaggaac cctggtcacc gtctcctcag gtggaggcgg ttcaggcgga      1200
ggtggatccg gcggtggcgg atcgggtggc ggcggatctg acatccagat gacccagtct      1260
ccttccaccc tgtctgcatc tgtaggagac agagtcacca tgacttgcag tgccagctca      1320
agtgtaagtt acatgaactg gtatcagcag aaaccaggga aagcccctaa gagatggatt      1380
tatgactcat ccaaactggc ttctggggtc ccatcaaggt tcagcggcag tggatctggg      1440
acagagttca ctctcaccat cagcagcctg cagcctgatg attttgcaac ttattactgc      1500
caacagtgga gtcgtaaccc acccactttc ggcggaggga ccaaggtgga gatcaaacgg      1560
tcctccagct aa                                                         1572
```

(SEQ ID NO:59)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC394:

```
EPKSSDKTHT CPPCPAPEAA GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF        60
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKAYACAVSN KALPAPIEKT       120
ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP       180
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GQRHNNSSLN       240
TGTQMAGHSP NSQVQLVQSG PEVKKPGSSV KVSCKASGYT FSRSTMHWVR QAPGQGLEWI       300
GYINPSSAYT NYNQKFKDRV TITADKSTST AYMELSSLRS EDTAVYYCAR PQVHYDYNGF       360
PYWGQGTLVT VSSGGGGSGG GGSGGGGSGG GGSDIQMTQS PSTLSASVGD RVTMTCSASS       420
SVSYMNWYQQ KPGKAPKRWI YDSSKLASGV PSRFSGSGSG TEFTLTISSL QPDDFATYYC       480
QQWSRNPPTF GGGTKVEIKR SSS                                               503
```

(SEQ ID NO:60)

DNA sequence of TSC408:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gatatccaga tgacccagtc tccatccgcc atgtctgcat ctgtaggaga cagagtcacc       120
atcacttgcc gggcgagtaa gagcattagc aaatatttag cctggtttca gcagaaacca       180
gggaaagttc ctaagctccg catccattct ggatctactt tgcaatcagg ggtcccatct       240
cggttcagtg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct       300
gaagattttg caacttatta ctgtcaacag catattgaat acccgtggac gttcggccaa       360
gggaccaagg tggaaatcaa acgaggtggc ggagggtctg ggggtggcgg atccggaggt       420
ggtggctctc aggtccagct ggtacagtct ggggctgagg tgaagaagcc tggggcttca       480
gtgaaggtct cctgcaaggc ttctggatac acattcactg actactacat gcactgggtg       540
cgacaggccc ctggacaagg gcttgagtgg atgggatatt ttaatcctta taatgattat       600
actagatacg cacagaagtt ccagggcaga gtcaccatga ccagggacac gtctatcagc       660
acagcctaca tggagctgag cagcctgaga tctgacgaca cggccgtgta ttactgtgca       720
agatcggatg gttactacga tgctatggac tactggggtc aaggaaccac agtcaccgtc       780
tcctcgagtg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct       840
gaagccgcgg gtgcaccgtc agtcttcctc ttccccccaa aacccaagga caccctcatg       900
atctcccgga ccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag       960
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg      1020
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac      1080
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agcccccatc      1140
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc      1200
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc      1260
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag      1320
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg      1380
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg      1440
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtcagaggca caacaattct      1500
tccctgaata caggaactca gatggcaggt cattctccga attctcaggt ccagctggtg      1560
caatctgggc ctgaggtgaa gaagcctggg tcctcggtga aggtctcctg caaggcttct      1620
ggatatacct tcagcagatc tacgatgcac tgggtgcgac aggcccctgg acaagggctt      1680
gagtggatag gatacattaa tcctagcagt gcttatacta attacaatca gaaattcaag      1740
gacagagtca cgattaccgc ggacaaatcc acgagcacag cctacatgga gctgagcagc      1800
ctgagatctg aggacacggc cgtgtattac tgtgcgagac cccaagtcca ctatgattac      1860
aacgggtttc cttactgggg ccaaggaacc ctggtcaccg tctcctcagg tggaggcggt      1920
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catccagatg      1980
acccagtctc cttccaccct gtctgcatct gtaggagaca gagtcaccat cacttgcagt      2040
```

```
gccagctcaa gtgtaagtta catgaactgg tatcagcaga aaccagggaa agcccctaag      2100
agatggattt atgactcatc caaactggct tctggggtcc catcaaggtt cagcggcagt      2160
ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact      2220
tattactgcc aacagtggag tcgtaaccca cccactttcg gcggagggac caaggtggag      2280
atcaaacggt cctccagcta a                                                2301
```

(SEQ ID NO:61)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC408:

```
DIQMTQSPSA MSASVGDRVT ITCRASKSIS KYLAWFQQKP GKVPKLRIHS GSTLQSGVPS        60
RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HIEYPWTFGQ GTKVEIKRGG GGSGGGGSGG       120
GGSQVQLVQS GAEVKKPGAS VKVSCKASGY TFTDYYMHWV RQAPGQGLEW MGYFNPYNDY       180
TRYAQKFQGR VTMTRDTSIS TAYMELSSLR SDDTAVYYCA RSDGYYDAMD YWGQGTTVTV       240
SSSEPKSSDK THTCPPCPAP EAAGAPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE       300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKAYACA VSNKALPAPI       360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK       420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGQRHNNS       480
SLNTGTQMAG HSPNSQVQLV QSGPEVKKPG SSVKVSCKAS GYTFSRSTMH WVRQAPGQGL       540
EWIGYINPSS AYTNYNQKFK DRVTITADKS TSTAYMELSS LRSEDTAVYY CARPQVHYDY       600
NGFPYWGQGT LVTVSSGGGG SGGGGSGGGG SGGGGSDIQM TQSPSTLSAS VGDRVTITCS       660
ASSSVSYMNW YQQKPGKAPK RWIYDSSKLA SGVPSRFSGS GSGTEFTLTI SSLQPDDFAT       720
YYCQQWSRNP PTFGGGTKVE IKRSSS                                            746
```

(SEQ ID NO:62)

DNA sequence of TSC409:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gatatccaga tgacccagtc tccatccgcc atgtctgcat ctgtaggaga cagagtcacc       120
atcacttgcc gggcgagtaa gagcattagc aaatatttag cctggtttca gcagaaacca       180
gggaaagttc ctaagctccg catccattct ggatctactt tgcaatcagg ggtcccatct       240
cggttcagtg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct       300
gaagattttg caacttatta ctgtcaacag catattgaat acccgtggac gttcggccaa       360
gggaccaagg tggaaatcaa acgaggtggc ggagggtctg ggggtggcgg atccggaggt       420
ggtggctctc aggtccagct ggtacagtct ggggctgagg tgaagaagcc tggggcttca       480
gtgaaggtct cctgcaaggc ttctggatac acattcactg actactacat gcactgggtg       540
cgacaggccc ctggacaagg gcttgagtgg atgggatatt ttaatcctta taatgattat       600
actagatacg cacagaagtt ccagggcaga gtcaccatga ccagggacac gtctatcagc       660
acagcctaca tggagctgag cagcctgaga tctgacgaca cggccgtgta ttactgtgca       720
agatcggatg gttactacga tgctatggac tactggggtc aaggaaccac agtcaccgtc       780
tcctcgagtg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct       840
gaagccgcgg gtgcaccgtc agtcttcctc ttccccccaa aacccaagga caccctcatg       900
atctcccgga ccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag       960
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg      1020
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac      1080
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agccccatc       1140
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc      1200
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc      1260
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag      1320
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg      1380
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg      1440
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtcagaggca caacaattct      1500
tccctgaata caggaactca gatggcaggt cattctccga attctcaggt ccagctggtg      1560
caatctgggc ctgaggtgaa gaagcctggg tcctcggtga aggtctcctg caaggcttct      1620
ggatatacct tcagcagatc tacgatgcac tgggtgcgac aggcccctgg acaagggctt      1680
gagtggatgg gatacattaa tcctagcagt gcttatacta attacaatca gaaattcaag      1740
gacagagtca cgattaccgc ggacaaatcc acgagcacag cctacatgga gctgagcagc      1800
ctgagatctg aggacacggc cgtgtattac tgtgcgagac cccaagtcca ctatgattac      1860
aacgggtttc cttactgggg ccaaggaacc ctggtcaccg tctcctcagg tggaggcggt      1920
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catccagatg      1980
acccagtctc cttccaccct gtctgcatct gtaggagaca gagtcaccat gacttgcagt      2040
```

```
gccagctcaa gtgtaagtta catgaactgg tatcagcaga aaccagggaa agcccctaag      2100
agatggattt atgactcatc caaactggct tctggggtcc catcaaggtt cagcggcagt      2160
ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact      2220
tattactgcc aacagtggag tcgtaaccca cccactttcg gcggagggac caaggtggag      2280
atcaaacggt cctccagcta a                                                2301
```

(SEQ ID NO:63)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC409:

```
DIQMTQSPSA MSASVGDRVT ITCRASKSIS KYLAWFQQKP GKVPKLRIHS GSTLQSGVPS        60
RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HIEYPWTFGQ GTKVEIKRGG GGSGGGGSGG       120
GGSQVQLVQS GAEVKKPGAS VKVSCKASGY TFTDYYMHWV RQAPGQGLEW MGYFNPYNDY       180
TRYAQKFQGR VTMTRDTSIS TAYMELSSLR SDDTAVYYCA RSDGYYDAMD YWGQGTTVTV       240
SSSEPKSSDK THTCPPCPAP EAAGAPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE       300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKAYACA VSNKALPAPI       360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK       420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGQRHNNS       480
SLNTGTQMAG HSPNSQVQLV QSGPEVKKPG SSVKVSCKAS GYTFSRSTMH WVRQAPGQGL       540
EWMGYINPSS AYTNYNQKFK DRVTITADKS TSTAYMELSS LRSEDTAVYY CARPQVHYDY       600
NGFPYWGQGT LVTVSSGGGG SGGGGSGGGG SGGGGSDIQM TQSPSTLSAS VGDRVTMTCS       660
ASSSVSYMNW YQQKPGKAPK RWIYDSSKLA SGVPSRFSGS GSGTEFTLTI SSLQPDDFAT       720
YYCQQWSRNP PTFGGGTKVE IKRSSS                                            746
```

(SEQ ID NO:64)

DNA sequence of TSC410:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gatatccaga tgacccagtc tccatccgcc atgtctgcat ctgtaggaga cagagtcacc       120
atcacttgcc gggcgagtaa gagcattagc aaatatttag cctggtttca gcagaaacca       180
gggaaagttc ctaagctccg catccattct ggatctactt tgcaatcagg ggtcccatct       240
cggttcagtg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct       300
gaagattttg caacttatta ctgtcaacag catattgaat acccgtggac gttcggccaa       360
gggaccaagg tggaaatcaa acgaggtggc ggagggtctg ggggtggcgg atccggaggt       420
ggtggctctc aggtccagct ggtacagtct ggggctgagg tgaagaagcc tggggcttca       480
gtgaaggtct cctgcaaggc ttctggatac acattcactg actactacat gcactgggtg       540
cgacaggccc ctggacaagg gcttgagtgg atgggatatt ttaatcctta taatgattat       600
actagatacg cacagaagtt ccagggcaga gtcaccatga ccagggacac gtctatcagc       660
acagcctaca tggagctgag cagcctgaga tctgacgaca cggccgtgta ttactgtgca       720
agatcggatg gttactacga tgctatggac tactggggtc aaggaaccac agtcaccgtc       780
tcctcgagtg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct       840
gaagccgcgg gtgcaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg       900
atctcccgga ccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag       960
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg      1020
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac      1080
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agcccccatc      1140
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc      1200
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc      1260
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag      1320
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg      1380
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg      1440
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtcagaggca caacaattct      1500
tccctgaata caggaactca gatggcaggt cattctccga attctcaggt ccagctggtg      1560
caatctgggg ctgaggtgaa gaagcctggg tcctcggtga aggtctcctg caaggcttct      1620
ggatatacct tcagcagatc tacgatgcac tgggtgcgac aggcccctgg acaagggctt      1680
gagtggatag gatacattaa tcctagcagt gcttatacta attacaatca gaaattcaag      1740
gacagagtca cgattaccgc ggacaaatcc acgagcacag cctacatgga gctgagcagc      1800
ctgagatctg aggacacggc cgtgtattac tgtgcgagac cccaagtcca ctatgattac      1860
aacgggtttc cttactgggg ccaaggaacc ctggtcaccg tctcctcagg tggaggcggt      1920
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catccagatg      1980
acccagtctc cttccaccct gtctgcatct gtaggagaca gagtcaccat gacttgcagt      2040
gccagctcaa gtgtaagtta catgaactgg tatcagcaga aaccagggaa agcccctaag      2100
agatggattt atgactcatc caaactggct tctggggtcc catcaaggtt cagcggcagt      2160
```

```
ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact      2220
tattactgcc aacagtggag tcgtaaccca cccactttcg gcggagggac caaggtggag      2280
atcaaacggt cctccagcta a                                                2301
```

(SEQ ID NO:65)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC410:

```
DIQMTQSPSA MSASVGDRVT ITCRASKSIS KYLAWFQQKP GKVPKLRIHS GSTLQSGVPS        60
RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HIEYPWTFGQ GTKVEIKRGG GGSGGGGSGG       120
GGSQVQLVQS GAEVKKPGAS VKVSCKASGY TFTDYYMHWV RQAPGQGLEW MGYFNPYNDY       180
TRYAQKFQGR VTMTRDTSIS TAYMELSSLR SDDTAVYYCA RSDGYYDAMD YWGQGTTVTV       240
SSSEPKSSDK THTCPPCPAP EAAGAPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE       300
VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKAYACA VSNKALPAPI       360
EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK       420
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGQRHNNS       480
SLNTGTQMAG HSPNSQVQLV QSGAEVKKPG SSVKVSCKAS GYTFSRSTMH WVRQAPGQGL       540
EWIGYINPSS AYTNYNQKFK DRVTITADKS TSTAYMELSS LRSEDTAVYY CARPQVHYDY       600
NGFPYWGQGT LVTVSSGGGG SGGGGSGGGG SGGGGSDIQM TQSPSTLSAS VGDRVTMTCS       660
ASSSVSYMNW YQQKPGKAPK RWIYDSSKLA SGVPSRFSGS GSGTEFTLTI SSLQPDDFAT       720
YYCQQWSRNP PTFGGGTKVE IKRSSS                                            746
```

(SEQ ID NO:66)

DNA sequence of TSC411:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gatatccaga tgacccagtc tccatccgcc atgtctgcat ctgtaggaga cagagtcacc       120
atcacttgcc gggcgagtaa gagcattagc aaatatttag cctggtttca gcagaaacca       180
gggaaagttc ctaagctccg catccattct ggatctactt tgcaatcagg ggtcccatct       240
cggttcagtg gcagtggatc tgggacagaa tttactctca ccatcagcag cctgcagcct       300
gaagattttg caacttatta ctgtcaacag catattgaat acccgtggac gttcggccaa       360
gggaccaagg tggaaatcaa acgaggtggc ggagggtctg ggggtggcgg atccggaggt       420
ggtggctctc aggtccagct ggtacagtct ggggctgagg tgaagaagcc tggggcttca       480
gtgaaggtct cctgcaaggc ttctggatac acattcactg actactacat gcactgggtg       540
cgacaggccc ctggacaagg gcttgagtgg atgggatatt ttaatcctta taatgattat       600
actagatacg cacagaagtt ccagggcaga gtcaccatga ccagggacac gtctatcagc       660
acagcctaca tggagctgag cagcctgaga tctgacgaca cggccgtgta ttactgtgca       720
agatcggatg gttactacga tgctatggac tactggggtc aaggaaccac agtcaccgtc       780
tcctcgagtg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct       840
gaagccgcgg gtgcaccgtc agtcttcctc ttccccccaa aacccaagga caccctcatg       900
atctcccgga ccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag       960
gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg      1020
gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac      1080
tggctgaatg gcaaggcgta cgcgtgcgcg gtctccaaca aagccctccc agccccatc       1140
gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgta caccctgccc      1200
ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc      1260
tatccaagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag      1320
accacgcctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg      1380
gacaagagca ggtggcagca ggggaacgtc ttctcatgct ccgtgatgca tgaggctctg      1440
cacaaccact acacgcagaa gagcctctcc ctgtctccgg gtcagaggca caacaattct      1500
tccctgaata caggaactca gatggcaggt cattctccga attctcaggt ccagctggtg      1560
caatctgggc ctgaggtgaa gaagcctggg tcctcggtga aggtctcctg caaggcttct      1620
ggatatacct tcagcagatc tacgatgcac tgggtgcgac aggcccctgg acaagggctt      1680
gagtggatag gatacattaa tcctagcagt gcttatacta attacaatca gaaattcaag      1740
gacagagtca cgattaccgc ggacaaatcc acgagcacag cctacatgga gctgagcagc      1800
ctgagatctg aggacacggc cgtgtattac tgtgcgagac cccaagtcca ctatgattac      1860
aacgggtttc cttactgggg ccaaggaacc ctggtcaccg tctcctcagg tggaggcggt      1920
tcaggcggag gtggatccgg cggtggcgga tcgggtggcg gcggatctga catccagatg      1980
acccagtctc cttccaccct gtctgcatct gtaggagaca gagtcaccat gacttgcagt      2040
gccagctcaa gtgtaagtta catgaactgg tatcagcaga aaccagggaa agcccctaag      2100
agatggattt atgactcatc caaactggct tctggggtcc catcaaggtt cagcggcagt      2160
ggatctggga cagagttcac tctcaccatc agcagcctgc agcctgatga ttttgcaact      2220
tattactgcc aacagtggag tcgtaaccca cccactttcg gcggagggac caaggtggag      2280
```

```
     atcaaacggt cctccagcta a                                                2301
```

(SEQ ID NO:67)

Signal sequence is residue 1 to 60

Mature protein sequence of TSC411:

```
     DIQMTQSPSA MSASVGDRVT ITCRASKSIS KYLAWFQQKP GKVPKLRIHS GSTLQSGVPS        60
     RFSGSGSGTE FTLTISSLQP EDFATYYCQQ HIEYPWTFGQ GTKVEIKRGG GGSGGGGSGG       120
     GGSQVQLVQS GAEVKKPGAS VKVSCKASGY TFTDYYMHWV RQAPGQGLEW MGYFNPYNDY       180
     TRYAQKFQGR VTMTRDTSIS TAYMELSSLR SDDTAVYYCA RSDGYYDAMD YWGQGTTVTV       240
     SSSEPKSSDK THTCPPCPAP EAAGAPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE       300
     VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNGKAYACA VSNKALPAPI       360
     EKTISKAKGQ PREPQVYTLP PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK       420
     TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS LSPGQRHNNS       480
     SLNTGTQMAG HSPNSQVQLV QSGPEVKKPG SSVKVSCKAS GYTFSRSTMH WVRQAPGQGL       540
     EWIGYINPSS AYTNYNQKFK DRVTITADKS TSTAYMELSS LRSEDTAVYY CARPQVHYDY       600
     NGFPYWGQGT LVTVSSGGGG SGGGGSGGGG SGGGGSDIQM TQSPSTLSAS VGDRVTMTCS       660
     ASSSVSYMNW YQQKPGKAPK RWIYDSSKLA SGVPSRFSGS GSGTEFTLTI SSLQPDDFAT       720
     YYCQQWSRNP PTFGGGTKVE IKRSSS                                            746
```

(SEQ ID NO:68)

DNA sequence of CAS105:

```
     atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
     gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt       120
     tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg       180
     cccgggaaag gcctggagtg gatgggcaat attgatcctt attatggtgg tactacctac       240
     aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac       300
     ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc       360
     ggcccttccg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc       420
     tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc       480
     tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc       540
     accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa       600
     cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca       660
     gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag       720
     cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc       780
     caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac       840
     acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc       900
     ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg       960
     gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg      1020
     cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc      1080
     gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc      1140
     aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga      1200
     gaaccacagg tgtacaccct gccccatcc cgggatgagc tgaccaagaa ccaggtcagc      1260
     ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat      1320
     gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc      1380
     ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca      1440
     tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct      1500
     ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct      1560
     ccgaattctc aggtccagct ggtggagtct gggggcggag tggtgcagcc tgggcggtca      1620
     ctgaggctgt cctgcaaggc ttctggctac acctttacta gatctacgat gcactgggta      1680
     aggcaggccc ctggacaagg tctggaatgg attggataca ttaatcctag cagtgcttat      1740
     actaattaca atcagaaatt caaggacagg ttcacaatca gcgcagacaa atccaagagc      1800
     acagccttcc tgcagatgga cagcctgagg cccgaggaca ccggcgtcta tttctgtgca      1860
     cggccccaag tccactatga ttacaacggg tttccttact ggggccaagg gactcccgtc      1920
     actgtctcta gcggtggcgg agggtctggg ggtggcggat ccggaggtgg tggctctgca      1980
     caagacatcc agatgaccca gtctccaagc agcctgtctg caagcgtggg ggacagggtc      2040
     accatgacct gcagtgccag ctcaagtgta agttacatga actggtacca gcagaagccg      2100
     ggcaaggccc ccaaaagatg gatttatgac tcatccaaac tggcttctgg agtccctgct      2160
     cgcttcagtg gcagtgggtc tgggaccgac tataccctca caatcagcag cctgcagccc      2220
     gaagatttcg ccacttatta ctgccagcag tggagtcgta acccacccac gttcggaggg      2280
     gggaccaagc tacaaattac atcctccagc taa                                  2313
```

(SEQ ID NO:69)

Signal sequence is residue 1 to 60

Mature protein sequence of CAS105:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY        60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG       120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK       180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG       240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV       300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS       360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN       420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS       480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVES GGGVVQPGRS LRLSCKASGY TFTRSTMHWV       540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR FTISADKSKS TAFLQMDSLR PEDTGVYFCA       600
RPQVHYDYNG FPYWGQGTPV TVSSGGGGSG GGGSGGGGSA QDIQMTQSPS SLSASVGDRV       660
TMTCSASSSV SYMNWYQQKP GKAPKRWIYD SSKLASGVPA RFSGSGSGTD YTLTISSLQP       720
EDFATYYCQQ WSRNPPTFGG GTKLQITSSS                                        750
```

(SEQ ID NO:70)

DNA sequence of Anti-CD37 X TSC445:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt        60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt       120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg       180
cccgggaaag gcctggagtg gatgggcaat attgatcctt attatggtgg tactacctac       240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac       300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc       360
ggcccttttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc      420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc       480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc       540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa       600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca       660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag       720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc       780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac       840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc       900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg       960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg      1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc      1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc      1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga      1200
gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc      1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat      1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc      1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca      1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct      1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct      1560
ccgaattctc aggtccagct ggtgcaatct gggcctgagg tgaagaagcc tgggtcctcg      1620
gtgaaggtct cctgcaaggc ttctggatat accttcagca gatctacgat gcactgggtg      1680
cgacaggccc ctggacaagg gcttgagtgg ataggataca ttaatcctag cagtgcttat      1740
actaattaca atcagaaatt caaggacaga gtcacgatta ccgcggacaa atccacgagc      1800
acagcctaca tggagctgag cagcctgaga tctgaggaca cggccgtgta ttactgtgcg      1860
agaccccaag tccactatga ttacaacggg tttccttact ggggccaagg aaccctggtc      1920
accgtctcct caggtggagg cggttcaggc ggaggtggat ccggcggtgg cggatcgggt      1980
ggcggcggat ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga      2040
gacagagtca ccatgacttg cagtgccagc tcaagtgtaa gttacatgaa ctggtatcag      2100
cagaaaccag ggaaagcccc taagagatgg atttatgact catccaaact ggcttctggg      2160
gtcccatcaa ggttcagcgg cagtggatct gggacagagt tcactctcac catcagcagc      2220
ctgcagcctg atgattttgc aacttattac tgccaacagt ggagtcgtaa cccacccact      2280
ttcggcggag ggaccaaggt ggagatcaaa cggtcctcca gctaa                      2325
```

(SEQ ID NO:71)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC445:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY   60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG  120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK  180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG  240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV  300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS  360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN  420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS  480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVQS GPEVKKPGSS VKVSCKASGY TFSRSTMHWV  540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR VTITADKSTS TAYMELSSLR SEDTAVYYCA  600
RPQVHYDYNG FPYWGQGTLV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSTLSASVG  660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPSRFSGSGS GTEFTLTISS  720
LQPDDFATYY CQQWSRNPPT FGGGTKVEIK RSSS                               754
```

(SEQ ID NO:72)

DNA sequence of Anti-CD37 X TSC452:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt   60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt  120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg  180
cccgggaaag gcctggagtg gatgggcaat attgatcctt attatggtgg tactacctac  240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac  300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc  360
ggccctttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc  420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc  480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc  540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa  600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca  660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag  720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc  780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac  840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc  900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg  960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc 1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat 1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct 1560
ccgaattctc aggtccagct ggtggagtct gggggcggag tggtgcagcc tgggcggtca 1620
ctgaggctgt cctgcaaggc ttctggctac acctttacta gatctacgat gcactgggta 1680
aggcaggccc ctggacaagg tctggaatgg attggatacа ttaatcctag cagtgcttat 1740
actaattaca atcagaaatt caaggacagg ttcacaatca gcgcagacaa atccaagagc 1800
acagccttcc tgcagatgga gcgcctgagg cccgaggaca ccggcgtcta tttctgtgca 1860
cggccccaag tccactatga ttacaacggg tttccttact ggggccaagg gactcccgtc 1920
actgtctcta gcggtggcgg agggtctggg ggtggcggat ccggcggtgg cggatcgggt 1980
ggcggcggat ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga 2040
gacagagtca ccatgacttg cagtgccagc tcaagtgtaa gttacatgaa ctggtatcag 2100
cagaaaccag ggaaagcccc taagagatgg atttatgact catccaaact ggcttctggg 2160
gtcccatcaa ggttcagcgg cagtggatct gggacagagt tcactctcac catcagcagc 2220
ctgcagcctg atgattttgc aacttattac tgccaacagt ggagtcgtaa cccacccact 2280
ttcggcggag ggaccaaggt ggagatcaaa cggtcctcca gctaa                  2325
```

(SEQ ID NO:73)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC452:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY   60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG  120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK  180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG  240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV  300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS  360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN  420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS  480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVES GGGVVQPGRS LRLSCKASGY TFTRSTMHWV  540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR FTISADKSKS TAFLQMDSLR PEDTGVYFCA  600
RPQVHYDYNG FPYWGQGTPV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSTLSASVG  660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPSRFSGSGS GTEFTLTISS  720
LQPDDFATYY CQQWSRNPPT FGGGTKVEIK RSSS                               754
```

(SEQ ID NO:74)

DNA sequence of Anti-CD37 X TSC453:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt   60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt  120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg  180
cccgggaaag gcctggagtg gatgggcaat attgatcctt attatggtgg tactacctac  240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac  300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc  360
ggccctttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc  420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc  480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc  540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa  600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca  660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag  720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc  780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac  840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc  900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg  960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc 1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat 1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct 1560
ccgaattctc aggtccagct ggtgcaatct gggcctgagg tgaagaagcc tgggtcctcg 1620
gtgaaggtct cctgcaaggc ttctggatat accttcagca gatctacgat gcactgggtg 1680
cgacaggccc ctggacaagg gcttgagtgg ataggataca ttaatcctag cagtgcttat 1740
actaattaca atcagaaatt caaggacaga gtcacgatta ccgcggacaa atccacgagc 1800
acagcctaca tggagctgag cagcctgaga tctgaggaca cggccgtgta ttactgtgcg 1860
agaccccaag tccactatga ttacaacggg tttccttact ggggccaagg aaccctggtc 1920
accgtctcct caggtggagg cggttcaggc ggaggtggat ccggaggtgg tggctctggt 1980
ggcggcggat ctgacatcca gatgacccag tctccaagca gcctgtctgc aagcgtgggg 2040
gacagggtca ccatgacctg cagtgccagc tcaagtgtaa gttacatgaa ctggtaccag 2100
cagaagccgg gcaaggcccc caaaagatgg atttatgact catccaaact ggcttctgga 2160
gtccctgctc gcttcagtgg cagtgggtct gggaccgact ataccctcac aatcagcagc 2220
ctgcagcccg aagatttcgc cacttattac tgccagcagt ggagtcgtaa cccacccacg 2280
ttcggagggg ggaccaagct acaaattaca tcctccagct aa                     2322
```

(SEQ ID NO:75)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC453:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY   60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG  120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK  180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG  240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV  300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS  360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN  420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS  480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVQS GPEVKKPGSS VKVSCKASGY TFSRSTMHWV  540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR VTITADKSTS TAYMELSSLR SEDTAVYYCA  600
RPQVHYDYNG FPYWGQGTLV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSSLSASVG  660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPARFSGSGS GTDYTLTISS  720
LQPEDFATYY CQQWSRNPPT FGGGTKLQIT SSS                               753
```

(SEQ ID NO:76)

DNA sequence of Anti-CD37 X TSC454:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt   60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt  120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg  180
cccgggaaag cctggagtg gatgggcaat attgatcctt attatggtgg tactacctac  240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac  300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc  360
ggcccttttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc  420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc  480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc  540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa  600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca  660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag  720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc  780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac  840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc  900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg  960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc 1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat 1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct 1560
ccgaattctc aggtccagct ggtgcaatct gggcctgagg tgaagaagcc tgggtcctcg 1620
gtgaaggtct cctgcaaggc ttctggatat accttcagca gatctacgat gcactgggtg 1680
cgacaggccc ctggacaagg gcttgagtgg ataggataca ttaatcctag cagtgcttat 1740
actaattaca atcagaaatt caaggacaga gtcacgatta ccgcggacaa atccacgagc 1800
acagcctaca tggagctgag cagcctgaga tctgaggaca cggccgtgta ttactgtgcg 1860
agaccccaag tccactatga ttacaacggg tttccttact ggggccaagg aaccctggtc 1920
accgtctcct caggtggagg cggttcaggc ggaggtggat ccggcggtgg cggatcgggt 1980
ggcggcggat ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga 2040
gacagagtca ccatgacttg cagtgccagc tcaagtgtaa gttacatgaa ctggtatcag 2100
cagaaaccag ggaaagcccc taagagatgg atttatgact catccaaact ggcttctggg 2160
gtcccatcaa ggttcagcgg cagtggatct gggacagatt tcactctcac catcagcagc 2220
ctgcagcctg atgattttgc aacttattac tgccaacagt ggagtcgtaa cccacccact 2280
ttcggcggag ggaccaaggt ggagatcaaa cggtcctcca gctaa                  2325
```

(SEQ ID NO:77)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC454:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY   60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG  120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK  180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG  240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV  300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS  360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN  420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS  480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVQS GPEVKKPGSS VKVSCKASGY TFSRSTMHWV  540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR VTITADKSTS TAYMELSSLR SEDTAVYYCA  600
RPQVHYDYNG FPYWGQGTLV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSTLSASVG  660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPSRFSGSGS GTDFTLTISS  720
LQPDDFATYY CQQWSRNPPT FGGGTKVEIK RSSS                               754
```

(SEQ ID NO:78)

DNA sequence of Anti-CD37 X TSC455:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt   60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt  120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg  180
cccgggaaag cctggagtg gatgggcaat attgatcctt attatggtgg tactacctac  240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac  300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc  360
ggcccttttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc  420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc  480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc  540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa  600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca  660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag  720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc  780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac  840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc  900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg  960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc 1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat 1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct 1560
ccgaattctc aggtccagct ggtgcaatct gggcctgagg tgaagaagcc tgggtcctcg 1620
gtgaaggtct cctgcaaggc ttctggatat accttcagca gatctacgat gcactgggtg 1680
cgacaggccc ctggacaagg gcttgagtgg ataggataca ttaatcctag cagtgcttat 1740
actaattaca atcagaaatt caaggacaga gtcacgatta ccgcggacaa atccacgagc 1800
acagcctaca tggagctgag cagcctgaga tctgaggaca cggccgtgta ttactgtgcg 1860
agaccccaag tccactatga ttacaacggg tttccttact ggggccaagg aaccctggtc 1920
accgtctcct caggtggagg cggttcaggc ggaggtggat ccggcggtgg cggatcgggt 1980
ggcggcggat ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga 2040
gacagagtca ccatgacttg cagtgccagc tcaagtgtaa gttacatgaa ctggtatcag 2100
cagaaaccag ggaaagcccc taagagatgg atttatgact catccaaact ggcttctggg 2160
gtcccatcaa ggttcagcgg cagtggatct gggacagagt atactctcac catcagcagc 2220
ctgcagcctg atgattttgc aacttattac tgccaacagt ggagtcgtaa cccacccact 2280
ttcggcggag ggaccaaggt ggagatcaaa cggtcctcca gctaa                  2325
```

(SEQ ID NO:79)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC455:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY   60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG  120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK  180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG  240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV  300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS  360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN  420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS  480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVQS GPEVKKPGSS VKVSCKASGY TFSRSTMHWV  540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR VTITADKSTS TAYMELSSLR SEDTAVYYCA  600
RPQVHYDYNG FPYWGQGTLV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSTLSASVG  660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPSRFSGSGS GTEYTLTISS  720
LQPDDFATYY CQQWSRNPPT FGGGTKVEIK RSSS                               754
```

(SEQ ID NO:80)

DNA sequence of Anti-CD37 X TSC456:

```
atggaagcac cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccggt   60
gaggtgcagc tggtgcagtc tggagcagag gtgaaaaagc ccggagagtc tctgaagatt  120
tcctgtaagg gctccggtta ctcattcact ggctacaata tgaactgggt gcgccagatg  180
cccgggaaag gcctggagtg gatgggcaat attgatcctt attatggtgg tactacctac  240
aaccggaagt tcaagggcca ggtcactatc tccgccgaca agtccatcag caccgcctac  300
ctgcaatgga gcagcctgaa ggcctcggac accgccatgt attactgtgc acgctcagtc  360
ggcccttttcg actcctgggg ccagggcacc ctggtcactg tctcctctgg gggtggaggc  420
tctggtggcg gtggctctgg cggaggtgga tccggtggcg gcggatctgg cgggggtggc  480
tctgaaattg tgttgacaca gtctccagcc accctgtctt tgtctccagg cgaaagagcc  540
accctctcct gccgagcaag tgaaaatgtt tacagctact tagcctggta ccaacagaaa  600
cctggccagg ctcctaggct cctcatctat tttgcaaaaa ccttagcaga aggtattcca  660
gccaggttca gtggcagtgg ctccgggaca gacttcactc tcaccatcag cagcctagag  720
cctgaagatt ttgcagttta ttactgtcaa catcattccg ataatccgtg gacattcggc  780
caagggacca aggtggaaat caaatcctcg agtgagccca aatcttctga caaaactcac  840
acatgcccac cgtgcccagc acctgaagcc gcgggtgcac cgtcagtctt cctcttcccc  900
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg  960
gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 1020
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 1080
gtcctcaccg tcctgcacca ggactggctg aatggcaagg catacgcgtg cgcggtctcc 1140
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1200
gaaccacagg tgtacaccct gccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1260
ctgacctgcc tggtcaaagg cttctatcca agcgacatcg ccgtggagtg ggagagcaat 1320
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1380
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1440
tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1500
ccgggtcaga ggcacaacaa ttcttccctg aatacaggaa ctcagatggc aggtcattct 1560
ccgaattctc aggtccagct ggtgcaatct gggcctgagg tgaagaagcc tgggtcctcg 1620
gtgaaggtct cctgcaaggc ttctggatat accttcagca gatctacgat gcactgggtg 1680
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acagcctaca tggagctgag cagcctgaga tctgaggaca cggccgtgta ttactgtgcg 1860
agaccccaag tccactatga ttacaacggg tttccttact ggggccaagg aaccctggtc 1920
accgtctcct caggtggagg cggttcaggc ggaggtggat ccggcggtgg cggatcgggt 1980
ggcggcggat ctgacatcca gatgacccag tctccttcca ccctgtctgc atctgtagga 2040
gacagagtca ccatgacttg cagtgccagc tcaagtgtaa gttacatgaa ctggtatcag 2100
cagaaaccag ggaaagcccc taagagatgg atttatgact catccaaact ggcttctggg 2160
gtcccatcaa ggttcagcgg cagtggatct gggacagatt atactctcac catcagcagc 2220
ctgcagcctg atgattttgc aacttattac tgccaacagt ggagtcgtaa cccacccact 2280
ttcggcggag ggaccaaggt ggagatcaaa cggtcctcca gctaa                  2325
```

(SEQ ID NO:81)

Signal sequence is residue 1 to 60

Mature protein sequence of Anti-CD37 X TSC456:

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT GYNMNWVRQM PGKGLEWMGN IDPYYGGTTY        60
NRKFKGQVTI SADKSISTAY LQWSSLKASD TAMYYCARSV GPFDSWGQGT LVTVSSGGGG       120
SGGGGSGGGG SGGGGSGGGG SEIVLTQSPA TLSLSPGERA TLSCRASENV YSYLAWYQQK       180
PGQAPRLLIY FAKTLAEGIP ARFSGSGSGT DFTLTISSLE PEDFAVYYCQ HHSDNPWTFG       240
QGTKVEIKSS SEPKSSDKTH TCPPCPAPEA AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV       300
DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKAYACAVS       360
NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN       420
GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS       480
PGQRHNNSSL NTGTQMAGHS PNSQVQLVQS GPEVKKPGSS VKVSCKASGY TFSRSTMHWV       540
RQAPGQGLEW IGYINPSSAY TNYNQKFKDR VTITADKSTS TAYMELSSLR SEDTAVYYCA       600
RPQVHYDYNG FPYWGQGTLV TVSSGGGGSG GGGSGGGGSG GGGSDIQMTQ SPSTLSASVG       660
DRVTMTCSAS SSVSYMNWYQ QKPGKAPKRW IYDSSKLASG VPSRFSGSGS GTDYTLTISS       720
LQPDDFATYY CQQWSRNPPT FGGGTKVEIK RSSS                                   754
```

(SEQ ID NO:82)

Protein sequence of TSC455 anti-CD3 scFv

```
QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVTITADK
STSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQS
PSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPSRFSGSGSGTEYTLTISSLQPDD
FATYYCQQWSRNPPTFGGGTKVEIKRSSS
```

(SEQ ID NO:83)

Protein sequence of TSC456 anti-CD3 scFv

```
QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVTITADK
STSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQS
PSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPSRFSGSGSGTDYTLTISSLQPDD
FATYYCQQWSRNPPTFGGGTKVEIKRSSS
```

(SEQ ID NO:84)

Protein sequence of DRA222 anti-CD3 scFv

```
QVQLVESGGGVVQPGRSLRLSCKASGYTFTRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRFTISADK
SKSTAFLQMDSLRPEDTGVYFCARPQVHYDYNGFPYWGQGTPVTVSSGGGGSGGGGSGGGGSAQDIQMTQSPSS
LSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPARFSGSGSGTDYTLTISSLQPEDFAT
YYCQQWSRNPPTFGGGTKLQITSSS
```

(SEQ ID NO:85)

Protein sequence of TSC455 and TSC456 variable heavy domain

```
QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVTITADK
STSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSS
```

(SEQ ID NO:86)

Protein sequence of DRA222 variable heavy domain

```
QVQLVESGGGVVQPGRSLRLSCKASGYTFTRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRFTISADK
SKSTAFLQMDSLRPEDTGVYFCARPQVHYDYNGFPYWGQGTPVTVSS
```

(SEQ ID NO:87)

Protein sequence of TSC455 variable light domain

DIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPSRFSGSGSGTEYTLTI
SSLQPDDFATYYCQQWSRNPPTFGGGTKVEIKRS
(SEQ ID NO:88)

Protein sequence of TSC456 variable light domain

DIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPSRFSGSGSGTDYTLTI
SSLQPDDFATYYCQQWSRNPPTFGGGTKVEIKRS
(SEQ ID NO:89)

Protein sequence of DRA222 variable light domain

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPARFSGSGSGTDYTLTI
SSLQPEDFATYYCQQWSRNPPTFGGGTKLQITS
(SEQ ID NO:90)

Cris7 and DRA222 VH CDR1 (Kabat)	RSTMH **(SEQ ID NO:91)**
Cris7 and DRA222 VH CDR2 (Kabat)	YINPSSAYTNYNQKFK **(SEQ ID NO:92)**
Cris7 and DRA222 VH CDR3 (Kabat)	QVHYDYNGFPY **(SEQ ID NO:93)**
Cris7 and DRA222 VL CDR1 (Kabat)	SASSSVSYMN **(SEQ ID NO:94)**
Cris7 and DRA222 VL CDR2 (Kabat)	DSSKLAS **(SEQ ID NO:95)**
Cris7 and DRA222 VL CDR3 (Kabat)	QQWSRNPPT **(SEQ ID NO:96)**

Cris7 and DRA222 VH CDR1 (IMGT)	GYTFTRST **(SEQ ID NO:199)**
Cris7 and DRA222 VH CDR2 (IMGT)	INPSSAYT **(SEQ ID NO:200)**
Cris7 and DRA222 VH CDR3 (IMGT)	QQWSRNPPT **(SEQ ID NO:201)**
Cris7 and DRA222 VL CDR1 (IMGT)	ASSSVSY **(SEQ ID NO:202)**
Cris7 and DRA222 VL CDR2 (IMGT)	DSS **(SEQ ID NO:203)**
Cris7 and DRA222 VL CDR3 (IMGT)	QQWSRNPPT **(SEQ ID NO:204)**

DNA sequence of ROR133:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctccccggttctccggctccggctccggcaccgacttca
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cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
atgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttctggtggaggcggttcaggcgga
ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactga
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tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
agatgacccagtctccaagcagcctgtctgcaagcgtgggggacagggtcaccatgacctgcagtgccagctcaagtgtaagttacatga
actggtaccagcagaagccgggcaaggcccccaaaagatggatttatgactcatccaaactggcttctggagtccctgctcgcttcagtgg
cagtgggtctgggaccgactatacctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggaggggggaccaagctacaaattacatcctccagctaa
(SEQ ID NO:97)

Mature protein sequence of ROR133:
diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypiswvrqapgkglewigf
insggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyygdfniwgqgtlvtvsssepkssdkthtcppcpapea
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cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflyskl
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ssggggsggggsggggsaqdiqmtqspsslsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsslasgvparfsgsgs
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(SEQ ID NO:98)

DNA sequence of ROR193:
atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtcccctcctccctg
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(SEQ ID NO:99)

Mature protein sequence of ROR193:
Diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclgg
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rfsgsgsgteytltisslqpddfatyycqqwsrnpptfgggtkveikrsss
(SEQ ID NO:100)

DNA sequence of ROR134:
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tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
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cacccacgttcggagggggggaccaagctacaaattacatcctccagctaa
(SEQ ID NO:101)

Mature protein sequence of ROR134:
Diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclgg
vgavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpggslrlsctasgsdindypiswvrqapgkglewi
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kcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennyk1tppvldsdgsfflys
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(SEQ ID NO:102)

DNA sequence of ROR189:
atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
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agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagctaa
(SEQ ID NO:103)

Mature protein sequence of ROR189:
diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpggslrlsctasgsdindypiswvrqapgkglewig
finsggstwyadsvkgrftisrhssknt1ylqmnslraedtavyfcargystyygdfniwgqgtlvtvsssepkssdkthtcppcpapea
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sgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss
(SEQ ID NO:104)

DNA sequence of ROR154:
atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
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cagtgggtctgggaccgactataccctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggaggggggaccaagctacaaattacatcctccagctaa

(SEQ ID NO:105)

Mature protein sequence of ROR154:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgkglewigf
insggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapea
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gtdytltisslqpedfatyycqqwsrnpptfgggtklqitsss

(SEQ ID NO:106)

DNA sequence of ROR185:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
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acattaatcctagcagtgcttatactaattacaatcagaaattcaaggacagagtcacgattaccgcggacaaatccacgagcacagcctaca
tggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaccccaagtccactatgattacaacgggtttccttactgg
ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
ctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatgacttgcagtgccagctcaagtgtaagtt
acatgaactggtatcagcagaaaccagggaaagcccctaagagatggatttatgactcatccaaactggcttctggggtcccatcaaggttc
agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagctaa

(SEQ ID NO:107)

Mature protein sequence of ROR185:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgkglewigf
insggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapea
agapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeyk
cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflyskl
tvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvsckasgytfs
rstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtlv
tvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvpsrf
sgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss
(SEQ ID NO:108)

DNA sequence of ROR179:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgcctcccggttctccggctccggctccggcaccgacttca
ccctgaccatctcctccctgcagccccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctactggacctccttcgg
cggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatctg
aggtgcagctggtggagtccggcggcggcctggtgcagccccggccggtccctgcggctgtcctgcaccgcctccggctccgacatcaac
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cgccgtgtactattgcgcccccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcgagt
gagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttcccccaa
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ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactga
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tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
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cagtgggtctgggaccgactataccctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggaggggggaccaagctacaaattacatcctccagctaa
(SEQ ID NO:109)

Mature protein sequence of ROR179:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsywtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgkglewig
finsggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpape
aagapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkey

kcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflys
kltvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvesgggvvqpgrslrlsckasgytft
rstmhwvrqapgqglewigyinpssaytnynqkfkdrftisadkskstaflqmdslrpedtgvyfcarpqvhydyngfpywgqgtp
vtvssggggsggggsggggsaqdiqmtqspsslsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsskiasgvparfsg
sgsgtdytltisslqpedfatyycqqwsrnpptfgggtklqitsss
(SEQ ID NO:110)

DNA sequence of ROR186:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctccccggttctccggctccggctccggcaccgacttca
ccctgaccatctcctccctgcagccccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctactggacctccttcgg
cggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatctg
aggtgcagctggtggagtccggcggcggcctggtgcagccccggccggtccctgcggctgtcctgcaccgcctccggctccgacatcaac
gactaccccatcacctgggtgcggcaggccccccggcaagggcctggagtggatcggcttcatcaactccggcggctccacctggtacgc
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ccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatcccgggatgagctgaccaagaaccaggtcag
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cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
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ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtgcaatctgggcctgaggtgaagaagcctgggtcctcggtgaa
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tggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaccccaagtccactatgattacaacgggtttccttactgg
ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
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agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagctaa

(SEQ ID NO:111)

Mature protein sequence of ROR186:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsywtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgkglewig
finsggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpape
aagapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkey
kcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflys
kltvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvsckasgyt
fsrstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtl
vtvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvpsr
fsgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss

(SEQ ID NO:112)

DNA sequence of ROR181:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctcccggttctccggctccggctccggcaccgacttca
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gcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatct
gaggtgcagctggtggagtccggcggcggcctggtgcagccccggcggctccctgcggctgtcctgcaccgtgtccggcaccgacatca
acgactaccccatctcctgggtgcggcaggccccccggcaagggcctggagtggatcggcttcatcaactccggcggctccaccctggtac
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accgccgtgtacttctgcgccccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
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aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
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cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
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ggtggctcccggcggtggcggatcgccgggctctcaggtccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactga
ggctgtcctgcaaggcttctggctacacctttactagatctacgatgcactgggtaaggcaggccctggacaaggtctggaatggattgga
tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggcccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
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cagtgggtctgggaccgactatacctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggaggggggaccaagctacaaattacatcctccagctaa

(SEQ ID NO:113)

Mature protein sequence of ROR181:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpggslrlsctvsgtdindypiswvrqapgkglewig
finsggstwyadsvkgrftisrhssknt lylqmnslraedtavyfcargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapeaa
gapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeykc
avsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflysklt
vdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvesgggvvqpgrslrlsckasgytftrst
mhwvrqapgqglewigyinpssaytnynqkfkdrftisadkskstaflqmdslrpedtgvyfcarpqvhydyngfpywgqgtpvtv
ssggggsggggsggggsaqdiqmtqspsslsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvparfsgsgs
gtdytltisslqpedfatyycqqwsrnpptfgggtklqitsss

(SEQ ID NO:114)

DNA sequence of ROR191:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctcccggttctccggctccggctccggcaccgacttca
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gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccccca
aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
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ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtgcaatctgggcctgaggtgaagaagcctgggtcctcggtgaa
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ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
ctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatgacttgcagtgccagctcaagtgtaagtt
acatgaactggtatcagcagaaaccagggaaagcccctaagagatggatttatgactcatccaaactggcttctggggtcccatcaaggttc
agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagctaa

(SEQ ID NO:115)

Mature protein sequence of ROR191:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgkppklliyrasnlasgvpsrfsgsgsgtdftltisslqpedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpggslrlsctvsgtdindypiswvrqapgkglewig
finsggstwyadsvkgrftisrhssknt lylqmnslraedtavyfcargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapeaa
gapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeykc
avsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflysklt
vdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvsckasgytfsr
stmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtlvt
vssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsskl asgvpsrfs
gsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss

(SEQ ID NO:116)

DNA sequence of ROR182:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
cagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgcccgaccggttctccggctccggctccggcaccgacttc
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accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccccca
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aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcg
tcctcaccgtcctgcaccaggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagccccatcgagaaaa
ccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcag
cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
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tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggcccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
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actggtaccagcagaagccgggcaaggcccccaaaagatggatttatgactcatccaaactggcttctggagtccctgctcgcttcagtgg
cagtgggtctgggaccgactatacctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggaggggggaccaagctacaaattacatcctccagctaa

(SEQ ID NO:117)

Mature protein sequence of ROR182:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgqppklliyrasnlasgvpdrfsgsgsgtdftltissleaedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgqglewigf
insggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapea
agapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeyk
cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflyskl
tvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvesgggvvqpgrslrlsckasgytftrst
mhwvrqapgqglewigyinpssaytnynqkfkdrftisadkskstaflqmdslrpedtgvyfcarpqvhydyngfpywgqgtpvtv
ssggggsggggsggggsaqdiqmtqspsslsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvparfsgsgs
gtdytltisslqpedfatyycqqwsrnpptfgggtklqitsss

(SEQ ID NO:118)

DNA sequence of ROR192:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
cagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgcccgaccggttctccggctccggctccggcaccgacttc
accctgaccatctcctccctggaggccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctaccggacctccttc
ggcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatc
tgaggtgcagctggtggagtccggcggcggcctggtgcagcccggccggtccctgcggctgtcctgcaccgcctccggctccgacatca
acgactaccccatcacctgggtgcggcaggccccggccagggcctggagtggatcggcttcatcaactccggcggctccacctggtac
gcctcctgggtgaagggccggttcaccatctccgggacgactccaagtccatcgcctacctgcagatgaactccctgaagaccgaggac
accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
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aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
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atgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttctggtggaggcggttcaggcgga
ggtggctcccggcggtggcggatcgccgggctctcaggtccagctggtgcaatctgggcctgaggtgaagaagcctgggtcctcggtgaa
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tggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaccccaagtccactatgattacaacgggtttccttactgg
ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
ctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatgacttgcagtgccagctcaagtgtaagtt
acatgaactggtatcagcagaaaccagggaaagcccctaagagatggatttatgactcatccaaactggcttctggggtcccatcaaggttc
agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagctaa

(SEQ ID NO:119)

Mature protein sequence of ROR192:

diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgqppklliyrasnlasgvpdrfsgsgsgtdftltissleaedvatyyclggv
gavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgqglewigf
insggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpapea
agapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeyk
cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennyklttppvldsdgsfflyskl
tvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvsckasgytfs
rstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtlv
tvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvpsrf
sgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss

(SEQ ID NO:120)

Chimeric bispecific anti-CD123 (VLVH) x anti-CD3 (TSC456) scFv-Fc-scFv

Dimmsqspsslavsvgekftmtckssqslffgstqknylawyqqkpgqspklliywastresgvpdrftgsgsgtdftlaissvmped
lavyycqqyynypwtfgggtkleikggggsggggsggggsggggsvqlqesgpglvkpsqslsltcsvtdysitsgyywnwirqfp
gnklewmgyisydgsnnynpslknrisitrdtsknqfflklssvttedtatyycsrgegfyfdswgqgttltvsssepkssdkthtcppcp
apeaagapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlng

keykcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsff
lyskltvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvsckas
gytfsrstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywg
qgtlvtvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsskiasg
vpsrfsgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss **(SEQ ID NO:197)**

Chimeric bispecific anti-CD123 (VHVL) x anti-CD3 (TSC456) scFv-Fc-scFv

Vqlqesgpglvkpsqslsltcsvtdysitsgyywnwirqfpgnklewmgyisydgsnnynpslknrisitrdtsknqfflklssvttedt
atyycsrgegfyfdswgqgttltvssggggsggggsggggsggggsdimmsqspsslavsvgekftmtckssqslffgstqknylaw
yqqkpgqspklliywastresgvpdrftgsgsgtdftlaissvmpedlavyycqqyynypwtfgggtkleiksssepkssdkthtcppc
papeaagapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwln
gkeykcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgs
fflyskltvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspgsqvqlvqsgpevkkpgssvkvscka
sgytfsrstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpyw
gqgtlvtvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsskias
gvpsrfsgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrsss **(SEQ ID NO:198)**

DNA sequence of TSC471:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgatatccagatgacccagtctccatccgccatg
tctgcatctgtaggagacagagtcaccatcacttgccgggcgagtaagagcattagcaaatatttagcctggtttcagcagaaaccagggaa
agttcctaagctccgcatccattctggatctactttgcaatcaggggtcccatctcggttcagtggcagtggatctgggacagaatttactctca
ccatcagcagcctgcagcctgaagattttgcaacttattactgtcaacagcatattgaataccgtggacgttcggccaagggaccaaggtg
gaaatcaaacgaggtggcggagggtctgggggtggcggatccggaggtggtggctctcaggtccagctggtacagtctggggctgaggt
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gatgctatggactactggggtcaaggaaccacagtcaccgtctcctcgagtgagcccaaatcttctgacaaaactcacacatgcccaccgtg
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gaagagcctctccctgtctccgggttccggaggtggcggttcgggaggtggcgggtcaggaggtgggggctctccttcacaggtgcagct
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gcattgggtgaggcaggctcctggacagggcctggagtggatcggctacatcaaccccagcagcgcttataccaactacaatcagaagttt
aaggaccgggtgaccatcaccgccgataagtccaccagcaccgcctacatggagctgtccagcctgaggagcgaggataccgccgtgta
ctattgcgcccggccccaggtccattacgactacaacggcttcccctattggggccagggaaccctggtgaccgtgtccagcggtggcggt
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tcccaagaggtggatttacgactccagcaagctggcctctggtgtccccagcaggttctctggtagcggcagcggcacagactacaccctg
accatctcctccctgcagcccgacgatttcgccacctactattgccagcagtggtcccggaatcccccctacctttggcggcggcaccaaggt
ggagatcaagaggagctaa **(SEQ ID NO:205)**

Mature protein sequence of TSC471:

Diqmtqspsamsasvgdrvtitcrasksiskylawfqqkpgkvpklrihsgstlqsgvpsrfsgsgsgteftltisslqpedfatyycqqh
ieypwtfgqgtkveikrggggsggggsggggsqvqlvqsgaevkkpgasvkvsckasgytftdyymhwvrqapgqglewmgyf
npyndytryaqkfqgrvtmtrdtsistaymelsslrsddtavyycarsdgyydamdywgqgttvtvsssepkssdkthtcppcpapea
agapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkeyk
cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfflyskl
tvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspsqvqlvqsgpevkkpgssvkvsckasgytfsrs
tmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtlvtv
ssgggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydsskiasgvpsrfsg
sgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrs **(SEQ ID NO:206)**

DNA sequence of ROR243:

atggaggctcccgctcagctgctgttcctcctgctgctctggctgcccgacaccacaggcgacatccagatgacccagtccccttcctccct
gtccgctagcgtgggcgatagggtgaccatcaactgccaggcctcccagtccattgactccaatctggcctggttccagcagaagccccgg
acagccccccaagctgctgatttacagggcctccaacctggcttccggcgtgcctgacaggttctccggatccggcagcggcaccgacttc
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gcggcggcaccaaggtggagatcaagggcggcggcggcagcggcggcggcggcagcggcggcggaggctccggcggcggcggc
agcgaggtgcagctggtggaaagcggaggaggcctggtgcagcctggaaggtccctgaggctgtcctgcacagccagcggctccgac
atcaacgactaccccatcacctgggtgaggcaggctcctggccagggcctggaatggatcggctttatcaacagcggcggcagcacctg
gtatgcttcctgggtgaagggccggttcaccattagcagggacgactccaagtccattgcctacctgcagatgaactccctgaagaccgag
gacaccgccgtgtactactgcgccaggggctacagcacctattaccgggactttaacatctggggccagggcacactggtcaccgtgtcct
cgagtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtca
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aaggttagctgcaaagcctctggctacacattttccaggagtacaatgcactgggtgaggcaggctcctggacagggactcgagtggatcg
ggtatatcaacccatctagcgcctataccaattacaaccaaaagtttaaggaccgagttaccattaccgctgacaaatccaccagtacagctta
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gaattggtatcagcagaagcccgggaaagcacctaagcgctggatctatgactcttccaagctggcaagtggtgtccctcacggttctctg
gctcaggttctggtactgactatactttgactatctcctccctccagcccgatgatttcgctacctattattgtcagcagtggagccgtaacccac
ccactttcggaggcggtaccaaagtggagatcaagaggtcatga **(SEQ ID NO:207)**

Mature protein sequence of ROR243:

Diqmtqspsslsasvgdrvtincqasqsidsnlawfqqkpgqppklliyrasnlasgvpdrfsgsgsgtdftltissleaedvatyyclgg
vgavsyrtsfgggtkveikggggsggggsggggsggggsevqlvesggglvqpgrslrlsctasgsdindypitwvrqapgqglewi
gfinsggstwyaswvkgrftisrddsksiaylqmnslktedtavyycargystyyrdfniwgqgtlvtvsssepkssdkthtcppcpap
eaagapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngke
ykcavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennykttppvldsdgsfffly
skltvdksrwqqgnvfscsvmhealhnhytqkslslspgsggggsggggsggggspsqvqlvqsgpevkkpgssvkvsckasgyt

fsrstmhwvrqapgqglewigyinpssaytnynqkfkdrvtitadkststaymelsslrsedtavyycarpqvhydyngfpywgqgtl
vtvssggggsggggsggggsggggsdiqmtqspstlsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvpsr
fsgsgsgtdytltisslqpddfatyycqqwsrnpptfgggtkveikrs **(SEQ ID NO:208)**

DNA sequence of TSC266:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgatatccagatgacccagtctccatccgccatg
tctgcatctgtaggagacagagtcaccatcacttgccgggcgagtaagagcattagcaaatatttagcctggtttcagcagaaaccagggaa
agttcctaagctccgcatccattctggatctactttgcaatcaggggtcccatctcggttcagtggcagtggatctgggacagaatttactctca
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gaaatcaaacgaggtggcggagggtctgggggtggcggatccggaggtggtggctctcaggtccagctggtacagtctggggctgaggt
gaagaagcctggggcttcagtgaaggtctcctgcaaggcttctggatacacattcactgactactacatgcactgggtgcgacaggcccctg
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aaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggcgt
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gaagagcctctccctgtctccgggtcagaggcacaacaattcttccctgaatacaggaactcagatggcaggtcattctccgaattctcaggt
ccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactgaggctgtcctgcaaggcttctggctacacctttactagatct
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agggtctgggggtggcggatccggaggtggtggctctgcacaagacatccagatgacccagtctccaagcagcctgtctgcaagcgtgg
gggacagggtcaccatgacctgcagtgccagctcaagtgtaagttacatgaactggtaccagcagaagccgggcaaggccccaaaaga
tggatttatgactcatccaaactggcttctggagtccctgctcgcttcagtggcagtgggtctgggaccgactataccctcacaatcagcagc
ctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacccacccacgttcggaggggggaccaagctacaaattacat
cctccagctaa **(SEQ ID NO:209)**

Proten sequence of TSC266:

Diqmtqspsamsasvgdrvtitcrasksiskylawfqqkpgkvpklrihsgstlqsgvpsrfsgsgsgteftltisslqpedfatyycqqh
ieypwtfgqgtkveikrggggsggggsggggsqvqlvqsgaevkkpgasvkvsckasgytftdyymhwvrqapgqglewmgyf
npyndytryaqkfqgrvtmtrdtsistaymelsslrsddtavyycarsdgyydamdywgqgttvtvsssepkssdkthtcppcpapea
agapsvflfppkpkdtlmisrtpevtcvvvdvshedpevkfnwyvdgvevhnaktkpreeqynstyrvvsvltvlhqdwlngkaya
cavsnkalpapiektiskakgqprepqvytlppsrdeltknqvsltclvkgfypsdiavewesngqpennyklttppvldsdgsfflyskl
tvdksrwqqgnvfscsvmhealhnhytqkslslspgqrhnnsslntgtqmaghspnsqvqlvesgggvvqpgrslrlsckasgytftr
stmhwvrqapgqglewigyinpssaytnynqkfkdrftisadkskstaflqmdslrpedtgvyfcarpqvhydyngfpywgqgtpv
tvssggggsggggsggggsaqdiqmtqspsslsasvgdrvtmtcsasssvsymnwyqqkpgkapkrwiydssklasgvparfsgs
gsgtdytltisslqpedfatyycqqwsrnpptfgggtklqitsss **(SEQ ID NO:210)**

DNA sequence of ROR206:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtcccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc

aagcccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctcccggttctccggctccggctccggcaccgacttca
ccctgaccatctcctccctgcagcccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctaccggacctccttcg
gcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatct
gaggtgcagctggtggagtccggcggcggcctggtgcagcccggcggtccctgcggctgtcctgcaccgcctccggctccgacatca
acgactaccccatcacctgggtgcggcaggcccccggcaagggcctggagtggatcggcttcatcaactccggcggctccacctggtac
gcctcctgggtgaagggccggttcaccatctcccgggacgactccaagtccatcgcctacctgcagatgaactccctgaagaccgaggac
accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccccca
aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcg
tcctcaccgtcctgcaccaggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagccccatcgagaaaa
ccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatcccgggatgagctgaccaagaaccaggtcag
cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
atgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttctggtggaggcggttcaggcgga
ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactga
ggctgtcctgcaaggcttctggctacacctttactagatctacgatgcactgggtaaggcaggccctggacaaggtctggaatggattgga
tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggcccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
agatgacccagtctccaagcagcctgtctgcaagcgtgggggacagggtcaccatgacctgcagtgccagctcaagtgtaagttacatga
actggtaccagcagaagccgggcaaggccccaaaagatggatttatgactcatccaaactggcttctggagtccctgctcgcttcagtgg
cagtgggtctgggaccgactataccctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggagggggggaccaagctacaaattacatcctccagc **(SEQ ID NO:211)**

Proten sequence of ROR206:
MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GKPPKLLIYRASNLASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGGVGAVSYRTSF
GGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGKGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVESGGGV
VQPGRSLRLSCKASGYTFTRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRFTI
SADKSKSTAFLQMDSLRPEDTGVYFCARPQVHYDYNGFPYWGQGTPVTVSSGGGGSG
GGGSGGGGSAQDIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWI
YDSSKLASGVPARFSGSGSGTDYTLTISSLQPEDFATYYCQQWSRNPPTFGGGTKLQITS
SS **(SEQ ID NO:212)**

DNA sequence of ROR207:
atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtcccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
aagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgccctcccggttctccggctccggctccggcaccgacttca
ccctgaccatctcctccctgcagcccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctaccggacctccttcg

gcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatct
gaggtgcagctggtggagtccggcggcggcctggtgcagcccggccggtccctgcggctgtcctgcaccgcctccggctccgacatca
acgactaccccatcacctgggtgcggcaggcccccggcaagggcctggagtggatcggcttcatcaactccggcggctccacctggtac
gcctcctgggtgaagggccggttcaccatctccgggacgactccaagtccatcgcctacctgcagatgaactccctgaagaccgaggac
accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccccca
aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcg
tcctcaccgtcctgcaccaggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagccccatcgagaaaa
ccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatcccgggatgagctgaccaagaaccaggtcag
cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
atgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttctggtggaggcggttcaggcgga
ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtgcaatctgggcctgaggtgaagaagcctgggtcctcggtgaa
ggtctcctgcaaggcttctggatatacttcagcagatctacgatgcactgggtgcgacaggccctggacaagggcttgagtggataggat
acattaatcctagcagtgcttatactaattacaatcagaaattcaaggacagagtcacgattaccgcggacaaatccacgagcacagcctaca
tggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaccccaagtccactatgattacaacgggtttccttactgg
ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
ctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatgacttgcagtgccagctcaagtgtaagtt
acatgaactggtatcagcagaaaccagggaaagcccctaagagatggatttatgactcatccaaactggcttctggggtcccatcaaggttc
agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagc **(SEQ ID NO:213)**

Protein sequence of ROR207:

MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GKPPKLLIYRASNLASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGGVGAVSYRTSF
GGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGKGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVQSGPEV
KKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVT
ITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSG
GGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAP
KRWIYDSSKLASGVPSRFSGSGSGTDYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKV
EIKRSSS **(SEQ ID NO:214)**

DNA sequence of ROR208:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtcccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
cagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgcccgaccggttctcggctccggctccggcaccgacttc
accctgaccatctcctccctggaggccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctaccggacctccttc
ggcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatc
tgaggtgcagctggtggagtccggcggcggcctggtgcagcccggccggtccctgcggctgtcctgcaccgcctccggctccgacatca

acgactaccccatcacctgggtgcggcaggcccccggccagggcctggagtggatcggcttcatcaactccggcggctccacctggtac
gcctcctgggtgaagggccggttcaccatctcccgggacgactccaagtccatcgcctacctgcagatgaactccctgaagaccgaggac
accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttcccccca
aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcg
tcctcaccgtcctgcaccaggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagcccccatcgagaaaa
ccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcag
cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
atgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggttctggtggaggcggttcaggcgga
ggtggctccggcggtggcggatcgccgggctctcaggtccagctggtggagtctgggggcggagtggtgcagcctgggcggtcactga
ggctgtcctgcaaggcttctggctacacctttactagatctacgatgcactgggtaaggcaggcccctggacaaggtctggaatggattgga
tacattaatcctagcagtgcttatactaattacaatcagaaattcaaggacaggttcacaatcagcgcagacaaatccaagagcacagccttc
ctgcagatggacagcctgaggcccgaggacaccggcgtctatttctgtgcacggccccaagtccactatgattacaacgggtttccttactg
gggccaagggactcccgtcactgtctctagcggtggcggagggtctgggggtggcggatccggaggtggtggctctgcacaagacatcc
agatgacccagtctccaagcagcctgtctgcaagcgtgggggacagggtcaccatgacctgcagtgccagctcaagtgtaagttacatga
actggtaccagcagaagccgggcaaggcccccaaaagatggatttatgactcatccaaactggcttctggagtccctgctcgcttcagtgg
cagtgggtctgggaccgactataccctcacaatcagcagcctgcagcccgaagatttcgccacttattactgccagcagtggagtcgtaacc
cacccacgttcggagggggggaccaagctacaaattacatcctccagc **(SEQ ID NO:215)**

Protein sequence of ROR208:

MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GQPPKLLIYRASNLASGVPDRFSGSGSGTDFTLTISSLEAEDVATYYCLGGVGAVSYRTS
FGGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGQGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVESGGGV
VQPGRSLRLSCKASGYTFTRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRFTI
SADKSKSTAFLQMDSLRPEDTGVYFCARPQVHYDYNGFPYWGQGTPVTVSSGGGGSG
GGGSGGGGSAQDIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWI
YDSSKLASGVPARFSGSGSGTDYTLTISSLQPEDFATYYCQQWSRNPPTFGGGTKLQITS
SS **(SEQ ID NO:216)**

DNA sequence of ROR209:

atggaagcaccagcgcagcttctcttcctcctgctactctggctcccagataccaccggtgacatccagatgacccagtccccctcctccctg
tccgcctccgtgggcgaccgggtgaccatcaactgccaggcctcccagtccatcgactccaacctggcctggttccagcagaagccccggc
cagccccccaagctgctgatctaccgggcctccaacctggcctccggcgtgcccgaccggttctccggctccggctccggcaccgacttc
accctgaccatctcctccctggaggccgaggacgtggccacctactactgcctgggcggcgtgggcgccgtgtcctaccggacctccttc
ggcggcggcaccaaggtggagatcaagggtggaggcggttcaggcggaggtggatccggcggtggcggctccggtggcggcggatc
tgaggtgcagctggtggagtccggcggcggcctggtgcagcccggccggtccctgcggctgtcctgcaccgcctccggctccgacatca
acgactaccccatcacctgggtgcggcaggcccccggccagggcctggagtggatcggcttcatcaactccggcggctccacctggtac
gcctcctgggtgaagggccggttcaccatctcccgggacgactccaagtccatcgcctacctgcagatgaactccctgaagaccgaggac

accgccgtgtactattgcgcccggggctactccacctactaccgggacttcaacatctggggccagggcaccctggtgaccgtgtcctcga
gtgagcccaaatcttctgacaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttccccca
aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
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tcctcaccgtcctgcaccaggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagccccatcgagaaaa
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cctgacctgcctggtcaaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagacca
cgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctc
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ggtggctccggcggtggcggatcgcccgggctctcaggtccagctggtgcaatctgggcctgaggtgaagaagcctgggtcctcggtgaa
ggtctcctgcaaggcttctggatataccttcagcagatctacgatgcactgggtgcgacaggcccctggacaagggcttgagtggataggat
acattaatcctagcagtgcttatactaattacaatcagaaattcaaggacagagtcacgattaccgcggacaaatccacgagcacagcctaca
tggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaccccaagtccactatgattacaacgggtttccttactgg
ggccaaggaaccctggtcaccgtctcctcaggtggaggcggttcaggcggaggtggatccggcggtggcggatcgggtggcggcggat
ctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatgacttgcagtgccagctcaagtgtaagtt
acatgaactggtatcagcagaaaccagggaaagcccctaagagatggatttatgactcatccaaactggcttctggggtcccatcaaggttc
agcggcagtggatctgggacagattatactctcaccatcagcagcctgcagcctgatgattttgcaacttattactgccaacagtggagtcgt
aacccacccactttcggcggagggaccaaggtggagatcaaacggtcctccagc **(SEQ ID NO:217)**

Protein sequence of ROR209:
MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GQPPKLLIYRASNLASGVPDRFSGSGSGTDFTLTISSLEAEDVATYYCLGGVGAVSYRTS
FGGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGQGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVQSGPEV
KKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVT
ITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSG
GGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAP
KRWIYDSSKLASGVPSRFSGSGSGTDYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKV
EIKRSSS **(SEQ ID NO:218)**

DNA sequence of ROR231:
atggaggcacccgcccagctgctgttcttgttgctgctgtggctccctgataccaccggagacatccagatgacccaatccccttctagtctct
ccgctagcgtcggagaccgcgtgaccatcaattgtcaagcatctcagagtattgacagcaatctcgcctggtttcagcagaagccaggaaa
gccacccaagctcctgatttatagggctagcaacctggcttctggtgtccctagtaggttcagcggctctgggagtggcacagacttcaccct
gaccattagtagtctgcagcccgaagatgtcgctacctattactgcctcggaggagtgggtgccgtttcttatcgcacctcatttggaggtggc
accaaagtggagatcaaaggtggtggcggctccgggggtggcgggtcagggggggggagggtctggaggcggcggatcagaagttca
gctggtggaatctggaggaggtctggtgcagccaggcaggtccctccggctgagctgcactgcatccggctctgacattaatgactaccct
atcacctgggtgaggcaggccccggtaaaggcctggagtggatcgggttcatcaattctggtggatctacttggtacgcaagctgggtga
aaggacgcttcacaattagtagagacgactctaagtctatcgcatatctgcagatgaatagcttgaagacagaggacaccgccgtgtactatt
gtgcaagaggatactccacttactacgcgatttcaatatctggggccagggaaccctggtgacagtgtcctcgagtgagcccaaatcttctg
acaaaactcacacatgcccaccgtgcccagcacctgaagccgcgggtgcaccgtcagtcttcctcttcccccaaaacccaaggacaccc

tcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg
gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcac
caggactggctgaatggcaaggaatacaagtgcgcggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaa
agggcagccccgagaaccacaggtgtacaccctgccccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtc
aaaggcttctatccaagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctgg
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Protein sequence of ROR231:
MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GKPPKLLIYRASNLASGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCLGGVGAVSYRTSF
GGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGKGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVQSGPEV
KKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVT
ITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSG
GGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAP
KRWIYDSSKLASGVPSRFSGSGSGTDYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKV
EIKRSSS **(SEQ ID NO:220)**

DNA sequence of ROR233:
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gcggcggcaccaaggtggagatcaagggcggcggcggcagcggcggcggcggcagcggcggcggaggctccggcggcggcggc
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cagcggcggaggaggctccgacattcagatgacccagtcccctccaccctgtccgctagcgtgggcgatcgggtgaccatgacctgca
gcgccagcagctccgtgtcctacatgaactggtaccagcagaagcccggcaaggctcccaagaggtggatttacgactccagcaagctg
gcctctggtgtccccagcaggttctctggtagcggcagcggcacagactacaccctgaccatctcctccctgcagcccgacgatttcgcca
cctactattgccagcagtggtcccggaatccccctacctttggcggcggcaccaaggtggagatcaagaggagctccagc **(SEQ ID NO:221)**

Protein sequence of ROR233:

MEAPAQLLFLLLLWLPDTTGDIQMTQSPSSLSASVGDRVTINCQASQSIDSNLAWFQQKP
GQPPKLLIYRASNLASGVPDRFSGSGSGTDFTLTISSLEAEDVATYYCLGGVGAVSYRTS
FGGGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCTASGSDI
NDYPITWVRQAPGQGLEWIGFINSGGSTWYASWVKGRFTISRDDSKSIAYLQMNSLKTE
DTAVYYCARGYSTYYRDFNIWGQGTLVTVSSSEPKSSDKTHTCPPCPAPEAAGAPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGSGGGGSGGGGSGGGGSPGSQVQLVQSGPEV
KKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKFKDRVT
ITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSG
GGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAP
KRWIYDSSKLASGVPSRFSGSGSGTDYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKV
EIKRSSS **(SEQ ID NO:222)**

Table 15. Summary of SEQ ID NOs

Designation	Description	DNA SEQ ID NO	Protein SEQ ID NO
TSC311 or TSC312	Fc DRA222	1	2
TSC313	Fc H7L1	3	4
TSC314	Fc H7L4	5	6
TSC315	Fc H7L5	7	8
TSC316	Fc H8L1	9	10
TSC317	Fc H8L4	11	12
TSC318	Fc H8L5	13	14
TSC319	Fc H9L1	15	16
TSC320	Fc H9L4	17	18
TSC321	Fc H9L5	19	20
TSC322	Fc H10L1	21	22
TSC323	Fc H10L4	23	24
TSC324	Fc H10L5	25	26
TSC334	Fc H7L6	27	28
TSC335	Fc H7L7	29	30
TSC336	Fc H7L8	31	32
TSC337	Fc H8L6	33	34
TSC338	Fc H8L7	35	36
TSC339	Fc H8L8	37	38
TSC340	Fc H10L6	39	40
TSC341	Fc H10L7	41	42
TSC342	Fc H10L8	43	44
TSC370	TSC342 G27Y	45	46
TSC371	TSC342 M53I	47	48
TSC372	TSC342 I21M	49	50
TSC390	TSC370 A9P	51	52
TSC391	TSC370 A9P M53I	53	54
TSC392	TSC370 A9P I21M	55	56
TSC393	TSC370 M53I I21M	57	58
TSC394	TSC370 A9P M53I I21M	59	60
TSC408	Anti-PSMA X TSC391	61	62
TSC409	Anti-PSMA X TSC392	63	64
TSC410	Anti-PSMA X TSC393	65	66
TSC411	Anti-PSMA X TSC394	67	68
TSC471	Anti-PSMA X TSC456	205	206
TSC266	Anti-PSMA X DRA222 (huVL-VH 107-1A4 scFv-Fc-DRA222 scFv)	209	210
CAS105	Anti-CD37 X DRA222	69	70
Anti-CD37 X TSC445	Anti-CD37 X TSC394	71	72
Anti-CD37 X TSC452	Anti-CD37 X (TSC394 VL + DRA222 VH)	73	74
Anti-CD37 X	Anti-CD37 X (TSC394 VH + DRA222 VL)	75	76

TSC453			
Anti-CD37 X TSC454	Anti-CD37 X TSC394 E86D	77	78
Anti-CD37 X TSC455	Anti-CD37 X TSC394 F87Y	79	80
Anti-CD37 X TSC456	Anti-CD37 X TSC394 E86D F87Y	81	82
TSC455	TSC394 F87Y scFv (anti-CD3 scFv)		83
TSC456	TSC394 E86D F87Y scFv (anti-CD3 scFv)		84
DRA222	Anti-CD3 scFv		85
TSC455 and TSC456 VH	TSC455 and TSC456 variable heavy domain		86
DRA222 VH	DRA222 variable heavy domain		87
TSC455 VL	TSC455 variable light domain		88
TSC456 VL	TSC456 variable light domain		89
DRA222 VL	DRA222 variable light domain		90
Cris7 and DRA222 VH CDR1 (Kabat)	Anti-CD3 VH CDR1		91
Cris7 and DRA222 VH CDR2 (Kabat)	Anti-CD3 VH CDR2		92
Cris7 and DRA222 VH CDR3 (Kabat)	Anti-CD3 VH CDR3		93
Cris7 and DRA222 VL CDR1 (Kabat)	Anti-CD3 VL CDR1		94
Cris7 and DRA222 VL CDR2 (Kabat)	Anti-CD3 VL CDR2		95
Cris7 and DRA222 VL CDR3 (Kabat)	Anti-CD3 VL CDR3		96
Cris7 and DRA222 VH CDR1 (IMGT)	Anti-CD3 VH CDR1		199
Cris7 and DRA222 VH CDR2 (IMGT)	Anti-CD3 VH CDR2		200
Cris7 and DRA222 VH CDR3 (IMGT)	Anti-CD3 VH CDR3		201
Cris7 and DRA222 VL CDR1 (IMGT)	Anti-CD3 VL CDR1		202
Cris7 and DRA222 VL CDR2 (IMGT)	Anti-CD3 VL CDR2		203
Cris7 and DRA222 VL CDR3 (IMGT)	Anti-CD3 VL CDR3		204
ROR133	Anti-ROR1 (R11 L7H15) X DRA222	97	98
ROR193	Anti-ROR1 (R11 L7H15) X TSC394 F87Y	99	100
ROR134	Anti-ROR1 (R11 L7H10) X DRA222	101	102
ROR189	Anti-ROR1 (R11 L7H10) X TSC394 E86D F87Y	103	104
ROR154	Anti-ROR1 (R11 L7H16) X DRA222	105	106
ROR185	Anti-ROR1 (R11 L7H15) X TSC394 E86D	107	108

	F87Y		
ROR179	Anti-ROR1 (R11 L8H16) X DRA222	109	110
ROR186	Anti-ROR1 (R11 L8H16) X TSC394 E86D F87Y	111	112
ROR181	Anti-ROR1 (R11 L7H17) X DRA222	113	114
ROR191	Anti-ROR1 (R11 L7H17) X TSC394 E86D F87Y	115	116
ROR182	Anti-ROR1 (R11 L9H18) X DRA222	117	118
ROR192	Anti-ROR1 (R11 L9H18) X TSC394 E86D F87Y	119	120
ROR243	Humanized, codon optimized anti-ROR1 X anti-CD3 (parent anti-ROR1 molecule is ROR192) scFv-Fc-scFv	207	208
ROR206	ROR133 S40T G113R x DRA222 Fc ADCC- K322A-H111 in pEE12.4	211	212
ROR207	ROR133 S40T G113R x TSC456 Fc ADCC-K322A-H111 in pEE12.4	213	214
ROR208	ROR174 S40T G113R x DRA222 Fc ADCC- K322A-H111 in pEE12.4	215	216
ROR209	ROR174 S40T G113R x TSC456 Fc ADCC-K322A-H111 in pEE12.4	217	218
ROR231	Anti-ROR1 X anti-CD3	219	220
ROR233	Anti-ROR1 X anti-CD3	221	222
	Chimeric bispecific anti-CD123 (VLVH) x anti-CD3 (TSC456) scFv-Fc-scFv		197
	Chimeric bispecific anti-CD123 (VHVL) x anti-CD3 (TSC456) scFv-Fc-scFv		198

CLAIMS:

1. A CD3-binding protein comprising a CD3-binding domain that binds specifically to human CD3 and that comprises a humanized immunoglobulin light chain variable region and a humanized immunoglobulin heavy chain variable region wherein the immunoglobulin light chain variable region comprises an LCDR1 amino acid sequence of SEQ ID NO:94, an LCDR2 amino acid sequence of SEQ ID NO:95, and an LCDR3 amino acid sequence of SEQ ID NO:96 and wherein the immunoglobulin heavy chain variable region comprises an HCDR1 amino acid sequence of SEQ ID NO:91, an HCDR2 amino acid sequence of SEQ ID NO:92, and an HCDR3 amino acid sequence of SEQ ID NO:93;

wherein the amino acid residue at position 9 according to the IMGT numbering system of the immunoglobulin heavy chain variable region is proline; and

wherein the amino acid residue at position 21 according to the IMGT numbering system of the immunoglobulin light chain variable region is methionine; and

wherein the amino acid residue at position 87 according to the IMGT numbering system of the immunoglobulin light chain variable region is tyrosine.

2. The CD3-binding protein of claim 1, wherein the immunoglobulin light chain variable region comprises framework regions based on the human IGKV3D-20*1 germline amino acid sequence.

3. The CD3-binding protein of claim 1, wherein the immunoglobulin heavy chain variable region comprises framework regions based on the human IGHV1-69*02 germline amino acid sequence.

4. The CD3-binding protein of claim 1, wherein the amino acid residue at position 52 according to the IMGT numbering system of the immunoglobulin light chain variable region is arginine and/or the amino acid residue at position 53 according to the IMGT numbering system of the immunoglobulin light chain variable region is tryptophan.

5. The CD3-binding protein of claim 1, wherein the amino acid residue at position 27 according to the IMGT numbering system of the immunoglobulin heavy chain variable region is tyrosine.

6. The CD3-binding protein of claim 1, wherein the amino acid residue at position 53 according to the IMGT numbering system of the immunoglobulin heavy chain variable region is isoleucine.

7. The CD3-binding protein of claim 1, wherein the amino acid residue at position 86 according to the IMGT numbering system of the immunoglobulin light chain variable region is aspartic acid.

8. The CD3-binding protein of claim 1, wherein the CD3-binding domain comprises SEQ ID NO:83 or SEQ ID NO:84.

9. The CD3-binding protein of claim 1, wherein the CD3-binding domain is a single chain variable fragment (scFv).

10. The CD3-binding protein of claim 9, wherein said scFv comprises a linker between the heavy chain variable region and the light chain variable region of said scFv and wherein said linker comprises the amino acid sequence QRHNNSSLNTGTQMAGHSPNS (SEQ ID NO:148).

11. The CD3-binding protein of claim 9, wherein the heavy chain variable region of said scFv is amino-terminal to the light chain variable region of said scFv.

12. The CD3-binding protein of claim 1, wherein the CD3-binding protein binds specifically to cynomolgus CD3.

13. The CD3-binding protein of claim 1, wherein the CD3-binding protein comprises an immunoglobulin constant region.

14. The CD3-binding protein of claim 1, further comprising a second binding domain.

15. The CD3-binding protein of claim 14, wherein said CD3-binding protein is a single chain molecule comprising, in order from amino-terminus to carboxyl-terminus, (i) the second binding domain, (ii) a hinge region, (iii) an immunoglobulin constant region, (iv) a carboxyl-terminus linker, and (v) the CD3-binding domain.

16. The CD3-binding protein of claim 14, wherein the second binding domain comprises (a) an immunoglobulin light chain variable region comprising LCDR1, LCDR2, and LCDR3, and (b) an immunoglobulin heavy chain variable region comprising HCDR1, HCDR2, and HCDR3.

17. The CD3-binding protein of claim 15, wherein the hinge region is derived from an immunoglobulin hinge region.

18. The CD3-binding protein of claim 15, wherein the carboxyl-terminus linker comprises or consists of SEQ ID NO:196.

19. The CD3-binding protein of claim 13, wherein the immunoglobulin constant region comprises immunoglobulin CH2 and CH3 domains of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgD.

20. The CD3-binding protein of claim 19, wherein the immunoglobulin constant region comprises a human IgG1 CH2 domain comprising the substitutions L234A, L235A, G237A, and K322A, according to the EU numbering system.

21. The CD3-binding protein of claim 14, wherein the CD3-binding protein induces redirected T-cell cytotoxicity (RTCC).

22. The CD3-binding protein of claim 14, wherein the second binding domain is a single chain variable fragment (scFv).

23. The CD3-binding protein of claim 14, wherein the second binding domain binds a tumor associated antigen.

24. The CD3-binding protein of claim 23, wherein said CD3-binding protein induces T-cell-dependent lysis of cells expressing the tumor associated antigen.

25. The CD3-binding protein of claim 23, wherein the tumor associated antigen is selected from the group consisting of PSMA, CD19, CD20, CD37, CD38, CD123, Her2, ROR1, RON, glycoprotein A33 antigen (gpA33), and CEA.

26. The CD3-binding protein of claim 1, wherein said CD3-binding protein further comprises an immunoglobulin heterodimerization domain.

27. The CD3-binding protein of claim 26, wherein the immunoglobulin heterodimerization domain comprises an immunoglobulin CH1 domain or an immunoglobulin CL domain.

28. The CD3-binding protein of claim 1, wherein said CD3-binding protein is a bispecific single chain antibody molecule comprising a CD3-binding domain and a second binding domain, wherein the binding domains are arranged in the order VH CD3-VL CD3-VH second binding domain-VL second binding domain, VL CD3-VH CD3-VH second binding domain -VL second binding domain, VH second binding domain-VL second binding domain-VH CD3-VL CD3 or VH second binding domain-VL second binding domain-VL CD3-VH CD3.

29. A pharmaceutical composition comprising the CD3-binding protein of claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

30. The CD3-binding protein of claim 23 for use in the treatment of cancer in a subject in need thereof.

31. Use of the CD3-binding protein of claim 23 for the manufacture of a medicament for treating cancer in a subject in need thereof.

32. The CD3-binding protein of claim 30 for use in the treatment of cancer, or the use of claim 31 for the manufacture of a medicament for treating cancer, wherein the cancer is prostate cancer, colorectal cancer, renal cell carcinoma, bladder cancer, salivary gland cancer, pancreatic cancer, ovarian cancer, non-small cell lung cancer, breast cancer, melanoma, adrenal cancer, mantle cell lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, Non-Hodgkin's lymphoma, acute myeloid leukemia (AML), B-lymphoid leukemia, blastic plasmocytoid dendritic neoplasm (BPDCN), or hairy cell leukemia.

33. A CD3-binding protein that is a dimer of two identical proteins, wherein each protein is the CD3-binding protein of claim 15.

34. The CD3-binding protein of claim 1, wherein

(a) the immunoglobulin light chain variable region comprises SEQ ID NO:88 and the immunoglobulin heavy chain variable region comprises SEQ ID NO:86; or

(b) the immunoglobulin light chain variable region comprises SEQ ID NO:89 and the immunoglobulin heavy chain variable region comprises SEQ ID NO:86.

35. The CD3-binding protein of claim 1, wherein

(a) the immunoglobulin light chain variable region comprises an amino acid sequence that is at least 96% identical to SEQ ID NO:88 and the immunoglobulin heavy chain variable region comprises an amino acid sequence that is at least 96% identical to SEQ ID NO:86; or

(b) the immunoglobulin light chain variable region comprises an amino acid sequence that is at least 96% identical to SEQ ID NO:89 and the immunoglobulin heavy chain variable region comprises an amino acid sequence that is at least 96% identical to SEQ ID NO:86.

36. The CD3-binding protein of claim 32 for use in the treatment of cancer, or the use of claim 32 for the manufacture of a medicament for treating cancer, wherein the breast cancer is triple negative breast cancer.