

Proteins comprising HLA-G antigen binding domains and their uses.**CROSS REFERENCE TO RELATED APPLICATIONS**

- 5 This application claims priority to United States Provisional Application Serial Number 63/057,960, filed July 29, 2020. The disclosure of each of the aforementioned applications is incorporated herein by reference in its entirety.

SEQUENCE LISTING

- 10 The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 12, 2021, is named JBI6358WOPCT1_SL.txt and is 747 KB in size.

TECHNICAL FIELD

- 15 The disclosure provides proteins comprising antigen binding domains that bind human leukocyte antigen G (HLA-G) protein, polynucleotides encoding them, vectors, host cells, methods of making and using them.

BACKGROUND

- 20 The human leukocyte antigen G (HLA-G) belongs to the non-classical MHC class Ib family of proteins. Seven alternative mRNAs were described, which encode four membrane bound (HLA-G1, G2, G3, G4) and three soluble (HLA-G5, G6, G7) protein isoforms (Carosella et al., 2003). In contrast to high polymorphic classical HLA class I genes, HLA-G gene polymorphism is very limited. Only 50 alleles are listed for HLA-G encoding 16 full-length proteins. The HLA-G1 and its soluble counterpart HLA-G5
25 have an identical extracellular structure, which is classical HLA class I-like: a heavy chain of three globular domains noncovalently bound to beta-2-microglobulin ($\beta 2m$) and suitable to bind restricted peptides such as histone H2A peptide¹⁻³. The HLA-G1 monomer differs from classical HLA-class I molecules at the level of its peptide-binding groove (a key structural element to the activating functions of HLA molecules) and its $\alpha 3$ domain (a key structural element to the inhibitory functions of HLA-class I
30 molecules). Proteolytic shedding of membrane isoform(s) additionally creates soluble molecules (Dong et al., 2003; Park et al., 2004). Monomers, homo- and possible hetero-multimers, and ubiquitinated proteins have been reported structures for HLA-G. The inhibitory function of HLA-G is thought to be mostly due to dimers, not monomers, to block the human inhibitory receptors Ig-like transcript 2 and 4 (ILT2 and ILT4) as the best characterized receptors. HLA-G1 homodimers take an oblique orientation that exposes

the ILT2- and ILT4-binding sites of the $\alpha 3$ domain and thereby bind with a higher affinity and slower dissociation rates than HLA-G monomers.

The known receptors for HLA-G include inhibitory receptors ILT2 (expressed on monocytes, DCs, B cells, and subsets of natural killer and T cells,) and ILT4 (exclusively expressed by cells of the myelomonocytic lineage) - the main HLA-G receptors on peripheral immune cells (Colonna et al., 1997, 1998) -, non-inhibitory receptors CD8 and CD160, and the KIR2DL4 receptor which status remains ambiguous with respect to HLA-G. ILT2 and ILT4 recognize and bind to the $\alpha 3$ domain and $\beta 2m$ of MHCIs.

Most of the functions described for HLA-G are immune functions, although non-immune functions have also been reported, such as inhibiting angiogenesis and osteogenesis. HLA-G-ILT2 interaction was repeatedly shown to inhibit NK cell functions, thus protecting the HLA-G-expressing cells from NK-mediated cytotoxicity. Further, the function of ILT-2 expressing T cells (activated and/or clonal T cells) and B cells is directly inhibited by HLA-G. HLA-G also induces an alternate differentiation in myeloid APCs, induces the differentiation of regulatory myeloid cells and regulatory T cells, and inhibits phagocytic function of neutrophils.

This immunosuppressive capability of HLA-G to inhibit signaling pathways required for NK mediated cytotoxicity, T-cell proliferation and induction of regulatory/suppressor cells, and thereby to evade the immune system can be exploited by tumor cells to escape immune surveillance leading to uncontrolled growth of cells with higher invasive and metastatic abilities. HLA-G is not only capable of evading host immune surveillance but also enhances the metastasis during the progression of malignancies. Numerous studies have demonstrated tumoral HLA-G expression (not in the normal surrounding zones) that could be correlated with disease stage or worsening patient outcome. HLA-G expression has been implicated in tumor evolution and progression as well as advanced tumor stage, higher invasive and metastatic abilities and poor clinical prognosis. Its aberrant expression was associated with decreased survival time.

While various cancers show expression of HLA-G, the expression in normal tissues is mainly restricted to the fetal-maternal interface on the extravillous cytotrophoblast, to the placenta, to the amnion, and to specific healthy adult tissues such as thymus, cornea, bronchial epithelial cells, pancreas and specific types of cells such as mesenchymal stem cells, activated monocytes, erythroid and endothelial precursors (reviewed in Carosella et al., 2015).

Bearing in mind its potent and broad immune-suppressive functional role and restricted expression pattern in normal tissues, HLA-G may be designated as an attractive therapeutic target in solid tumors and B-cell malignancies overexpressing HLA-G.

Of the few specific anti-HLA-G antibodies that have been generated only the following available antibodies bind native cell-expressed HLA-G (87G, MEM-G9, MEM-G11, G223). The percentage of inhibition of HLA-G interaction with ligands ILT-2 and/or ILT-4 with these antibodies is not complete even at high dose of the respective antibody. Further, even though it has been described that in particularly 87G antibody is capable of enhancing tumor killing *in vitro*, there is no report of the efficacy of blocking HLA-G by administering the antibody *in vivo*.

There is a need for next generation HLA-G binding domains for therapeutic and diagnostic purposes.

10 SUMMARY

The present invention provides specific anti-HLA-G monoclonal antibodies that strongly block the binding between HLA-G and its cognate receptors ILT-2 and/or ILT-4. The generated anti-HLA-G antibodies bind either recombinant or endogenous HLA-G proteins in the absence of cross-reactivity with classical MHC class I molecules. The antibodies of the invention are the first HLA-G-specific antibodies to our knowledge to demonstrate the specificity to HLA-G and no cross-reactivity with HLA-A, HLA-B, HLA-C, and HLA-E; and/or complete blocking of HLA-G interaction with ILT-2/4 ligands. Additionally, the antibodies of the invention demonstrated the tumor growth inhibition following *in vivo* administration.

The invention also relates to the use of such antibodies or proteins comprising variable domains derived from these antibodies, in order to eliminate tumor cells with elevated expression of HLA-G on the surface by engaging the immune system, either by blocking the interaction of HLA-G with immune-suppressive ligands or by Fc- or bispecific protein-mediated recruiting of immune cells. Accordingly, the antibodies are suitable to treat or alleviate a condition diagnosed in patients, when said condition takes advantage of the induced expression of HLA-G in a patient.

The disclosure provides an isolated protein comprising an antigen binding domain that binds human leukocyte antigen G (HLA-G), wherein the antigen binding domain that binds HLA-G comprises

a) a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or

b) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or

c) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or

d) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or

e) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or

f) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or

5 g) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or

h) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

i) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, 10 the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or

j) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

In certain embodiments, the isolated protein comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

15 a) SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;

b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;

c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;

d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;

e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;

20 f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;

g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;

h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or

i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In certain embodiments, the antigen binding domain that binds HLA-G is a scFv, a (scFv)₂, a Fv, 25 a Fab, a F(ab')₂, a Fd, a dAb or a VHH.

In other embodiments, the antigen binding domain that binds HLA-G is the Fab.

In other embodiments, the antigen binding domain that binds HLA-G is the VHH.

In other embodiments, the antigen binding domain that binds HLA-G is the scFv.

In other embodiments, the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) 30 and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).

In certain embodiments, the L1 comprises

a) about 5-50 amino acids;

b) about 5-40 amino acids;

c) about 10-30 amino acids; or

d) about 10-20 amino acids.

In certain embodiments, the L1 comprises an amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.

5 In certain embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 8.

In other embodiments, the antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In other embodiments, the antigen binding domain that binds HLA-G comprises:

- 10 a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
- b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
- c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
- d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
- e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
- 15 f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
- g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
- h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
- i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
- j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69;

20 In other embodiments, the antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

In other embodiments, the protein of the disclosure is conjugated to a half-life extending moiety.

25 In other embodiments, the half-life extending moiety is an immunoglobulin (Ig), a fragment of the Ig, an Ig constant region, a fragment of the Ig constant region, a Fc region, transferrin, albumin, an albumin binding domain or polyethylene glycol.

In other embodiments, the isolated protein is a monospecific protein.

In other embodiments, the isolated protein is a multispecific protein.

30 In other embodiments, the multispecific protein is a bispecific protein.

In other embodiments, the multispecific protein is a trispecific protein.

In other embodiments, the isolated protein of the disclosure further comprises an immunoglobulin (Ig) constant region or a fragment of the Ig constant region thereof.

In other embodiments, the fragment of the Ig constant region comprises a Fc region.

In other embodiments, the fragment of the Ig constant region comprises a CH2 domain.

In other embodiments, the fragment of the Ig constant region comprises a CH3 domain.

In other embodiments, the fragment of the Ig constant region comprises the CH2 domain and the CH3 domain.

5 In other embodiments, the fragment of the Ig constant region comprises at least portion of a hinge, the CH2 domain and the CH3 domain.

In other embodiments, the fragment of the Ig constant region comprises a hinge, the CH2 domain and the CH3 domain.

10 In other embodiments, the antigen binding domain that binds HLA-G is conjugated to the N-terminus of the Ig constant region or the fragment of the Ig constant region.

In other embodiments, the antigen binding domain that binds HLA-G is conjugated to the C-terminus of the Ig constant region or the fragment of the Ig constant region.

In other embodiments, the antigen binding domain that binds HLA-G is conjugated to the Ig constant region or the fragment of the Ig constant region via a second linker (L2).

15 In other embodiments, the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.

In other embodiments, the multispecific protein comprises an antigen binding domain that binds an antigen on a lymphocyte.

20 In other embodiments, the lymphocyte is a T cell.

In other embodiments, the T cell is a CD8+ T cell

In other embodiments, the lymphocyte is a natural killer (NK) cell.

25 In other embodiments, the multispecific protein comprises an antigen binding domain that binds CD3, CD3 epsilon (CD3ε), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.

In other embodiments, the multispecific protein comprises an antigen binding domain that binds CD3ε.

In other embodiments, the antigen binding domain that binds CD3ε comprises:

30 a) a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 361, a HCDR2 of SEQ ID NO: 362, a HCDR3 of SEQ ID NO: 363, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 367, a LCDR2 of SEQ ID NO: 368 and a LCDR3 of SEQ ID NO: 369;

b) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;

c) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;

- d) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
- 5 e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
- f) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
- g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344;
- h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345;
- i) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
- j) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347; or
- k) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349.

In other embodiments, the Ig constant region or the fragment of the Ig constant region is an IgG1,
15 an IgG2, an IgG3 or an IgG4 isotype.

In other embodiments, the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in reduced binding of the protein to a Fcγ receptor (FcγR).

In other embodiments, the at least one mutation that results in reduced binding of the protein to the FcγR is selected from the group consisting of L235A/D265S, F234A/L235A, L234A/L235A,
20 L234A/L235A/D265S, V234A/G237A/ P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A, V234A/G237A, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein
25 residue numbering is according to the EU index.

In other embodiments, the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in enhanced binding of the protein to the FcγR.

In other embodiments, the at least one mutation that results in enhanced binding of the protein to the FcγR is selected from the group consisting of S239D/I332E, S298A/E333A/K334A,
30 F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.

In other embodiments, the FcγR is FcγRI, FcγRIIA, FcγRIIB or FcγRIII, or any combination thereof.

In other embodiments, the Ig constant region of the fragment of the Ig constant region comprises at least one mutation that modulates a half-life of the protein.

In other embodiments, the at least one mutation that modulates the half-life of the protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H,
5 M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.

In other embodiments, the protein comprises at least one mutation in a CH3 domain of the Ig constant region.

In other embodiments, the at least one mutation in the CH3 domain of the Ig constant region is
10 selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.

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In certain embodiments, the disclosure provides an isolated multispecific protein comprising a first antigen binding domain that binds HLA-G and a second antigen binding domain that binds a lymphocyte antigen.

In other embodiments, the lymphocyte antigen is a T cell antigen.

20 In other embodiments, the T cell antigen is a CD8⁺ T cell antigen.

In other embodiments, the lymphocyte antigen is a NK cell antigen.

In other embodiments, the lymphocyte antigen is CD3, CD3 epsilon (CD3 ϵ), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.

In other embodiments, the lymphocyte antigen is CD3 ϵ .

25 In other embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.

In other embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fab.

30 In other embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the VHH.

In other embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the scFv.

In other embodiments, the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).

In other embodiments, the L1 comprises

- a) about 5-50 amino acids;
- 5 b) about 5-40 amino acids;
- c) about 10-30 amino acids; or
- d) about 10-20 amino acids.

In other embodiments, the L1 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 10 or 40.

In other embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 8.

In other embodiments, the first antigen binding domain that binds HLA-G comprises the HCDR1 of SEQ ID NOs: 70, 73, 75, 78, 81, or 85, the HCDR2 of SEQ ID NOs: 71, 76, 79, 82, or 86, the HCDR3 of SEQ ID NOs: 72, 74, 77, 80, 83, 84, or 87, the LCDR1 of SEQ ID NOs: 88, 91, 93, 95, 97, 99, 101, or 15 102, the LCDR2 of SEQ ID NOs: 89 or 103, and the LCDR3 of SEQ ID NOs: 90, 92, 94, 96, 98, 100, or 104.

In other embodiments, the first antigen binding domain that binds HLA-G comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

- a) SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
- 20 b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
- c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
- d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
- e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
- f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
- 25 g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
- h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
- i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In other embodiments, the first antigen binding domain that binds HLA-G comprises

- a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
- 30 b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
- c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
- d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
- e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
- f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;

- g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
- h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
- i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
- j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

5 In other embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68, and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In other embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262,
10 263, 264, 265, 266, 267, 268, or 269.

In other embodiments, the second antigen binding domain that binds the lymphocyte antigen comprises

- a) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ
15 ID NO: 369;
- b) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;
- c) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;
- 20 d) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
- e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
- f) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
- g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344;
- h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345;
- 25 i) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
- j) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347; or
- k) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349.

30 In other embodiments, the first antigen binding domain that binds HLA-G is conjugated to a first immunoglobulin (Ig) constant region or a fragment of the first Ig constant region and/or the second antigen binding domain that binds the lymphocyte antigen is conjugated to a second immunoglobulin (Ig) constant region or a fragment of the second Ig constant region.

In other embodiments, the isolated multispecific protein further comprises a second linker (L2) between the first antigen binding domain that binds HLA-G and the first Ig constant region or the fragment of the first Ig constant region and the second antigen binding domain that binds the lymphocyte antigen and the second Ig constant region or the fragment of the second Ig constant region.

5 In other embodiments, the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.

In other embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG1, an IgG2, 10 and IgG3 or an IgG4 isotype.

In other embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in reduced binding of the multispecific protein to a FcγR.

In other embodiments, the at least one mutation that results in reduced binding of the 15 multispecific protein to the FcγR is selected from the group consisting of L235A/D265S, F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/ P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/ L235A, N297A, V234A/G237A, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, 20 S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index.

In other embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in enhanced binding of the multispecific protein to a Fcγ receptor (FcγR).

25 In other embodiments, the at least one mutation that results in enhanced binding of the multispecific protein to the FcγR is selected from the group consisting of S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.

30 In other embodiments, the FcγR is FcγRI, FcγRIIA, FcγRIIB or FcγRIII, or any combination thereof.

In other embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that modulates a half-life of the multispecific protein.

In other embodiments, the at least one mutation that modulates the half-life of the multispecific protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.

5 In other embodiments, the at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region.

10 In other embodiments, the at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, 15 T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.

In other embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprise the following mutations:

- 20 a) L235A_L235A_D265S_T350V_L351Y_F405A_Y407V in the first Ig constant region and L235A_L235A_D265S_T350V_T366L_K392L_T394W in the second Ig constant region; or
b) L235A_L235A_D265S_T350V_T366L_K392L_T394W in the first Ig constant region and L235A_L235A_D265S_T350V_L351Y_F405A_Y407V in the second Ig constant region.

25 In certain embodiments, the disclosure provides an immunoconjugate comprising the isolated protein of the disclosure conjugated to a therapeutic agent or an imaging agent.

In certain embodiments, the disclosure provides a pharmaceutical composition comprising the isolated protein of the disclosure and a pharmaceutically acceptable carrier.

30 In certain embodiments, the disclosure provides a polynucleotide encoding the isolated protein of the disclosure.

In certain embodiments, the disclosure provides a vector comprising the polynucleotide encoding the isolated protein of the disclosure.

In certain embodiments, the disclosure provides a host cell comprising the vector encoding the isolated protein of the disclosure.

In certain embodiments, the disclosure provides a method of producing the isolated protein of the disclosure, comprising culturing the host cell of the disclosure in conditions that the protein is expressed, and recovering the protein produced by the host cell.

5 In certain embodiments, the disclosure provides an immunoconjugate comprising the isolated multispecific protein of the disclosure conjugated to a therapeutic agent or an imaging agent.

In certain embodiments, the disclosure provides a pharmaceutical composition comprising the isolated multispecific protein of the disclosure and a pharmaceutically acceptable carrier.

In certain embodiments, the disclosure provides a polynucleotide encoding the isolated multispecific protein of the disclosure.

10 In certain embodiments, the disclosure provides a vector comprising the polynucleotide encoding the isolated multispecific protein of the disclosure.

In certain embodiments, the disclosure provides a host cell comprising the vector comprising the polynucleotide encoding the isolated multispecific protein of the disclosure.

15 In certain embodiments, the disclosure provides a method of producing the isolated multispecific protein of the disclosure, comprising culturing the host cell in conditions that the multispecific protein is expressed, and recovering the multispecific protein produced by the host cell.

20 In certain embodiments, the disclosure provides a method of treating a HLA-G expressing cancer in a subject, comprising administering a therapeutically effective amount of the isolated protein of the disclosure, the isolated multispecific protein of the disclosure, the immunoconjugate of the disclosure, or the pharmaceutical composition of the disclosure to the subject for a time sufficient to treat the HLA-G expressing cancer.

25 In certain embodiments, the disclosure provides a method of reducing the amount of HLA-G expressing tumor cells in a subject, comprising administering the isolated protein of the disclosure, the isolated multispecific protein of the disclosure, the immunoconjugate of the disclosure, or the pharmaceutical composition of the disclosure to the subject for a time sufficient to reduce the amount of HLA-G expressing tumor cells.

30 In certain embodiments, the disclosure provides a method of preventing establishment of a HLA-G expressing cancer in a subject, comprising administering the isolated protein of the disclosure, the isolated multispecific protein of the disclosure, the immunoconjugate of the disclosure, or the pharmaceutical composition of the disclosure to the subject to prevent establishment of the HLA-G expressing cancer in the subject.

In certain embodiments, the disclosure provides a method of treating a non-cancerous condition in a subject at risk of developing a HLA-G expressing cancer, comprising administering the isolated

protein of the disclosure, the isolated multispecific protein of the disclosure, the immunoconjugate of the disclosure, or the pharmaceutical composition of the disclosure to the subject to treat the noncancerous condition.

5 In other embodiments, the HLA-G expressing cancer is a lung cancer, a pancreatic cancer, a renal cancer, a head and neck cancer, an ovarian cancer, an esophageal cancer, or a breast cancer.

In other embodiments, the isolated protein or the isolated multispecific protein is administered in combination with a second therapeutic agent.

In other embodiments, the second therapeutic agent is surgery, chemotherapy, hormone receptor deprivation therapy or radiation, or any combination thereof.

10 In certain embodiments, the disclosure provides a method of detecting the presence of in a subject, comprising administering the immunoconjugate of the disclosure to a subject suspected to have cancer and visualizing the biological structures to which the immunoconjugate is bound, thereby detecting the presence of cancer.

15 In certain embodiments, the disclosure provides a kit comprising the isolated protein of the disclosure, the isolated multispecific protein of the disclosure, the immunoconjugate of the disclosure, or the pharmaceutical composition of the disclosure.

In certain embodiments, the disclosure provides aa anti-idiotypic antibody binding to the isolated protein of the disclosure.

20 In certain embodiments, the disclosure provides aa isolated protein comprising an antigen binding domain that binds to an epitope on HLA-G, wherein the epitope is a discontinuous epitope comprising the amino acid sequences of HHPVFDYE (SEQ ID NO: 485) and VPS.

In certain embodiments, the disclosure provides an isolated protein comprising an amino acid sequence of SEQ ID NOs: 478 or 479.

25 In certain embodiments, the disclosure provides an isolated protein comprising an amino acid sequence of SEQ ID NOs: 478.

In certain embodiments, the disclosure provides an isolated protein comprising an amino acid sequence of SEQ ID NOs: 479.

30 In certain embodiments, the isolated protein comprises an amino acid sequence of SEQ ID NO: 490.

In certain embodiments, the isolated protein comprises amino acid sequences of SEQ ID NOs: 489 and 447. In certain embodiments, the isolated protein comprises an amino acid sequence of SEQ ID NO: 439.

In certain embodiments, the disclosure provides an isolated protein comprising amino acid sequences of SEQ ID NOs: 465 and 468.

In certain embodiments, the disclosure provides an isolated protein comprising amino acid sequences of SEQ ID NOs: 466 and 469.

5 In certain embodiments, the disclosure provides an isolated protein comprising amino acid sequences of SEQ ID NOs: 467 and 470.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The foregoing will be apparent from the following more particular description of example embodiments, as illustrated in the accompanying drawings.

Figure 1 shows the ability of γ -regions to bind recombinant HLA-G after heat treatment when formatted as scFv.

15 **Figure 2** shows the epitope mapping of select antibodies on HLA-G (SEQ ID NO: 1) using the hydrogen-deuterium exchange-based LC-MS. The sequence shown is the fragment of SEQ ID NO: 1, with the amino acid residue numbering starting from the first residue of the mature HLA-G (residues 183-274 are shown, SEQ ID NO: 497).

Figures 3A-3B show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB665-derived variable region engineered on either IgG1 (MHGB665) or IgG4 (MHGB523).

Figure 3A shows NKL cell-mediated cytotoxicity; **Figure 3B** shows NK-92 cell-mediated cytotoxicity.

20 **Figures 4A-4B** show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB669-derived variable region engineered on either IgG1 (MHGB669) or IgG4 (MHGB526).

Figure 4A shows NKL cell-mediated cytotoxicity; **Figure 4B** shows NK-92 cell-mediated cytotoxicity.

Figures 5A-5B show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB688-derived variable region engineered on either IgG1 (MHGB688) or IgG4 (MHGB596).

25 **Figure 5A** shows NKL cell-mediated cytotoxicity; **Figure 5B** shows NK-92 cell-mediated cytotoxicity.

Figures 6A-6B show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB694-derived variable region engineered on either IgG1 (MHGB694) or IgG4 (MHGB616).

Figure 6A shows NKL cell-mediated cytotoxicity; **Figure 6B** shows NK-92 cell-mediated cytotoxicity.

30 **Figures 7A-7B** show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB687-derived variable region engineered on either IgG1 (MHGB687) or IgG4 (MHGB585).

Figure 7A shows NKL cell-mediated cytotoxicity; **Figure 7B** shows NK-92 cell-mediated cytotoxicity.

Figures 8A-8B show the enhancement of NK cell-mediated cytotoxicity of K562-HLA-G cells by the MHGB672-derived variable region engineered on either IgG1 (MHGB672) or IgG4 (MHGB508).

Figure 8A shows NKL cell-mediated cytotoxicity; **Figure 8B** shows NK-92 cell-mediated cytotoxicity.

Figure 9 shows ADCC activity against JEG-3 cells, mediated by the select antibodies MHGB665 (“B665”), MHGB669 (“B669”), MHGB672 (“B672”), MHGB682 (“B682”), MHGB687 (“B687”), and MHGB688 (“B688”).

Figures 10A-10B show ADCC activity of the select antibodies.

5 **Figures 10C-10D** show CDC activity of the select antibodies.

Figures 11A-11B show binding of hybridoma supernatants to primary human T cells. Clone UCHT1 was used as a positive control (**11B**); mouse IgG1 isotype (mIgG1) was used as a negative control.

Figure 12 shows binding of anti-CD3 scFv variants, expressed in *E. coli*, to CD3.

10 **Figure 13** shows the alignment of the VL regions of CD3B815 (SEQ ID NO: 340), CD3W244 (SEQ ID NO: 341), CD3W245 (SEQ ID NO: 342), CD3W246 (SEQ ID NO: 343), CD3W247 (SEQ ID NO: 344), and CD3W248 (SEQ ID NO: 345).

15 **Figure 14** shows hydrogen-deuterium exchange rates determined using hydrogen-deuterium exchange mass spectrometry (HDX-MS) measured for the complex of CD3W245 bound to human CD3ε (CD3ε:CD3W245), or the complex of OKT3 bound to human CD3ε (CD3ε:OKT3) (SEQ ID No: 484 which is a fragment of SEQ ID No: 375 is shown). Single underline indicates segments with 10% - 30% decrease in deuteration levels and double underline indicates segments with >30% decrease in deuteration levels in the presence of the antibody, as compared to CD3ε alone.

Figures 15A-15B show cytotoxicity of HC3B125 against HLA-G expressing tumor cells HUP-T3 and % T-cell activation.

20 **Figures 15C-15D** show cytotoxicity of HC3B125 against HLA-G expressing tumor cells RERF-LC-Ad-1 and % T-cell activation.

Figure 16 shows cytotoxicity of HC3B258 and HC3B125 against RERF-LC-Ad-1 cells; Effector (T cell) : Target (RERF-LC-Ad1) ratios were 1:3, 1:1, or 3:1, as indicated.

25 **Figures 17A-17B** show group mean tumor volumes (17A) and individual tumor volumes at day 27 of established pancreatic PDX in CD34⁺ cell humanized NSG-SGM3 mice treated with either control (HLA-G x Null) or HCB125.

Figure 18 shows group mean tumor volumes of established Hup-T3 xenografts in T cell humanized NSG mice treated with either control (CD3 x Null) or HCB125.

30 DETAILED DESCRIPTION

The disclosed methods may be understood more readily by reference to the following detailed description taken in connection with the accompanying figures, which form a part of this disclosure. It is to be understood that the disclosed methods are not limited to the specific methods described and/or

shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed methods.

All patents, published patent applications and publications cited herein are incorporated by reference as if set forth fully herein.

5 When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as “**A, B, or C**” is to be interpreted as including the embodiments, “A,” “B,” “C,” “A or B,” “A or C,” “B or C,” or “A, B, or C.”

10 As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a cell” includes a combination of two or more cells, and the like.

15 The transitional terms “**comprising**,” “**consisting essentially of**,” and “**consisting of**” are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) “consisting of” excludes any element, step, or ingredient not specified in the claim; and (iii) “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. Embodiments described in terms of the phrase “comprising” (or its equivalents) also provide as embodiments those independently described in terms of “consisting of” and “consisting essentially of.”

20

25 “**About**” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, “about” means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

30 “**Activation**” or “**stimulation**” or “**activated**” or “**stimulated**” refers to induction of a change in the biologic state of a cell resulting in expression of activation markers, cytokine production, proliferation or mediating cytotoxicity of target cells. Cells may be activated by primary stimulatory signals. Co-stimulatory signals can amplify the magnitude of the primary signals and suppress cell death following initial stimulation resulting in a more durable activation state and thus a higher cytotoxic capacity. A “**co-stimulatory signal**” refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to T cell and/or NK cell proliferation and/or upregulation or downregulation of key molecules.

“**Alternative scaffold**” refers to a single chain protein framework that contains a structured core associated with variable domains of high conformational tolerance. The variable domains tolerate variation to be introduced without compromising scaffold integrity, and hence the variable domains can be engineered and selected for binding to a specific antigen.

5 **“Antibody-dependent cellular cytotoxicity”, “antibody-dependent cell-mediated cytotoxicity” or “ADCC”** refers to the mechanism of inducing cell death that depends upon the interaction of antibody-coated target cells with effector cells possessing lytic activity, such as natural killer cells (NK), monocytes, macrophages and neutrophils via Fc gamma receptors (FcγR) expressed on effector cells.

10 **“Antibody-dependent cellular phagocytosis” or “ADCP”** refers to the mechanism of elimination of antibody-coated target cells by internalization by phagocytic cells, such as macrophages or dendritic cells.

“Antigen” refers to any molecule (e.g., protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, portions thereof, or combinations thereof) capable of being bound by an antigen binding domain or a T-cell receptor that is capable of mediating an immune response. Exemplary
15 immune responses include antibody production and activation of immune cells, such as T cells, B cells or NK cells. Antigens may be expressed by genes, synthesized, or purified from biological samples such as a tissue sample, a tumor sample, a cell or a fluid with other biological components, organisms, subunits of proteins/antigens, killed or inactivated whole cells or lysates.

20 **“Antigen binding fragment” or “antigen binding domain”** refers to a portion of the protein that binds an antigen. Antigen binding fragments may be synthetic, enzymatically obtainable or genetically engineered polypeptides and include portions of an immunoglobulin that bind an antigen, such as VH, the VL, the VH and the VL, Fab, Fab', F(ab')₂, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, VHH
25 domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3, alternative scaffolds that bind an antigen, and multispecific proteins comprising the antigen binding fragments. Antigen binding fragments (such as VH and VL) may be linked together via a synthetic linker to form various types of single antibody designs where the VH/VL
30 domains may pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chains, to form a monovalent antigen binding domain, such as single chain Fv (scFv) or diabody. Antigen binding fragments may also be conjugated to other antibodies, proteins, antigen binding fragments or alternative scaffolds which may be monospecific or multispecific to engineer bispecific and multispecific proteins.

“**Antibodies**” is meant in a broad sense and includes immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antigen binding fragments, multispecific antibodies, such as bispecific, trispecific, tetraspecific etc., dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. “Full length antibodies” are comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (comprised of domains CH1, hinge, CH2 and CH3). Each light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The VH and the VL regions may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. Immunoglobulins may be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of any vertebrate species may be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

“**Bispecific**” refers to a molecule (such as an antibody) that specifically binds two distinct antigens or two distinct epitopes within the same antigen. The bispecific molecule may have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca cynomolgus* (cynomolgus, cyno) or *Pan troglodytes*, or may bind an epitope that is shared between two or more distinct antigens.

“**Cancer**” refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A “cancer” or “cancer tissue” can include a tumor.

“**Complement-dependent cytotoxicity**” or “**CDC**”, refers to the mechanism of inducing cell death in which the Fc effector domain of a target-bound protein binds and activates complement component C1q which in turn activates the complement cascade leading to target cell death. Activation of complement may also result in deposition of complement components on the target cell surface that facilitate CDC by binding complement receptors (e.g., CR3) on leukocytes

“**Complementarity determining regions**” (CDR) are antibody regions that bind an antigen. There are three CDRs in the VH (HCDR1, HCDR2, HCDR3) and three CDRs in the VL (LCDR1,

LCDR2, LCDR3). CDRs may be defined using various delineations such as Kabat (Wu et al. (1970) J Exp Med 132: 211-50; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia (Chothia et al. (1987) J Mol Biol 196: 901-17), IMGT (Lefranc et al. (2003) Dev Comp Immunol 27: 55-77) and AbM (Martin and Thornton J Biol Chem 263: 800-15, 1996). The correspondence between the various delineations and variable region numbering is described (see e.g. Lefranc et al. (2003) Dev Comp Immunol 27: 55-77; Honegger and Pluckthun, J Mol Biol (2001) 309:657-70; International ImMunoGeneTics (IMGT) database; Web resources, [http://www_imgt_org](http://www.imgt.org)). Available programs such as abYsis by UCL Business PLC may be used to delineate CDRs. The term “CDR”, “HCDR1”, “HCDR2”, “HCDR3”, “LCDR1”, “LCDR2” and “LCDR3” as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia, IMGT or AbM, unless otherwise explicitly stated in the specification.

“Decrease,” “lower,” “lessen,” “reduce,” or “abate” refers generally to the ability of a test molecule to mediate a reduced response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle. Exemplary responses are T cell expansion, T cell activation or T-cell mediated tumor cell killing or binding of a protein to its antigen or receptor, enhanced binding to a Fcγ or enhanced Fc effector functions such as enhanced ADCC, CDC and/or ADCP. Decrease may be a statistically significant difference in the measured response between the test molecule and the control (or the vehicle), or a decrease in the measured response, such as a decrease of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30 fold or more, such as 500, 600, 700, 800, 900 or 1000 fold or more (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7, 1.8, etc.).

“Differentiation” refers to a method of decreasing the potency or proliferation of a cell or moving the cell to a more developmentally restricted state.

“Encode” or “encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

“Enhance,” “promote,” “increase,” “expand” or “improve” refers generally to the ability of a test molecule to mediate a greater response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle. Exemplary responses are T cell expansion, T cell activation or T-cell

mediated tumor cell killing or binding of a protein to its antigen or receptor, enhanced binding to a $\text{Fc}\gamma$ or enhanced Fc effector functions such as enhanced ADCC, CDC and/or ADCP. Enhance may be a statistically significant difference in the measured response between the test molecule and control (or vehicle), or an increase in the measured response, such as an increase of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30 fold or more, such as 500, 600, 700, 800, 900 or 1000 fold or more (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7, 1.8, etc.).

“**Expansion**” refers to the outcome of cell division and cell death.

“**Express**” and “**expression**” refers to the well-known transcription and translation occurring in cells or *in vitro*. The expression product, e.g., the protein, is thus expressed by the cell or *in vitro* and may be an intracellular, extracellular or a transmembrane protein.

“**Expression vector**” refers to a vector that can be utilized in a biological system or in a reconstituted biological system to direct the translation of a polypeptide encoded by a polynucleotide sequence present in the expression vector.

“**dAb**” or “**dAb fragment**” refers to an antibody fragment composed of a VH domain (Ward et al., Nature 341:544 546 (1989)).

“**Fab**” or “**Fab fragment**” refers to an antibody fragment composed of VH, CH1, VL and CL domains.

“**F(ab')₂**” or “**F(ab')₂ fragment**” refers to an antibody fragment containing two Fab fragments connected by a disulfide bridge in the hinge region.

“**Fd**” or “**Fd fragment**” refers to an antibody fragment composed of VH and CH1 domains.

“**Fv**” or “**Fv fragment**” refers to an antibody fragment composed of the VH and the VL domains from a single arm of the antibody.

“**Full length antibody**” is comprised of two heavy chains (HC) and two light chains (LC) interconnected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable domain (VH) and a heavy chain constant domain, the heavy chain constant domain comprised of subdomains CH1, hinge, CH2 and CH3. Each light chain is comprised of a light chain variable domain (VL) and a light chain constant domain (CL). The VH and the VL may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

“**Genetic modification**” refers to the introduction of a “foreign” (*i.e.*, extrinsic or extracellular) gene, DNA or RNA sequence to a host cell, so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein or enzyme coded by the introduced gene or

sequence. The introduced gene or sequence may also be called a “cloned” or “foreign” gene or sequence, may include regulatory or control sequences operably linked to polynucleotide encoding the chimeric antigen receptor, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The gene or sequence may include nonfunctional sequences or sequences with no known function. A host cell that receives and expresses introduced DNA or RNA has been “genetically engineered.” The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or from a different genus or species.

“**Heterologous**” refers to two or more polynucleotides or two or more polypeptides that are not found in the same relationship to each other in nature.

“**Heterologous polynucleotide**” refers to a non-naturally occurring polynucleotide that encodes two or more neoantigens as described herein.

“**Heterologous polypeptide**” refers to a non-naturally occurring polypeptide comprising two or more neoantigen polypeptides as described herein.

“**Host cell**” refers to any cell that contains a heterologous nucleic acid. An exemplary heterologous nucleic acid is a vector (*e.g.*, an expression vector).

“**Human antibody**” refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are “derived from” sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. “Human antibody” typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, “human antibody” is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged immunoglobulin genes. In some cases, “human antibody” may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) J Mol Biol 296:57-86, or a synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) J Mol Biol 397:385-96, and in Int. Patent Publ. No.

WO2009/085462. Antibodies in which at least one CDR is derived from a non-human species are not included in the definition of “human antibody”.

“**Humanized antibody**” refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences.

- 5 Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

“**In combination with**” means that two or more therapeutic agents are administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

- 10 “**Isolated**” refers to a homogenous population of molecules (such as synthetic polynucleotides or polypeptides) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. “Isolated” refers to a molecule that is substantially free of other cellular material and/or chemicals and encompasses molecules that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,
15 95%, 96%, 97%, 98%, 99% or 100% purity.

“**Human leukocyte antigen G**” or “**HLA-G**” refers to a known protein which is also called “HLA class I histocompatibility antigen, alpha chain G” or “MHC class I antigen G”. All HLA-G isoforms and variants are encompassed in “HLA-G”. The amino acid sequences of the various isoforms are retrievable from Uniprot ID numbers P17693-1 through P17693-7 and are shown in Table 1.

20 **Table 1. Sequences of HLA-G isoforms**

Isoform	Uniprot ID	Protein Sequence
HLA-G1	P17693-1	SEQ ID NO: 1 <u>MVVMAPRTLFLLLSGALTLETWAGSHSMRYFSAAVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEETRNKKAHAQTDRMNL</u> <u>QTLRGYYNQSEASSHTLQWMIGCDLGSDGRLLRGYEQYAYDGKDYLALNED</u> <u>LRSWTAADTAAQISKRKCEANVAEQRRAYLEGTCVEWLHRYLENGKEMLO</u> <u>RADPPKTHVTHHPVFDYEATLRCWALGFYPAEIILTWQRDGEDQTQDVELV</u> <u>ETRPAGDGTFOKWAAVVPSGEEQRYTCHVQHEGLPEPLMLRWKQSSLPTI</u> <u>PIMGIVAGLVVLAAVVTGAAVA AVLWRKKSSD</u>
HLA-G2	P17693-2	SEQ ID NO: 2 <u>MVVMAPRTLFLLLSGALTLETWAGSHSMRYFSAAVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEETRNKKAHAQTDRMNL</u> <u>QTLRGYYNQSEAKPPKTHVTHHPVFDYEATLRCWALGFYPAEIILTWQRDG</u>

		<u>EDQTQDVELVETRPAGDGT</u> <u>FQKWA</u> <u>AVVPSGEEQRYTCHVQHEGLPEPLML</u> <u>RWKQSSLPTIP</u> <u>IMGIVAGLVVLA</u> <u>AVVTGA</u> <u>AAVAVLWRKKSSD</u>
HLA-G3	P17693-3	SEQ ID NO: 3 <u>MVVMAPRTLFLLLSGALT</u> <u>LTETWAGSHSMRYFSA</u> <u>AVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEET</u> <u>TRNTKAHAQTDRMNL</u> <u>QTLRGYYNQSEAKQSSLPTIP</u> <u>IMGIVAGLVVLA</u> <u>AVVTGA</u> <u>AAVAVLWRKKSS</u> D
HLA-G4	P17693-4	SEQ ID NO: 4 <u>MVVMAPRTLFLLLSGALT</u> <u>LTETWAGSHSMRYFSA</u> <u>AVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEET</u> <u>TRNTKAHAQTDRMNL</u> <u>QTLRGYYNQSEASSHTLQWMIGCDL</u> <u>GSDGRLLRGYEQYAYDGKDYALNED</u> LRSWTAADTAAQISKRKCEANVAEQRRAYLEGT CVEWLHRYLENGKEMLQ RAKQSSLPTIP <u>IMGIVAGLVVLA</u> <u>AVVTGA</u> <u>AAVAVLWRKKSSD</u>
HLA-G5	P17693-5	SEQ ID NO: 5 <u>MVVMAPRTLFLLLSGALT</u> <u>LTETWAGSHSMRYFSA</u> <u>AVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEET</u> <u>TRNTKAHAQTDRMNL</u> <u>QTLRGYYNQSEASSHTLQWMIGCDL</u> <u>GSDGRLLRGYEQYAYDGKDYALNED</u> LRSWTAADTAAQISKRKCEANVAEQRRAYLEGT CVEWLHRYLENGKEMLQ RADPPKTHVTHHPVFDYEAT <u>LR</u> <u>CWALGFYPAEI</u> <u>ILTW</u> <u>ORDGEDQDVELV</u> <u>ETRPAGDGT</u> <u>FQKWA</u> <u>AVVPSGEEQRYTCHVQHEGLPEPLML</u> <u>RWSKEGDGGI</u> MSVRESRSLSEDL
HLA-G6	P17693-6	SEQ ID NO: 6 <u>MVVMAPRTLFLLLSGALT</u> <u>LTETWAGSHSMRYFSA</u> <u>AVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEET</u> <u>TRNTKAHAQTDRMNL</u> <u>QTLRGYYNQSEAKPPKTHVTHHPVFDYEAT</u> <u>LR</u> <u>CWALGFYPAEI</u> <u>ILTW</u> <u>ORDG</u> <u>EDQTQDVELVETRPAGDGT</u> <u>FQKWA</u> <u>AVVPSGEEQRYTCHVQHEGLPEPLML</u> <u>RWSKEGDGGIMSVRESRSLSEDL</u>
HLA-G7	P17693-7	SEQ ID NO: 7 <u>MVVMAPRTLFLLLSGALT</u> <u>LTETWAGSHSMRYFSA</u> <u>AVSRPGRGEPRFIAMGY</u> <u>VDDTQFVRFDSDSACPRMEPRAPWVEQEGPEYWEET</u> <u>TRNTKAHAQTDRMNL</u> <u>QTLRGYYNQSEASE</u>
Signal sequence: italic; α 1 domain: underlined; α 2 domain: bold; α 3 domain: double underlined; transmembrane region: dashed underline.		

“**Modulate**” refers to either enhanced or decreased ability of a test molecule to mediate an enhanced or a reduced response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle.

“**Monoclonal antibody**” refers to an antibody obtained from a substantially homogenous population of antibody molecules, *i.e.*, the individual antibodies comprising the population are identical except for possible well-known alterations such as removal of C-terminal lysine from the antibody heavy chain or post-translational modifications such as amino acid isomerization or deamidation, methionine oxidation or asparagine or glutamine deamidation. Monoclonal antibodies typically bind one antigenic epitope. A bispecific monoclonal antibody binds two distinct antigenic epitopes. Monoclonal antibodies may have heterogeneous glycosylation within the antibody population. Monoclonal antibody may be monospecific or multispecific such as bispecific, monovalent, bivalent or multivalent.

“**Multispecific**” refers to a molecule, such as an antibody that specifically binds two or more distinct antigens or two or more distinct epitopes within the same antigen. Multispecific molecule may have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example *Macaca fascicularis* (cynomolgus, cyno) or *Pan troglodytes*, or may bind an epitope that is shared between two or more distinct antigens.

“**Natural killer cell**” and “**NK cell**” are used interchangeably and synonymously herein. NK cell refers to a differentiated lymphocyte with a CD16⁺ CD56⁺ and/or CD57⁺ TCR⁻ phenotype. NK cells are characterized by their ability to bind to and kill cells that fail to express “self” MHC/HLA antigens by the activation of specific cytolytic enzymes, the ability to kill tumor cells or other diseased cells that express a ligand for NK activating receptors, and the ability to release protein molecules called cytokines that stimulate or inhibit the immune response.

“**Operatively linked**” and similar phrases, when used in reference to nucleic acids or amino acids, refers to the operational linkage of nucleic acid sequences or amino acid sequence, respectively, placed in functional relationships with each other. For example, an operatively linked promoter, enhancer elements, open reading frame, 5' and 3' UTR, and terminator sequences result in the accurate production of a nucleic acid molecule (*e.g.*, RNA) and in some instances to the production of a polypeptide (*i.e.*, expression of the open reading frame). Operatively linked peptide refers to a peptide in which the functional domains of the peptide are placed with appropriate distance from each other to impart the intended function of each domain.

“**Pharmaceutical combination**” refers to a combination of two or more active ingredients administered either together or separately.

“**Pharmaceutical composition**” refers to a composition that results from combining an active ingredient and a pharmaceutically acceptable carrier.

“**Pharmaceutically acceptable carrier**” or “**excipient**” refers to an ingredient in a pharmaceutical composition, other than the active ingredient, which is nontoxic to a subject. Exemplary pharmaceutically acceptable carriers are a buffer, stabilizer or preservative.

“**Polynucleotide**” or “**nucleic acid**” refers to a synthetic molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. cDNA is a typical example of a polynucleotide. Polynucleotide may be a DNA or a RNA molecule.

“**Prevent**,” “**preventing**,” “**prevention**,” or “**prophylaxis**” of a disease or disorder means preventing that a disorder occurs in a subject.

“**Proliferation**” refers to an increase in cell division, either symmetric or asymmetric division of cells.

“**Promoter**” refers to the minimal sequences required to initiate transcription. Promoter may also include enhancers or repressor elements which enhance or suppress transcription, respectively.

“**Protein**” or “**polypeptide**” are used interchangeably herein and refers to a molecule that comprises one or more polypeptides each comprised of at least two amino acid residues linked by a peptide bond. Protein may be a monomer, or may be protein complex of two or more subunits, the subunits being identical or distinct. Small polypeptides of less than 50 amino acids may be referred to as “peptides”. Protein may be a heterologous fusion protein, a glycoprotein, or a protein modified by post-translational modifications such as phosphorylation, acetylation, myristoylation, palmitoylation, glycosylation, oxidation, formylation, amidation, citrullination, polyglutamylation, ADP-ribosylation, pegylation or biotinylation. Protein may be recombinantly expressed.

“**Recombinant**” refers to polynucleotides, polypeptides, vectors, viruses and other macromolecules that are prepared, expressed, created or isolated by recombinant means.

“**Regulatory element**” refers to any cis-or trans acting genetic element that controls some aspect of the expression of nucleic acid sequences.

“**Relapsed**” refers to the return of a disease or the signs and symptoms of a disease after a period of improvement after prior treatment with a therapeutic.

“**Refractory**” refers to a disease that does not respond to a treatment. A refractory disease can be resistant to a treatment before or at the beginning of the treatment, or a refractory disease can become resistant during a treatment.

“**Single chain Fv**” or “**scFv**” refers to a fusion protein comprising at least one antibody fragment comprising a light chain variable region (VL) and at least one antibody fragment comprising a heavy chain variable region (VH), wherein the VL and the VH are contiguously linked via a polypeptide linker, and capable of being expressed as a single chain polypeptide. Unless specified, as used herein, a scFv

may have the VL and VH variable regions in either order, e.g., with respect to the N- terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

“Specifically binds,” “specific binding,” “specifically binding” or “binds” refer to a proteinaceous molecule binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the proteinaceous molecule binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant (K_D) of about 1×10^{-7} M or less, for example about 5×10^{-8} M or less, about 1×10^{-8} M or less, about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 1×10^{-11} M or less, or about 1×10^{-12} M or less, typically with the K_D that is at least one hundred fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). In the context of the prostate neoantigens described here, “specific binding” refers to binding of the proteinaceous molecule to the prostate neoantigen without detectable binding to a wild-type protein the neoantigen is a variant of.

“Subject” includes any human or nonhuman animal. “Nonhuman animal” includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. The terms “subject” and “patient” can be used interchangeably herein.

“T cell” and “T lymphocyte” are interchangeable and used synonymously herein. T cell includes thymocytes, naïve T lymphocytes, memory T cells, immature T lymphocytes, mature T lymphocytes, resting T lymphocytes, or activated T lymphocytes. A T cell can be a T helper (Th) cell, for example a T helper 1 (Th1) or a T helper 2 (Th2) cell. The T cell can be a helper T cell (HTL; $CD4^+$ T cell) $CD4^+$ T cell, a cytotoxic T cell (CTL; $CD8^+$ T cell), a tumor infiltrating cytotoxic T cell (TIL; $CD8^+$ T cell), $CD4^+CD8^+$ T cell, or any other subset of T cells. Also included are “NKT cells”, which refer to a specialized population of T cells that express a semi-invariant $\alpha\beta$ T-cell receptor, but also express a variety of molecular markers that are typically associated with NK cells, such as NK1.1. NKT cells include $NK1.1^+$ and $NK1.1^-$, as well as $CD4^+$, $CD4^-$, $CD8^+$ and $CD8^-$ cells. The TCR on NKT cells is unique in that it recognizes glycolipid antigens presented by the MHC I-like molecule CD Id. NKT cells can have either protective or deleterious effects due to their abilities to produce cytokines that promote either inflammation or immune tolerance. Also included are “gamma-delta T cells ($\gamma\delta$ T cells),” which refer to a specialized population that to a small subset of T cells possessing a distinct TCR on their surface, and unlike the majority of T cells in which the TCR is composed of two glycoprotein chains designated α - and β -TCR chains, the TCR in $\gamma\delta$ T cells is made up of a γ -chain and a δ -chain. $\gamma\delta$ T cells can play a role in immunosurveillance and immunoregulation, and were found to be an important source of IL-17 and to induce robust $CD8^+$ cytotoxic T cell response. Also included are “regulatory T cells” or “Tregs” which refer to T cells that suppress an abnormal or excessive immune response and play a role in

immune tolerance. Tregs are typically transcription factor Foxp3-positive CD4⁺T cells and can also include transcription factor Foxp3-negative regulatory T cells that are IL-10-producing CD4⁺T cells.

“**Therapeutically effective amount**” or “**effective amount**” used interchangeably herein, refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Example indicators of an effective therapeutic or combination of therapeutics that include, for example, improved wellbeing of the patient, reduction of a tumor burden, arrested or slowed growth of a tumor, and/or absence of metastasis of cancer cells to other locations in the body.

“**Transduction**” refers to the introduction of a foreign nucleic acid into a cell using a viral vector.

“**Treat**,” “**treating**” or “**treatment**” of a disease or disorder such as cancer refers to accomplishing one or more of the following: reducing the severity and/or duration of the disorder, inhibiting worsening of symptoms characteristic of the disorder being treated, limiting or preventing recurrence of the disorder in subjects that have previously had the disorder, or limiting or preventing recurrence of symptoms in subjects that were previously symptomatic for the disorder.

“**Tumor cell**” or a “cancer cell” refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation may arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo*.

“**Variant**,” “**mutant**” or “**altered**” refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications, for example one or more substitutions, insertions or deletions.

The numbering of amino acid residues in the antibody constant region throughout the specification is according to the EU index as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), unless otherwise explicitly stated.

Mutations in the Ig constant regions are referred to as follows: L351Y_F405A_Y407V refers to L351Y, F405A and Y407V mutations in one immunoglobulin constant region.

L351Y_F405A_Y407V/T394W refers to L351Y, F405A and Y407V mutations in the first Ig constant region and T394W mutation in the second Ig constant region, which are present in one multimeric protein.

5 Antigen binding domains that bind HLA-G

The disclosure provides antigen binding domains that bind HLA-G, monospecific and multispecific proteins comprising the antigen binding domains that bind HLA-G, polynucleotides encoding the foregoing, vectors, host cells and methods of making and using the foregoing. The antigen binding domains that bind HLA-G identified herein demonstrated several unique properties such as

10 1) improved thermostability, 2) improved developability achieved by reducing the deamidation risk, 3) decreased immunogenicity, 4) specificity to HLA-G accompanied by the lack of cross-reactivity with HLA-A, HLA-B, HLA-C, and HLA-E, and 5) ability to overcome immune checkpoint ligand expression on tumor cells, and ensure tumor cell killing via T cell mediated cytotoxicity.

The disclosure provides an isolated protein comprising an antigen binding domain that binds

15 human leukocyte antigen G (HLA-G), wherein the antigen binding domain that binds HLA-G comprises a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or

20 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or

25 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or

30 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

The disclosure provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises the HCDR1, the HCDR1, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

- 5 SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
 SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
 SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
 SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
10 SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
 SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
 SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
 SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
 SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

- 15 The disclosure provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

The disclosure provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises

- 20 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
 the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
 the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
 the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
25 the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
 the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

- 30 The disclosure provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

The disclosure also provides an isolated protein comprising an antigen binding domain that binds human leukocyte antigen G (HLA-G), wherein the antigen binding domain that binds HLA-G comprises a mutation engineered to provide germline optimization, the mutation is selected from the group consisting of E1Q, L5Q, E6Q, S71P, D46E and H77N mutations in the VH domain, and K30E and G66V in the VL domain. The disclosure also provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises a mutation engineered to reduce the risk of post-translational modification, wherein the mutation is N92H in the VL domain.

The disclosure also provides an isolated protein comprising an antigen binding domain that binds HLA-G, wherein the antigen binding domain that binds HLA-G comprises

- 10 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 53;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 55;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 57;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 59;
- 15 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 61;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 63;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 65;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 67;
- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 69;
- 20 the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 51;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 55;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 57;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 59;
- 25 the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 61;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 63;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 65;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 67;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 69;
- 30 the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 51;
- the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 53;
- the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
- the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 57;
- the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 59;

the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 67;
5 the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
10 the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 67;
15 the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 57;
20 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 67;
25 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 57;
30 the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 67;

the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 55;
5 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 65;
10 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 55;
15 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
20 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 55;
25 the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 65;
30 the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 55;

- the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 57;
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 59;
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 61;
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 63;
 5 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 65;
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67; or
 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

The disclosure also provides an isolated protein comprising an antigen binding domain that binds
 10 HLA-G, wherein the antigen binding domain that binds HLA-G comprises the amino acid sequence of
 SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265,
 266, 267, 268, or 269.

- In some embodiments, the antigen binding domain that binds HLA-G is a scFv.
 In some embodiments, the antigen binding domain that binds HLA-G is a (scFv)₂.
 15 In some embodiments, the antigen binding domain that binds HLA-G is a Fv.
 In some embodiments, the antigen binding domain that binds HLA-G is a Fab.
 In some embodiments, the antigen binding domain that binds HLA-G is a F(ab')₂.
 In some embodiments, the antigen binding domain that binds HLA-G is a Fd.
 In some embodiments, the HLA-G antigen binding domain is a dAb.
 20 In some embodiments, the HLA-G antigen binding domain is a VHH.

HLA-G binding scFvs

- Any of the VH and the VL domains identified herein that bind HLA-G may be engineered into
 scFv format in either VH-linker-VL or VL-linker-VH orientation. Any of the VH and the VL domains
 25 identified herein may also be used to generate sc(Fv)₂ structures, such as VH-linker-VL-linker-VL-
 linker-VH, VH-linker-VL-linker-VH-linker-VL, VH-linker-VH-linker-VL-linker-VL, VL-linker-VH-
 linker-VH-linker-VL, VL-linker-VH-linker-VL-linker-VH or VL-linker-VL-linker-VH-linker-VH.

- The VH and the VL domains identified herein may be incorporated into a scFv format and the
 binding and thermostability of the resulting scFv to HLA-G may be assessed using known methods.
 30 Binding may be assessed using ProteOn XPR36, Biacore 3000 or KinExA instrumentation, ELISA or
 competitive binding assays known to those skilled in the art. Binding may be evaluated using purified
 scFvs or Ecoli supernatants or lysed cells containing the expressed scFv. The measured affinity of a test
 scFv to HLA-G may vary if measured under different conditions (e.g., osmolarity, pH). Thus,
 measurements of affinity and other binding parameters (e.g., K_D, K_{on}, K_{off}) are typically made with

standardized conditions and standardized buffers. Thermostability may be evaluated by heating the test scFv at elevated temperatures, such as at 50°C, 55°C or 60°C for a period of time, such as 5 minutes (min), 10 min, 15 min, 20 min, 25 min or 30 min and measuring binding of the test scFv to HLA-G. The scFvs retaining comparable binding to HLA-G when compared to a non-heated scFv sample are referred to as being thermostable.

In recombinant expression systems, the linker is a peptide linker and may include any naturally occurring amino acid. Exemplary amino acids that may be included into the linker are Gly, Ser Pro, Thr, Glu, Lys, Arg, Ile, Leu, His and The. The linker should have a length that is adequate to link the VH and the VL in such a way that they form the correct conformation relative to one another so that they retain the desired activity, such as binding to HLA-G.

The linker may be about 5-50 amino acids long. In some embodiments, the linker is about 10-40 amino acids long. In some embodiments, the linker is about 10-35 amino acids long. In some embodiments, the linker is about 10-30 amino acids long. In some embodiments, the linker is about 10-25 amino acids long. In some embodiments, the linker is about 10-20 amino acids long. In some embodiments, the linker is about 15-20 amino acids long. In some embodiments, the linker is 6 amino acids long. In some embodiments, the linker is 7 amino acids long. In some embodiments, the linker is 8 amino acids long. In some embodiments, the linker is 9 amino acids long. In some embodiments, the linker is 10 amino acids long. In some embodiments, the linker is 11 amino acids long. In some embodiments, the linker is 12 amino acids long. In some embodiments, the linker is 13 amino acids long. In some embodiments, the linker is 14 amino acids long. In some embodiments, the linker is 15 amino acids long. In some embodiments, the linker is 16 amino acids long. In some embodiments, the linker is 17 amino acids long. In some embodiments, the linker is 18 amino acids long. In some embodiments, the linker is 19 amino acids long. In some embodiments, the linker is 20 amino acids long. In some embodiments, the linker is 21 amino acids long. In some embodiments, the linker is 22 amino acids long. In some embodiments, the linker is 23 amino acids long. In some embodiments, the linker is 24 amino acids long. In some embodiments, the linker is 25 amino acids long. In some embodiments, the linker is 26 amino acids long. In some embodiments, the linker is 27 amino acids long. In some embodiments, the linker is 28 amino acids long. In some embodiments, the linker is 29 amino acids long. In some embodiments, the linker is 30 amino acids long. In some embodiments, the linker is 31 amino acids long. In some embodiments, the linker is 32 amino acids long. In some embodiments, the linker is 33 amino acids long. In some embodiments, the linker is 34 amino acids long. In some embodiments, the linker is 35 amino acids long. In some embodiments, the linker is 36 amino acids long. In some embodiments, the linker is 37 amino acids long. In some embodiments, the linker is 38 amino acids long. In some embodiments, the linker is 39 amino acids long. In some embodiments, the linker is 40 amino acids long.

Exemplary linkers that may be used are Gly rich linkers, Gly and Ser containing linkers, Gly and Ala containing linkers, Ala and Ser containing linkers, and other flexible linkers.

Other linker sequences may include portions of immunoglobulin hinge area, CL or CH1 derived from any immunoglobulin heavy or light chain isotype. Alternatively, a variety of non-proteinaceous polymers, including polyethylene glycol (PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers. Exemplary linkers that may be used are shown in Table 2. Additional linkers are described for example in Int. Pat. Publ. No. WO2019/060695.

In some embodiments, the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL).

In some embodiments, the scFv comprises, from the N-to C-terminus, the VL, the L1 and the VH (VL-L1-VH).

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 8.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 9.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 10.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 11.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 12.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 13.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 14.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 15.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 16.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 17.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 18.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 19.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 20.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 21.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 22.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 23.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 24.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 25.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 29.

- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 30.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 31.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 32.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 33.
- 5 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 34.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 35.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 36.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 37.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 38.
- 10 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 39.
- In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 40.

Table 2. Linkers.

Linker name	Amino acid sequence	SEQ ID NO:
Linker 1	GGSEGGKSSGSGSESKSTGGS	8
Linker 2	GGGSGGGG	9
Linker 3	GGGSGGGSGGGG	10
Linker 4	GGGSGGGSGGGSGGGG	11
Linker 5	GGGSGGGSGGGSGGGSGGGG	12
Linker 6	GGGSGGGSGGGSGGGG	13
Linker 7	GGGSGGGSGGGSGGGSGGGG	14
Linker 8	GGGSGGGSGGGSGGGSGGGSGGGG	15
Linker 9	GSTSGSGKPGSGEGSTKG	16
Linker 10	IRPRAIGGSKPRVA	17
Linker 11	GKGGSGKGGSGKGGG	18
Linker 12	GGKGGSGKGGSGKGGG	19
Linker 13	GGGKSGGGKSGGGKS	20
Linker 14	GKGKSGKGGKSGKGGK	21
Linker 15	GGGKSGGGKSGKGGG	22
Linker 16	GKPGSGKPGSGKPGS	23
Linker 17	GKPGSGKPGSGKPGSGKPGS	24

Linker 18	GKGKSGKKGKSGKKGKSGKGS	25
Linker 19	STAGDTHLGGEDFD	26
Linker 20	GEGGSGEGGSGEGGS	27
Linker 21	GGEGSGEGSGEGGS	28
Linker 22	GEGESGEGESGEGES	29
Linker 23	GGGESGGEGSGEGGS	30
Linker 24	GEGESGEGESGEGESGEGES	31
Linker 25	GSTSGSGKPGSGEGSTKG	32
Linker 26	PRGASKSGSASQTGSAPGS	33
Linker 27	GTAAAGAGAAGGAAAGAAG	34
Linker 28	GTSGSSGSGSGGSGSGGGG	35
Linker 29	GKPGSGKPGSGKPGSGKPGS	36
Linker 30	GSGS	37
Linker 31	APAPAPAPAP	38
Linker 32	APAPAPAPAPAPAPAPAPAP	39
Linker 33	AEAAAKEAAAKEAAAKEAAAKEAAAKAAA	40
Linker 34	GTEGKSSGSGSESKST	376

In some embodiments, the scFv comprises

- a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

5 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

10 In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;

SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;

SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;

SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;

15 SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;

SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;

SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;

SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or

SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

20 In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively.

25 In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively.

30 In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively.

In some embodiments, the scFv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

5 In some embodiments, the scFv comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

10 In some embodiments, the scFv comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57.

15 In some embodiments, the scFv comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61.

20 In some embodiments, the scFv comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.

25 In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 53.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 55.

30 In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 57.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 59.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 61.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 63.

In some embodiments, the scFv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 65.

[illegible]

[illegible]

- In some embodiments, the scFv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 63.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 67.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 69.
- 5 In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 51.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 53.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 55.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 57.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 59.
- 10 In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 61.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 63.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 65.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 69.
- 15 In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 51.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 53.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 55.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 57.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 59.
- 20 In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 61.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 63.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 65.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67.
- In some embodiments, the scFv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 25
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 248.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 249.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 250.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 251.
- 30 In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 252.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 253.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 254.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 255.
- In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 256.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 257.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 258.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 259.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 260.

5 In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 261.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 262.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 263.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 264.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 265.

10 In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 266.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 267.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 268.

In some embodiments, the scFv comprises the amino acid sequence of SEQ ID NO: 269.

15 **Other antigen binding domains that bind HLA-G**

Any of the VH and the VL domains identified herein that bind HLA-G may also be engineered into Fab, F(ab')₂, Fd or Fv format and their binding to HLA-G and thermostability may be assessed using the assays described herein.

In some embodiments, the Fab comprises

20 a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or

25 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and

30 the LCDR3 of the VL of SEQ ID NO: 59; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or

- 5 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

- SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
10 SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
15 SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively.

- 20 In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively.

- In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively.
25

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID Nos: 81, 82, 83, 97, 89, and 98, respectively.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively.

- 30 In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively.

In some embodiments, the Fab comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO:
5 51.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO:
53.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO:
55.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO:
10 57.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO:
59.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO:
15 61.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO:
63.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO:
65.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO:
20 67.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO:
69.

In some embodiments, the Fab comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64,
25 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 53.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 55.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 57.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 59.
30

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 61.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 63.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 65.

In some embodiments, the Fab comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 67.

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- In some embodiments, the Fab comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 67.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 69.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 51.
- 5 In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 53.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 55.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 57.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 59.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 61.
- 10 In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 63.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 65.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 69.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 51.
- 15 In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 53.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 55.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 57.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 59.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 61.
- 20 In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 63.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 65.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67.
- In some embodiments, the Fab comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 25 In some embodiments, the $F(ab')_2$ comprises
- a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and
- 30 the LCDR3 of the VL of SEQ ID NO: 53; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or

5 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and

10 the LCDR3 of the VL of SEQ ID NO: 67; or

the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

15 SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;

SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;

SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;

SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;

SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;

20 SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;

SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;

SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or

SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, 25 the LCDR2 and the LCDR3 of SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively.

In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively.

In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively.

30 In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively.

In some embodiments, the $F(ab')_2$ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID Nos: 81, 82, 83, 97, 89, and 98, respectively.

In some embodiments, the F(ab')₂ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively.

In some embodiments, the F(ab')₂ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively.

5 In some embodiments, the F(ab')₂ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively.

In some embodiments, the F(ab')₂ comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53.

15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59.

20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63.

25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 55.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 61.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 65.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 69.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 51.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 55.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 61.
- 30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 65.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 69.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 51.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 59.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 61.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 65.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 69.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 51.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 55.
- 30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 59.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 61.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 63.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 65.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 69.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 51.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 53.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 55.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 61.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 63.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 65.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 69.
- 30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 51.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 53.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 55.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 57.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 63.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 65.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 67.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 69.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 51.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 53.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 55.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 57.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 61.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63.
- 30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 65.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 67.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 69.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 51.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 55.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 57.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 61.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 67.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 69.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 51.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 55.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 57.
- 30 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 61.

- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 65.
- 5 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 69.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 51.
- 10 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 53.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 55.
- 15 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 57.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 59.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 61.
- 20 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 63.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 65.
- 25 In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67.
- In some embodiments, the F(ab')₂ comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 30 In some embodiments, the Fv comprises
a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or

- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or
- 5 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and
- 10 the LCDR3 of the VL of SEQ ID NO: 61; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or
- 15 the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or
- the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.

- In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the
- 20 LCDR2 and the LCDR3 of
- SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
- SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
- SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
- SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
- 25 SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
- SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
- SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
- SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
- SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

- 30 In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively.

5 In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID Nos: 81, 82, 83, 97, 89, and 98, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively.

10 In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively.

In some embodiments, the Fv comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

15 In some embodiments, the Fv comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53.

20 In some embodiments, the Fv comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57.

25 In some embodiments, the Fv comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63.

30 In some embodiments, the Fv comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.

[illegible]

[illegible]

In some embodiments, the Fv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67.

In some embodiments, the Fv comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 50.

5 In some embodiments, the Fd comprises the VH of SEQ ID NO: 52.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 54.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 56.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 58.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 60.

10 In some embodiments, the Fd comprises the VH of SEQ ID NO: 62.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 64.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 66.

In some embodiments, the Fd comprises the VH of SEQ ID NO: 68.

15 **Homologous antigen binding domains and antigen binding domains with conservative substitutions**

Variants of the antigen binding domains that bind HLA-G are within the scope of the disclosure.

For example, variants may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 amino acid substitutions in the antigen binding domain that bind HLA-G as long as they retain or have improved functional properties when compared to the parent antigen

20 binding domains. In some embodiments, the sequence identity may be about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to the antigen binding domains that bind HLA-G of the disclosure. In some embodiments, the variation is in the framework regions. In some embodiments, variants are generated by conservative substitutions.

For example, the antigen binding domains that bind HLA-G may comprise substitutions at
25 residue positions of E1Q, L5Q, E6Q, S71P, E1Q, L5Q, E6Q, and S71P in the VH (residue numbering according to the MHGB688-VH of SEQ ID NO: 52) and K30E and G66V in the VL (residue numbering according to the MHGB688-VL of SEQ ID NO: 53). Conservative substitutions may be made at any indicated positions and the resulting variant antigen binding domains that bind HLA-G are tested for their desired characteristics in the assays described herein.

30 Also provided are antigen binding domains that bind HLA-G comprising the VH and the VL which are at least 80% identical to

the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;

the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;

the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;

- the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
5 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

In some embodiments, the identity is 85%. In some embodiments, the identity is 90%. In some
embodiments, the identity is 91%. In some embodiments, the identity is 91%. In some embodiments, the
10 identity is 92%. In some embodiments, the identity is 93%. In some embodiments, the identity is 94%.
In some embodiments, the identity is 94%. In some embodiments, the identity is 95%. In some
embodiments, the identity is 96%. In some embodiments, the identity is 97%. In some embodiments, the
identity is 98%. In some embodiments, the identity is 99%.

The percent identity between the two sequences is a function of the number of identical positions
15 shared by the sequences (i.e., % identity = number of identical positions/total number of positions × 100),
taking into account the number of gaps, and the length of each gap, which need to be introduced for
optimal alignment of the two sequences.

The percent identity between two amino acid sequences may be determined using the algorithm
of E. Meyers and W. Miller (*Comput Appl Biosci* 4:11-17 (1988)) which has been incorporated into the
20 ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a
gap penalty of 4. In addition, the percent identity between two amino acid sequences may be determined
using the Needleman and Wunsch (*J Mol Biol* 48:444-453 (1970)) algorithm which has been
incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>),
using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a
25 length weight of 1, 2, 3, 4, 5, or 6.

In some embodiments, variant antigen binding domains that bind HLA-G comprise one or two
conservative substitutions in any of the CDR regions, while retaining desired functional properties of the
parent antigen binding fragments that bind HLA-G.

“Conservative modifications” refer to amino acid modifications that do not significantly affect or
30 alter the binding characteristics of the antibody containing the amino acid modifications. Conservative
modifications include amino acid substitutions, additions and deletions. Conservative amino acid
substitutions are those in which the amino acid is replaced with an amino acid residue having a similar
side chain. The families of amino acid residues having similar side chains are well defined and include
amino acids with acidic side chains (e.g., aspartic acid, glutamic acid), basic side chains (e.g., lysine,

arginine, histidine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), uncharged polar side chains (e.g., glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine, tryptophan), aromatic side chains (e.g., phenylalanine, tryptophan, histidine, tyrosine), aliphatic side chains (e.g., glycine, alanine, valine, leucine, isoleucine, serine, threonine), amide (e.g., asparagine, glutamine), beta-branched side chains (e.g., threonine, valine, isoleucine) and sulfur-containing side chains (cysteine, methionine). Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis (MacLennan *et al.*, (1988) *Acta Physiol Scand Suppl* 643:55-67; Sasaki *et al.*, (1988) *Adv Biophys* 35:1-24). Amino acid substitutions to the antibodies of the invention may be made by known methods for example by PCR mutagenesis (US Pat. No. 4,683,195). Alternatively, libraries of variants may be generated for example using random (NNK) or non-random codons, for example DVK codons, which encode 11 amino acids (Ala, Cys, Asp, Glu, Gly, Lys, Asn, Arg, Ser, Tyr, Trp). The resulting variants may be tested for their characteristics using assays described herein.

15 **Methods of generating antigen binding fragment that bind HLA-G**

Antigen binding domains that bind HLA-G provided in the disclosure may be generated using various technologies. For example, the hybridoma method of Kohler and Milstein may be used to identify VH/VL pairs that bind HLA-G. In the hybridoma method, a mouse or other host animal, such as a hamster, rat or chicken is immunized with human and/or cyno HLA-G, followed by fusion of spleen cells from immunized animals with myeloma cells using standard methods to form hybridoma cells. Colonies arising from single immortalized hybridoma cells may be screened for production of the antibodies containing the antigen binding domains that bind HLA-G with desired properties, such as specificity of binding, cross-reactivity or lack thereof, affinity for the antigen, and any desired functionality.

25 Antigen binding domains that bind HLA-G generated by immunizing non-human animals may be humanized. Exemplary humanization techniques including selection of human acceptor frameworks include CDR grafting (U.S. Patent No. 5,225,539), SDR grafting (U.S. Patent No. 6,818,749), Resurfacing (Padlan, (1991) *Mol Immunol* 28:489-499), Specificity Determining Residues Resurfacing (U.S. Patent Publ. No. 2010/0261620), human framework adaptation (U.S. Patent No. 8,748,356) or
30 superhumanization (U.S. Patent No. 7,709, 226). In these methods, CDRs or a subset of CDR residues of parental antibodies are transferred onto human frameworks that may be selected based on their overall homology to the parental frameworks, based on similarity in CDR length, or canonical structure identity, or a combination thereof.

Humanized antigen binding domains may be further optimized to improve their selectivity or affinity to a desired antigen by incorporating altered framework support residues to preserve binding affinity (backmutations) by techniques such as those described in Int. Patent Publ. Nos. WO1090/007861 and WO1992/22653, or by introducing variation at any of the CDRs for example to improve affinity of the antigen binding domain.

Transgenic animals, such as mice, rat or chicken carrying human immunoglobulin (Ig) loci in their genome may be used to generate antigen binding fragments that bind HLA-G, and are described in for example U.S. Patent No. 6,150,584, Int. Patent Publ. No. WO1999/45962, Int. Patent Publ. Nos. WO2002/066630, WO2002/43478, WO2002/043478 and WO1990/04036. The endogenous immunoglobulin loci in such animal may be disrupted or deleted, and at least one complete or partial human immunoglobulin locus may be inserted into the genome of the animal using homologous or non-homologous recombination, using transchromosomes, or using minigenes. Companies such as Regeneron (http://_www_regeneron_com), Harbour Antibodies (http://_www_harbourantibodies_com), Open Monoclonal Technology, Inc. (OMT) (http://_www_omtinc_net), KyMab (http://_www_kymab_com), Trianni (http://_www.trianni_com) and Ablexis (http://_www_ablexis_com) may be engaged to provide human antibodies directed against a selected antigen using technologies as described above.

Antigen binding domains that bind HLA-G may be selected from a phage display library, where the phage is engineered to express human immunoglobulins or portions thereof such as Fabs, single chain antibodies (scFv), or unpaired or paired antibody variable regions. The antigen binding domains that bind HLA-G may be isolated for example from phage display library expressing antibody heavy and light chain variable regions as fusion proteins with bacteriophage pIX coat protein as described in Shi *et al.*, (2010) *J Mol Biol* 397:385-96, and Int. Patent Publ. No. WO09/085462). The libraries may be screened for phage binding to human and/or cyno HLA-G and the obtained positive clones may be further characterized, the Fabs isolated from the clone lysates, and converted to scFvs or other configurations of antigen binding fragments.

Preparation of immunogenic antigens and expression and production of antigen binding domains of the disclosure may be performed using any suitable technique, such as recombinant protein production. The immunogenic antigens may be administered to an animal in the form of purified protein, or protein mixtures including whole cells or cell or tissue extracts, or the antigen may be formed *de novo* in the animal's body from nucleic acids encoding said antigen or a portion thereof.

Conjugation to half-life extending moieties

The antigen binding domains that bind HLA-G of the disclosure may be conjugated to a half-life extending moiety. Exemplary half-life extending moieties are albumin, albumin variants, albumin-

binding proteins and/or domains, transferrin and fragments and analogues thereof, immunoglobulins (Ig) or fragments thereof, such as Fc regions. Amino acid sequences of the aforementioned half-life extending moieties are known. Ig or fragments thereof include all isotypes, *i.e.*, IgG1, IgG2, IgG3, IgG4, IgM, IgA and IgE.

5 Additional half-life extending moieties that may be conjugated to the antigen binding domains that bind HLA-G of the disclosure include polyethylene glycol (PEG) molecules, such as PEG5000 or PEG20,000, fatty acids and fatty acid esters of different chain lengths, for example laurate, myristate, stearate, arachidate, behenate, oleate, arachidonate, octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like, polylysine, octane, carbohydrates (dextran, 10 cellulose, oligo- or polysaccharides) for desired properties. These moieties may be direct fusions with the antigen binding domains that bind HLA-G of the disclosure and may be generated by standard cloning and expression techniques. Alternatively, well known chemical coupling methods may be used to attach the moieties to recombinantly produced antigen binding domains that bind HLA-G of the disclosure.

A pegyl moiety may for example be conjugated to the antigen binding domain that bind HLA-G 15 of the disclosure by incorporating a cysteine residue to the C-terminus of the antigen binding domain that bind HLA-G of the disclosure, or engineering cysteines into residue positions that face away from the HLA-G binding site and attaching a pegyl group to the cysteine using well known methods.

In some embodiments, the antigen binding fragment that binds HLA-G is conjugated to a half-life extending moiety.

20 In some embodiments, the half-life extending moiety is an immunoglobulin (Ig), a fragment of the Ig, an Ig constant region, a fragment of the Ig constant region, a Fc region, transferrin, albumin, an albumin binding domain or polyethylene glycol. In some embodiments, the half-life extending moiety is an Ig constant region.

In some embodiments, the half-life extending moiety is the Ig.

25 In some embodiments, the half-life extending moiety is the fragment of the Ig.

In some embodiments, the half-life extending moiety is the Ig constant region.

In some embodiments, the half-life extending moiety is the fragment of the Ig constant region.

In some embodiments, the half-life extending moiety is the Fc region.

In some embodiments, the half-life extending moiety is albumin.

30 In some embodiments, the half-life extending moiety is the albumin binding domain.

In some embodiments, the half-life extending moiety is transferrin.

In some embodiments, the half-life extending moiety is polyethylene glycol.

The antigen binding domains that bind HLA-G conjugated to a half-life extending moiety may be evaluated for their pharmacokinetic properties utilizing known *in vivo* models.

Conjugation to immunoglobulin (Ig) constant regions or fragments of the Ig constant regions

The antigen binding domains that bind HLA-G of the disclosure may be conjugated to an Ig constant region or a fragment of the Ig constant region to impart antibody-like properties, including Fc effector functions C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis or down regulation of cell surface receptors (e.g., B cell receptor; BCR). The Ig constant region or the fragment of the Ig constant region functions also as a half-life extending moiety as discussed herein. The antigen binding domains that bind HLA-G of the disclosure may be engineered into conventional full length antibodies using standard methods. The full length antibodies comprising the antigen binding domain that binds HLA-G may further be engineered as described herein.

Immunoglobulin heavy chain constant region comprised of subdomains CH1, hinge, CH2 and CH3. The CH1 domain spans residues A118-V215, the CH2 domain residues A231-K340 and the CH3 domain residues G341-K447 on the heavy chain, residue numbering according to the EU Index. In some instances G341 is referred as a CH2 domain residue. Hinge is generally defined as including E216 and terminating at P230 of human IgG1. Ig Fc region comprises at least the CH2 and the CH3 domains of the Ig constant region, and therefore comprises at least a region from about A231 to K447 of Ig heavy chain constant region.

The invention also provides an antigen binding domain that binds HLA-G conjugated to an immunoglobulin (Ig) constant region or a fragment of the Ig constant region.

In some embodiments, the Ig constant region is a heavy chain constant region

In some embodiments, the Ig constant region is a light chain constant region.

In some embodiments, the fragment of the Ig constant region comprises a Fc region.

In some embodiments, the fragment of the Ig constant region comprises a CH2 domain.

In some embodiments, the fragment of the Ig constant region comprises a CH3 domain.

In some embodiments, the fragment of the Ig constant region comprises the CH2 domain and the CH3 domain.

In some embodiments, the fragment of the Ig constant region comprises at least portion of a hinge, the CH2 domain and the CH3 domain. Portion of the hinge refers to one or more amino acid residues of the Ig hinge.

In some embodiments, the fragment of the Ig constant region comprises the hinge, the CH2 domain and the CH3 domain.

In some embodiments, the antigen binding domain that binds HLA-G is conjugated to the N-terminus of the Ig constant region or the fragment of the Ig constant region.

In some embodiments, the antigen binding domain that binds HLA-G is conjugated to the C-terminus of the Ig constant region or the fragment of the Ig constant region.

In some embodiments, the antigen binding domain that binds HLA-G is conjugated to the Ig constant region or the fragment of the Ig constant region via a second linker (L2).

5 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 8.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 9.

10 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 10.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 11.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 12.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 13.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 14.

15 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 15.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 16.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 17.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 18.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 19.

20 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 20.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 21.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 22.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 23.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 24.

25 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 25.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 29.

30 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 31.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 32.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 33.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 34.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 35.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 36.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 37.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 38.

5 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 39.

In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NO: 40.

The antigen binding domains that binds HLA-G of the disclosure conjugated to Ig constant region or the fragment of the Ig constant region may be assessed for their functionality using several known assays. Binding to HLA-G may be assessed using methods described herein. Altered properties imparted
10 by the Ig constant domain or the fragment of the Ig constant region such as Fc region may be assayed in Fc receptor binding assays using soluble forms of the receptors, such as the FcγRI, FcγRII, FcγRIII or FcRn receptors, or using cell-based assays measuring for example ADCC, CDC or ADCP.

ADCC may be assessed using an *in vitro* assay using HLA-G expressing cells as target cells and NK cells as effector cells. Cytolysis may be detected by the release of label (e.g. radioactive substrates,
15 fluorescent dyes or natural intracellular proteins) from the lysed cells. In an exemplary assay, target cells are used with a ratio of 1 target cell to 4 effector cells. Target cells are pre-labeled with BATDA and combined with effector cells and the test antibody. The samples are incubated for 2 hours and cell lysis measured by measuring released BATDA into the supernatant. Data is normalized to maximal cytotoxicity with 0.67% Triton X-100 (Sigma Aldrich) and minimal control determined by spontaneous
20 release of BATDA from target cells in the absence of any antibody.

ADCP may be evaluated by using monocyte-derived macrophages as effector cells and any HLA-G expressing cells as target cells which are engineered to express GFP or other labeled molecule. In an exemplary assay, effector:target cell ratio may be for example 4:1. Effector cells may be incubated with target cells for 4 hours with or without the antibody of the invention. After incubation, cells may be
25 detached using accutase. Macrophages may be identified with anti-CD11b and anti-CD14 antibodies coupled to a fluorescent label, and percent phagocytosis may be determined based on % GFP fluorescence in the CD11⁺CD14⁺ macrophages using standard methods.

CDC of cells may be measured for example by plating Daudi cells at 1×10^5 cells/well (50 μL/well) in RPMI-B (RPMI supplemented with 1% BSA), adding 50 μL of test protein to the wells at
30 final concentration between 0-100 μg/mL, incubating the reaction for 15 min at room temperature, adding 11 μL of pooled human serum to the wells, and incubation the reaction for 45 min at 37° C. Percentage (%) lysed cells may be detected as % propidium iodide stained cells in FACS assay using standard methods.

Proteins comprising the antigen binding domains that bind HLA-G of the disclosure

The antigen binding domains that bind HLA-G of the disclosure may be engineered into monospecific or multispecific proteins of various designs using standard methods.

The disclosure also provides a monospecific protein comprising the antigen binding domain that
5 binds HLA-G of the disclosure.

In some embodiments, the monospecific protein is an antibody.

The disclosure also provides a multispecific protein comprising the antigen binding domain that binds HLA-G of the disclosure.

In some embodiments, the multispecific protein is bispecific.

10 In some embodiments, the multispecific protein is trispecific.

In some embodiments, the multispecific protein is tetraspecific.

In some embodiments, the multispecific protein is monovalent for binding to HLA-G.

In some embodiments, the multispecific protein is bivalent for binding to HLA-G.

The disclosure also provides an isolated multispecific protein comprising a first antigen binding
15 domain that binds HLA-G and a second antigen binding domain that binds a lymphocyte antigen.

In some embodiments, the lymphocyte antigen is a T cell antigen.

In some embodiments, the T cell antigen is a CD8⁺ T cell antigen.

In some embodiments, the lymphocyte antigen is a NK cell antigen.

In some embodiments, the lymphocyte antigen is CD3, CD3 epsilon (CD3ε), CD8, KI2L4,
20 NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.

In some embodiments, the lymphocyte antigen is CD3ε.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.

25 In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fab.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the F(ab')₂.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second
30 antigen binding domain that binds the lymphocyte antigen comprise the VHH.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fv.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fd.

In some embodiments, the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the scFv.

In some embodiments, the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).

- 5 In some embodiments, the L1 comprises about 5-50 amino acids.
 In some embodiments, the L1 comprises about 5-40 amino acids.
 In some embodiments, the L1 comprises about 10-30 amino acids.
 In some embodiments, the L1 comprises about 10-20 amino acids.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11,
10 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39
 or 40.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 8.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 9.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 10.
15 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 11.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 12.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 13.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 14.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 15.
20 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 16.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 17.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 18.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 19.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 20.
25 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 21.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 22.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 23.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 24.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 25.
30 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 26.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 27.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 28.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 29.
 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 31.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 32.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 33.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 34.

5 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 35.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 36.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 37.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 38.

In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 39.

10 In some embodiments, the L1 comprises the amino acid sequence of SEQ ID NO: 40.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the HCDR1 of SEQ ID NOs: 70, 73, 75, 78, 81, or 85, the HCDR2 of SEQ ID NOs: 71, 76, 79, 82, or 86, the HCDR3 of SEQ ID NOs: 72, 74, 77, 80, 83, 84, or 87, the LCDR1 of SEQ ID NOs: 88, 91, 93, 95, 97, 99, 101, or 102, the LCDR2 of SEQ ID NOs: 89 or 103, and the LCDR3 of SEQ ID NOs: 90, 92, 94, 96, 98, 100, or 15 104.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of

SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;

SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;

20 SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;

SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;

SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;

SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;

SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;

25 SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or

SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51.

30 In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61.

5 In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65.

10 In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

15 In some embodiments, the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In some embodiments, the first antigen binding domain that binds HLA-G comprises:

20 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 65;
25 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 55;
30 the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 65;

the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 53;
5 the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 63;
10 the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 53;
15 the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 63;
20 the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 53;
25 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 63;
30 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 53;

the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
5 the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 51;
10 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 61;
15 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 51;
20 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 61;
25 the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 69;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 51;
30 the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 61;

- the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 69;
5 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 59;
10 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 67; or
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 15 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.
- In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 248.
- 20 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 249.
- In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 250.
- In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 251.
- 25 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 252.
- In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 253.
- 30 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 254.
- In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 255.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 256.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 257.

5 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 258.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 259.

10 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 260.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 261.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 262.

15 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 263.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 264.

20 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 265.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 266.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 267.

25 In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 268.

In some embodiments, the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NO: 269.

30 In some embodiments, the second antigen binding domain that binds a lymphocyte antigen comprises the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370; the VH of SEQ ID NO: 339 and the VL of SEQ ID NOs: 340, 341, 342, 343, 344, or 345;

the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373; or the VH of SEQ ID NO: 346 or 348 and the VL of SEQ ID NO: 347 or 349.

5 In some embodiments, the first antigen binding domain that binds HLA-G is conjugated to a first immunoglobulin (Ig) constant region or a fragment of the first Ig constant region and/or the second antigen binding domain that binds the lymphocyte antigen is conjugated to a second immunoglobulin (Ig) constant region or a fragment of the second Ig constant region.

In some embodiments, the fragment of the first Ig constant region and/or the fragment of the second Ig constant region comprises a Fc region.

10 In some embodiments, the fragment of the first Ig constant region and/or the fragment of the second Ig constant region comprises a CH2 domain.

In some embodiments, the fragment of the first Ig constant region and/or the fragment of the second Ig constant region comprises a CH3 domain.

15 In some embodiments, the fragment of the first Ig constant region and/or the fragment of the second Ig constant region comprises the CH2 domain and the CH3 domain.

In some embodiments, the fragment of the first Ig constant region and/or the fragment of the second Ig constant region comprises at least portion of a hinge, the CH2 domain and the CH3 domain.

In some embodiments, the fragment of the Ig constant region comprises the hinge, the CH2 domain and the CH3 domain.

20 In some embodiments, the multispecific protein further comprises a second linker (L2) between the first antigen binding domain that binds HLA-G and the first Ig constant region or the fragment of the first Ig constant region and the second antigen binding domain that binds the lymphocyte antigen and the second Ig constant region or the fragment of the second Ig constant region.

25 In some embodiments, the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.

30 In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG1 isotype.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG2 isotype.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG3 isotype.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG4 isotype.

5 The first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region can further be engineered as described herein.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one
10 mutation that results in reduced binding of the multispecific protein to a Fc γ R.

In some embodiments, the at least one mutation that results in reduced binding of the multispecific protein to the Fc γ R is selected from the group consisting of L235A/D265S, F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/ P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/ L235A, N297A, V234A/G237A, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F,
15 L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index. In some embodiments, the at least one mutation that results in reduced binding of the multispecific protein to the Fc γ R is L234A/L235A/D265S.

20 In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in enhanced binding of the multispecific protein to a Fc γ receptor (Fc γ R).

In some embodiments, the at least one mutation that results in enhanced binding of the multispecific protein to the Fc γ R is selected from the group consisting of S239D/I332E,
25 S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.

In some embodiments, the Fc γ R is Fc γ RI, Fc γ RIIA, Fc γ RIIB or Fc γ RIII, or any combination thereof.

30 In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that modulates a half-life of the multispecific protein.

In some embodiments, the at least one mutation that modulates the half-life of the multispecific protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H,

M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.

In some embodiments, the multispecific protein comprises at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region.

In some embodiments, the at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.

In some embodiments, the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprise the following mutations

L235A_D265S_T350V_L351Y_F405A_Y407V in the first Ig constant region and
L235A_D265S_T350V_T366L_K392L_T394W in the second Ig constant region; or
L235A_D265S_T350V_T366L_K392L_T394W in the first Ig constant region and
L235A_D265S_T350V_L351Y_F405A_Y407V in the second Ig constant region.

Generation of multispecific proteins that comprise antigen binding fragments that bind HLA-G

The antigen binding fragments that bind HLA-G of the disclosure may be engineered into multispecific antibodies which are also encompassed within the scope of the invention.

The antigen binding fragments that bind HLA-G may be engineered into full length multispecific antibodies which are generated using Fab arm exchange, in which substitutions are introduced into two monospecific bivalent antibodies within the Ig constant region CH3 domain which promote Fab arm exchange *in vitro*. In the methods, two monospecific bivalent antibodies are engineered to have certain substitutions at the CH3 domain that promote heterodimer stability; the antibodies are incubated together under reducing conditions sufficient to allow the cysteines in the hinge region to undergo disulfide bond isomerization; thereby generating the bispecific antibody by Fab arm exchange. The incubation conditions may optimally be restored to non-reducing. Exemplary reducing agents that may be used are 2-mercaptoethylamine (2-MEA), dithiothreitol (DTT), dithioerythritol (DTE), glutathione, tris(2-

carboxyethyl)phosphine (TCEP), L-cysteine and beta-mercaptoethanol, preferably a reducing agent selected from the group consisting of: 2- mercaptoethylamine, dithiothreitol and tris(2-carboxyethyl)phosphine. For example, incubation for at least 90 min at a temperature of at least 20°C in the presence of at least 25 mM 2-MEA or in the presence of at least 0.5 mM dithiothreitol at a pH of from 5-8, for example at pH of 7.0 or at pH of 7.4 may be used.

CH3 mutations that may be used include technologies such as Knob-in-Hole mutations (Genentech), electrostatically-matched mutations (Chugai, Amgen, NovoNordisk, Oncomed), the Strand Exchange Engineered Domain body (SEEDbody) (EMD Serono), Duobody® mutations (Genmab), and other asymmetric mutations (e.g. Zymeworks).

Knob-in-hole mutations are disclosed for example in WO1996/027011 and include mutations on the interface of CH3 region in which an amino acid with a small side chain (hole) is introduced into the first CH3 region and an amino acid with a large side chain (knob) is introduced into the second CH3 region, resulting in preferential interaction between the first CH3 region and the second CH3 region. Exemplary CH3 region mutations forming a knob and a hole are T366Y/F405A, T366W/F405W, F405W/Y407A, T394W/Y407T, T394S/Y407A, T366W/T394S, F405W/T394S and T366W/T366S_L368A_Y407V.

Heavy chain heterodimer formation may be promoted by using electrostatic interactions by substituting positively charged residues on the first CH3 region and negatively charged residues on the second CH3 region as described in US2010/0015133, US2009/0182127, US2010/028637 or US2011/0123532.

Other asymmetric mutations that can be used to promote heavy chain heterodimerization are L351Y_F405A_Y407V/T394W, T366I_K392M_T394W/F405A_Y407V, T366L_K392M_T394W/F405A_Y407V, L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F, or T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W as described in US2012/0149876 or US2013/0195849 (Zymeworks).

SEEDbody mutations involve substituting select IgG residues with IgA residues to promote heavy chain heterodimerization as described in US20070287170.

Other exemplary mutations that may be used are R409D_K370E/D399K_E357K, S354C_T366W/Y349C_T366S_L368A_Y407V, Y349C_T366W/S354C_T366S_L368A_Y407V, T366K/L351D, L351K/Y349E, L351K/Y349D, L351K/L368E, L351Y_Y407A/T366A_K409F, L351Y_Y407A/T366V_K409F, K392D/D399K, K392D/E356K, K253E_D282K_K322D/D239K_E240K_K292D, K392D_K409D/D356K_D399K as described in WO2007/147901, WO 2011/143545, WO2013157954, WO2013096291 and US2018/0118849.

Duobody® mutations (Genmab) are disclosed for example in US9150663 and US2014/0303356 and include mutations F405L/K409R, wild-type/F405L_R409K, T350I_K370T_F405L/K409R, K370W/K409R, D399AFGHILMNRSTVWY/K409R, T366ADEF GHILMQVY/K409R, L368ADEGHNRSTVQ/K409AGRH, D399FHKRQ/K409AGRH, F405IKLSTVW/K409AGRH and
 5 Y407LWQ/K409AGRH.

Additional bispecific or multispecific structures into which the antigen binding domains that bind HLA-G can be incorporated include Dual Variable Domain Immunoglobulins (DVD) (Int. Pat. Publ. No. WO2009/134776; DVDs are full length antibodies comprising the heavy chain having a structure VH1-linker-VH2-CH and the light chain having the structure VL1-linker-VL2-CL; linker being optional),
 10 structures that include various dimerization domains to connect the two antibody arms with different specificity, such as leucine zipper or collagen dimerization domains (Int. Pat. Publ. No. WO2012/022811, U.S. Pat. No. 5,932,448; U.S. Pat. No. 6,833,441), two or more domain antibodies (dAbs) conjugated together, diabodies, heavy chain only antibodies such as camelid antibodies and engineered camelid antibodies, Dual Targeting (DT)-Ig (GSK/Domantis), Two-in-one Antibody (Genentech), Cross-linked
 15 Mabs (Karmanos Cancer Center), mAb2 (F-Star) and CovX-body (CovX/Pfizer), IgG-like Bispecific (InnClone/Eli Lilly), Ts2Ab (MedImmune/AZ) and BsAb (Zymogenetics), HERCULES (Biogen Idec) and TvAb (Roche), ScFv/Fc Fusions (Academic Institution), SCORPION (Emergent BioSolutions/Trubion, Zymogenetics/BMS), Dual Affinity Retargeting Technology (Fc-DART) (MacroGenics) and Dual(ScFv)₂-Fab (National Research Center for Antibody Medicine--China), Dual-
 20 Action or Bis-Fab (Genentech), Dock-and-Lock (DNL) (ImmunoMedics), Bivalent Bispecific (Biotecnol) and Fab-Fv (UCB-Celltech). ScFv-, diabody-based, and domain antibodies, include but are not limited to, Bispecific T Cell Engager (BiTE) (Micromet), Tandem Diabody (Tandab) (Affimed), Dual Affinity Retargeting Technology (DART) (MacroGenics), Single-chain Diabody (Academic), TCR-like Antibodies (AIT, ReceptorLogics), Human Serum Albumin ScFv Fusion (Merrimack) and COMBODY
 25 (Epigen Biotech), dual targeting nanobodies (Ablynx), dual targeting heavy chain only domain antibodies.

The antigen binding domains that bind HLA-G of the disclosure may also be engineered into multispecific proteins which comprise three polypeptide chains. In such designs, at least one antigen binding domain is in the form of a scFv. Exemplary designs include (in which “1” indicates the first
 30 antigen binding domain, “2” indicates the second antigen binding domain and “3” indicates the third antigen binding domain:

Design 1: Chain A) scFv1- CH2-CH3; Chain B) VL2-CL; Chain C) VH2-CH1-hinge-CH2-CH3

Design 2: Chain A) scFv1- hinge- CH2-CH3; Chain B) VL2-CL; Chain C) VH2-CH1-hinge-CH2-CH3

Design 3: Chain A) scFv1- CH1-hinge- CH2-CH3; Chain B) VL2-CL; Chain C) VH2-CH1-hinge-CH2-CH3

Design 4: Chain A) CH2-CH3-scFv1; Chain B) VL2-CL; Chain C) VH2-CH1-hinge-CH2-CH3

CH3 engineering may be incorporated to the Designs 1-4, such as mutations

5 L351Y_F405A_Y407V/T394W, T366L_K392M_T394W/F405A_Y407V,
T366L_K392M_T394W/F405A_Y407V, L351Y_Y407A/T366A_K409F,
L351Y_Y407A/T366V_K409F, Y407A/T366A_K409F, or
T350V_L351Y_F405A_Y407V/T350V_T366L_K392L_T394W as described in US2012/0149876 or
US2013/0195849 (Zymeworks).

10

Isotypes, allotypes and Fc engineering

The Ig constant region or the fragment of the Ig constant region, such as the Fc region present in the proteins of the disclosure may be of any allotype or isotype.

15 In some embodiments, the Ig constant region or the fragment of the Ig constant region is an IgG1 isotype.

In some embodiments, the Ig constant region or the fragment of the Ig constant region is an IgG2 isotype.

In some embodiments, the Ig constant region or the fragment of the Ig constant region is an IgG3 isotype.

20 In some embodiments, the Ig constant region or the fragment of the Ig constant region is an IgG4 isotype.

The Ig constant region or the fragment of the Ig constant region may be of any allotype. It is expected that allotype has no influence on properties of the Ig constant region, such as binding or Fc-mediated effector functions. Immunogenicity of therapeutic proteins comprising Ig constant regions of fragments thereof is associated with increased risk of infusion reactions and decreased duration of therapeutic response (Baert *et al.*, (2003) *N Engl J Med* 348:602-08). The extent to which therapeutic proteins comprising Ig constant regions of fragments thereof induce an immune response in the host may be determined in part by the allotype of the Ig constant region (Stickler *et al.*, (2011) *Genes and Immunity* 12:213-21). Ig constant region allotype is related to amino acid sequence variations at specific locations
30 in the constant region sequences of the antibody. Table 3 shows select IgG1, IgG2 and IgG4 allotypes.

Table 3.

Allotype	Amino acid residue at position of diversity (residue numbering: EU Index)							
	IgG2		IgG4		IgG1			
	189	282	309	422	214	356	358	431
G2m(n)	T	M						
G2m(n-)	P	V						
G2m(n)/(n-)	T	V						
nG4m(a)			L	R				
G1m(17)					K	E	M	A
G1m(17,1)					K	D	L	A
G1m(3)					R	E	M	A

C-terminal lysine (CTL) may be removed from the Ig constant region by endogenous circulating carboxypeptidases in the blood stream (Cai *et al.*, (2011) *Biotechnol Bioeng* 108:404-412). During manufacturing, CTL removal may be controlled to less than the maximum level by control of concentration of extracellular Zn^{2+} , EDTA or EDTA – Fe^{3+} as described in U.S. Patent Publ. No. US20140273092. CTL content of proteins may be measured using known methods.

In some embodiments, the antigen binding fragment that binds HLA-G conjugated to the Ig constant region has a C-terminal lysine content from about 10% to about 90%. In some embodiments, the C-terminal lysine content is from about 20% to about 80%. In some embodiments, the C-terminal lysine content is from about 40% to about 70%. In some embodiments, the C-terminal lysine content is from about 55% to about 70%. In some embodiments, the C-terminal lysine content is about 60%.

Fc region mutations may be made to the antigen binding domains that bind HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region to modulate their effector functions such as ADCC, ADCP and/or ADCC and/or pharmacokinetic properties. This may be achieved by introducing mutation(s) into the Fc that modulate binding of the mutated Fc to activating $Fc\gamma R$ s ($Fc\gamma RI$, $Fc\gamma RIIa$, $Fc\gamma RIII$), inhibitory $Fc\gamma RIIb$ and/or to $FcRn$.

In some embodiments, the antigen binding domain that binds HLA-Gs conjugated to the Ig constant region or the fragment of the Ig constant region comprises at least one mutation in the Ig constant region or in the fragment of the Ig constant region.

In some embodiments, the at least one mutation is in the Fc region.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen or fifteen mutations in the Fc region.

In some embodiments, the antigen binding domain that binds HLA-Gs conjugated to the Ig constant region or to the fragment of the Ig constant region comprises at least one mutation in the Fc region that modulates binding of the antibody to FcRn.

Fc positions that may be mutated to modulate half-life (e.g. binding to FcRn) include positions 250, 252, 253, 254, 256, 257, 307, 376, 380, 428, 434 and 435. Exemplary mutations that may be made singularly or in combination are mutations T250Q, M252Y, I253A, S254T, T256E, P257I, T307A, D376V, E380A, M428L, H433K, N434S, N434A, N434H, N434F, H435A and H435R. Exemplary singular or combination mutations that may be made to increase the half-life are mutations M428L/N434S, M252Y/S254T/T256E, T250Q/M428L, N434A and T307A/E380A/N434A. Exemplary singular or combination mutations that may be made to reduce the half-life are mutations H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises M252Y/S254T/T256E mutation.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises at least one mutation in the Fc region that reduces binding of the protein to an activating Fcγ receptor (FcγR) and/or reduces Fc effector functions such as C1q binding, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) or phagocytosis (ADCP).

Fc positions that may be mutated to reduce binding of the protein to the activating FcγR and subsequently to reduce effector function include positions 214, 233, 234, 235, 236, 237, 238, 265, 267, 268, 270, 295, 297, 309, 327, 328, 329, 330, 331 and 365. Exemplary mutations that may be made singularly or in combination are mutations K214T, E233P, L234V, L234A, deletion of G236, V234A, F234A, L235A, G237A, P238A, P238S, D265A, S267E, H268A, H268Q, Q268A, N297A, A327Q, P329A, D270A, Q295A, V309L, A327S, L328F, A330S and P331S in IgG1, IgG2, IgG3 or IgG4. Exemplary combination mutations that result in proteins with reduced ADCC are mutations L234A/L235A on IgG1, L234A/L235A/D265S on IgG1, V234A/G237A/P238S/H268A/V309L/A330S/P331S on IgG2, F234A/L235A on IgG4, S228P/F234A/L235A on IgG4, N297A on all Ig isotypes, V234A/G237A on IgG2, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M on IgG1, H268Q/V309L/A330S/P331S on IgG2, S267E/L328F on IgG1, L234F/L235E/D265A on IgG1, L234A/L235A/G237A/P238S/H268A/A330S/P331S on IgG1, S228P/F234A/L235A/G237A/P238S on IgG4, and S228P/F234A/L235A/G236-deleted/G237A/P238S on IgG4. Hybrid IgG2/4 Fc domains may also be used, such as Fc with residues 117-260 from IgG2 and residues 261-447 from IgG4.

Exemplary mutation that result in proteins with reduced CDC is a K322A mutation.

Well-known S228P mutation may be made in IgG4 to enhance IgG4 stability.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises at least one mutation selected from the group consisting of K214T, E233P, L234V, L234A, deletion of G236, V234A, F234A, L235A, G237A, P238A, P238S, D265A, S267E, H268A, H268Q, Q268A, N297A, A327Q, P329A, D270A, Q295A, V309L, A327S, L328F, K322, A330S and P331S.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises L234A/L235A/D265S mutation.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises L234A/L235A mutation.

In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region comprises at least one mutation in the Fc region that enhances binding of the protein to an Fcγ receptor (FcγR) and/or enhances Fc effector functions such as C1q binding, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and/or phagocytosis (ADCP).

Fc positions that may be mutated to increase binding of the protein to the activating FcγR and/or enhance Fc effector functions include positions 236, 239, 243, 256, 290, 292, 298, 300, 305, 312, 326, 330, 332, 333, 334, 345, 360, 339, 378, 396 or 430 (residue numbering according to the EU index).

Exemplary mutations that may be made singularly or in combination are G236A, S239D, F243L, T256A, K290A, R292P, S298A, Y300L, V305L, K326A, A330K, I332E, E333A, K334A, A339T and P396L. Exemplary combination mutations that result in proteins with increased ADCC or ADCP are a S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305L/P396L and G236A/S239D/I332E.

Fc positions that may be mutated to enhance CDC include positions 267, 268, 324, 326, 333, 345 and 430. Exemplary mutations that may be made singularly or in combination are S267E, F1268F, S324T, K326A, K326W, E333A, E345K, E345Q, E345R, E345Y, E430S, E430F and E430T. Exemplary combination mutations that result in proteins with increased CDC are K326A/E333A, K326W/E333A, H268F/S324T, S267E/H268F, S267E/S324T and S267E/H268F/S324T.

The specific mutations described herein are mutations when compared to the IgG1, IgG2 and IgG4 wild-type amino acid sequences of SEQ ID NOs: 130, 131 and 132, respectively.

SEQ ID NO: 486, wild-type IgG1

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG

PSVFLFPPKPKDTLMISRT

PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN

STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK

GQPREPQVYTLPPSRDE

- 5 LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 487; wild-type IgG2

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

- 10 GLYSLSSVTVTPSSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECPPCAPPVAGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDISVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

15

SEQ ID NO: 488; wild-type IgG4

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS

GLYSLSSVTVTPSSSLGKTYTCNVDHKPSNTKVDKRVESKYGPCCPSCPAPEFLGGPSV

FLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY

- 20 RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSPGK

- 25 Binding of the antibody to FcγR or FcRn may be assessed on cells engineered to express each
receptor using flow cytometry. In an exemplary binding assay, 2×10^5 cells per well are seeded in 96-well
plate and blocked in BSA Stain Buffer (BD Biosciences, San Jose, USA) for 30 min at 4°C. Cells are
incubated with a test antibody on ice for 1.5 hour at 4°C. After being washed twice with BSA stain
buffer, the cells are incubated with R-PE labeled anti-human IgG secondary antibody (Jackson
Immunoresearch Laboratories) for 45 min at 4°C. The cells are washed twice in stain buffer and then
30 resuspended in 150 μL of Stain Buffer containing 1:200 diluted DRAQ7 live/dead stain (Cell Signaling
Technology, Danvers, USA). PE and DRAQ7 signals of the stained cells are detected by Miltenyi
MACSQuant flow cytometer (Miltenyi Biotec, Auburn, USA) using B2 and B4 channel
respectively. Live cells are gated on DRAQ7 exclusion and the geometric mean
fluorescence signals are determined for at least 10,000 live events collected. FlowJo

software (Tree Star) is used for analysis. Data is plotted as the logarithm of antibody concentration versus mean fluorescence signals. Nonlinear regression analysis is performed.

Glycoengineering

- 5 The ability of the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region to mediate ADCC can be enhanced by engineering the Ig constant region or the fragment of the Ig constant region oligosaccharide component. Human IgG1 or IgG3 are N-glycosylated at Asn297 with the majority of the glycans in the well-known biantennary G0, G0F, G1, G1F, G2 or G2F forms. Ig constant region containing proteins may be produced by non-
- 10 engineered CHO cells typically have a glycan fucose content of about at least 85%. The removal of the core fucose from the biantennary complex-type oligosaccharides attached to the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region enhances the ADCC of the protein via improved FcγRIIIa binding without altering antigen binding or CDC activity. Such proteins can be achieved using different methods reported to lead to the successful
- 15 expression of relatively high defucosylated immunoglobulins bearing the biantennary complex-type of Fc oligosaccharides such as control of culture osmolality (Konno *et al.*, *Cytotechnology* 64(249-65, 2012), application of a variant CHO line Lec13 as the host cell line (Shields *et al.*, *J Biol Chem* 277:26733-26740, 2002), application of a variant CHO line EB66 as the host cell line (Olivier *et al.*, *MAbs* 2(4): 405-415, 2010; PMID:20562582), application of a rat hybridoma cell line YB2/0 as the host cell line
- 20 (Shinkawa *et al.*, *J Biol Chem* 278:3466-3473, 2003), introduction of small interfering RNA specifically against the α 1,6-fucosyltransferase (*FUT8*) gene (Mori *et al.*, *Biotechnol Bioeng* 88:901-908, 2004), or coexpression of β -1,4-N-acetylglucosaminyltransferase III and Golgi α -mannosidase II or a potent α -mannosidase I inhibitor, kifunensine (Ferrara *et al.*, *J Biol Chem* 281:5032-5036, 2006, Ferrara *et al.*, *Biotechnol Bioeng* 93:851-861, 2006; Xhou *et al.*, *Biotechnol Bioeng* 99:652-65, 2008).
- 25 In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region of the disclosure has a biantennary glycan structure with fucose content of about between 1% to about 15%, for example about 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1%. In some embodiments, the antigen binding domain that binds HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant
- 30 region has a glycan structure with fucose content of about 50%, 40%, 45%, 40%, 35%, 30%, 25%, or 20%.

“Fucose content” means the amount of the fucose monosaccharide within the sugar chain at Asn297. The relative amount of fucose is the percentage of fucose-containing structures related to all glycostructures. These may be characterized and quantified by multiple methods, for example: 1) using

MALDI-TOF of N-glycosidase F treated sample (e.g. complex, hybrid and oligo- and high-mannose structures) as described in Int Pat. Publ. No. WO2008/077546 2); 2) by enzymatic release of the Asn297 glycans with subsequent derivatization and detection/ quantitation by HPLC (UPLC) with fluorescence detection and/or HPLC-MS (UPLC-MS); 3) intact protein analysis of the native or reduced mAb, with or without treatment of the Asn297 glycans with Endo S or other enzyme that cleaves between the first and the second GlcNAc monosaccharides, leaving the fucose attached to the first GlcNAc; 4) digestion of the mAb to constituent peptides by enzymatic digestion (e.g., trypsin or endopeptidase Lys-C), and subsequent separation, detection and quantitation by HPLC-MS (UPLC-MS); 5) Separation of the mAb oligosaccharides from the mAb protein by specific enzymatic deglycosylation with PNGase F at Asn 297. The oligosaccharides thus released can be labeled with a fluorophore, separated and identified by various complementary techniques which allow: fine characterization of the glycan structures by matrix-assisted laser desorption ionization (MALDI) mass spectrometry by comparison of the experimental masses with the theoretical masses, determination of the degree of sialylation by ion exchange HPLC (GlycoSep C), separation and quantification of the oligosaccharide forms according to hydrophilicity criteria by normal-phase HPLC (GlycoSep N), and separation and quantification of the oligosaccharides by high performance capillary electrophoresis-laser induced fluorescence (HPCE-LIF).

“Low fucose” or “low fucose content” as used herein refers to the antigen binding domain that bind HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region with fucose content of about between 1%-15%.

“Normal fucose” or “normal fucose content” as used herein refers to the antigen binding domain that bind HLA-G conjugated to the Ig constant region or to the fragment of the Ig constant region with fucose content of about over 50%, typically about over 80% or over 85%.

Anti-idiotypic antibodies

Anti-idiotypic antibodies are antibodies that specifically bind to the antigen binding domain that binds HLA-G of the disclosure.

The invention also provides an anti-idiotypic antibody that specifically binds to the antigen binding domain that binds HLA-G of the disclosure.

The invention also provides an anti-idiotypic antibody that specifically binds to the antigen binding domain that binds HLA-G comprising

- the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
- the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
- the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
- the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;

the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
5 the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

An anti-idiotypic (Id) antibody is an antibody which recognizes the antigenic determinants (*e.g.* the paratope or CDRs) of the antibody. The Id antibody may be antigen-blocking or non-blocking. The antigen-blocking Id may be used to detect the free antigen binding domain in a sample (*e.g.* the antigen
10 binding domain that binds HLA-G of the disclosure). The non-blocking Id may be used to detect the total antibody (free, partially bound to antigen, or fully bound to antigen) in a sample. An Id antibody may be prepared by immunizing an animal with the antibody to which an anti-Id is being prepared.

An anti-Id antibody may also be used as an immunogen to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody. An anti-anti-Id may be epitopically identical
15 to the original antigen binding domain which induced the anti-Id. Thus, by using antibodies to the idiotypic determinants of the antigen binding domain, it is possible to identify other clones expressing antigen binding domains of identical specificity. Anti-Id antibodies may be varied (thereby producing anti-Id antibody variants) and/or derivatized by any suitable technique, such as those described elsewhere herein.

20

Immunoconjugates

The antigen binding domains that bind HLA-G of the disclosure, the proteins comprising the antigen binding domains that bind HLA-G or the multispecific proteins that comprise the antigen binding domains that bind HLA-G (collectively referred herein as to HLA-G binding proteins) may be conjugated
25 to a heterologous molecule. .

In some embodiments, the heterologous molecule is a detectable label or a cytotoxic agent.

The invention also provides an antigen binding domain that binds HLA-G conjugated to a detectable label.

The invention also provides a protein comprising an antigen binding domain that binds HLA-G
30 conjugated to a detectable label.

The invention also provides a multispecific protein comprising an antigen binding domain that binds HLA-G conjugated to a detectable label.

The invention also provides an antigen binding domain that binds HLA-G conjugated to a cytotoxic agent.

The invention also provides a protein comprising an antigen binding domain that binds HLA-G conjugated to a cytotoxic agent.

The invention also provides a multispecific protein comprising an antigen binding domain that binds HLA-G conjugated to a cytotoxic agent.

5 HLA-G binding proteins of the disclosure may be used to direct therapeutics to HLA-G expressing cells, such as prostate or breast cancer cells. Alternatively, HLA-G expressing cells may be targeted with a HLA-G binding protein of the disclosure coupled to a therapeutic intended to modify cell function once internalized.

In some embodiments, the detectable label is also a cytotoxic agent.

10 The HLA-G binding proteins of the disclosure conjugated to a detectable label may be used to evaluate expression of HLA-G on a variety of samples.

Detectable label includes compositions that when conjugated to the HLA-G binding proteins of the disclosure renders the latter detectable, via spectroscopic, photochemical, biochemical, immunochemical, or chemical means.

15 Exemplary detectable labels include radioactive isotopes, magnetic beads, metallic beads, colloidal particles, fluorescent dyes, electron-dense reagents, enzymes (for example, as commonly used in an ELISA), biotin, digoxigenin, haptens, luminescent molecules, chemiluminescent molecules, fluorochromes, fluorophores, fluorescent quenching agents, colored molecules, radioactive isotopes, scintillates, avidin, streptavidin, protein A, protein G, antibodies or fragments thereof, polyhistidine, Ni^{2+} ,
20 Flag tags, myc tags, heavy metals, enzymes, alkaline phosphatase, peroxidase, luciferase, electron donors/acceptors, acridinium esters, and colorimetric substrates.

A detectable label may emit a signal spontaneously, such as when the detectable label is a radioactive isotope. In other cases, the detectable label emits a signal as a result of being stimulated by an external field.

25 Exemplary radioactive isotopes may be γ -emitting, Auger-emitting, β -emitting, an alpha-emitting or positron-emitting radioactive isotope. Exemplary radioactive isotopes include ^3H , ^{11}C , ^{13}C , ^{15}N , ^{18}F , ^{19}F , ^{55}Co , ^{57}Co , ^{60}Co , ^{61}Cu , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{68}Ga , ^{72}As , ^{75}Br , ^{86}Y , ^{89}Zr , ^{90}Sr , $^{94\text{m}}\text{Tc}$, $^{99\text{m}}\text{Tc}$, ^{115}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{211}At , ^{212}Bi , ^{213}Bi , ^{223}Ra , ^{226}Ra , ^{225}Ac and ^{227}Ac .

30 Exemplary metal atoms are metals with an atomic number greater than 20, such as calcium atoms, scandium atoms, titanium atoms, vanadium atoms, chromium atoms, manganese atoms, iron atoms, cobalt atoms, nickel atoms, copper atoms, zinc atoms, gallium atoms, germanium atoms, arsenic atoms, selenium atoms, bromine atoms, krypton atoms, rubidium atoms, strontium atoms, yttrium atoms, zirconium atoms, niobium atoms, molybdenum atoms, technetium atoms, ruthenium atoms, rhodium atoms, palladium atoms, silver atoms, cadmium atoms, indium atoms, tin atoms, antimony atoms,

tellurium atoms, iodine atoms, xenon atoms, cesium atoms, barium atoms, lanthanum atoms, hafnium atoms, tantalum atoms, tungsten atoms, rhenium atoms, osmium atoms, iridium atoms, platinum atoms, gold atoms, mercury atoms, thallium atoms, lead atoms, bismuth atoms, francium atoms, radium atoms, actinium atoms, cerium atoms, praseodymium atoms, neodymium atoms, promethium atoms, samarium atoms, europium atoms, gadolinium atoms, terbium atoms, dysprosium atoms, holmium atoms, erbium atoms, thulium atoms, ytterbium atoms, lutetium atoms, thorium atoms, protactinium atoms, uranium atoms, neptunium atoms, plutonium atoms, americium atoms, curium atoms, berkelium atoms, californium atoms, einsteinium atoms, fermium atoms, mendelevium atoms, nobelium atoms, or lawrencium atoms.

10 In some embodiments, the metal atoms may be alkaline earth metals with an atomic number greater than twenty.

In some embodiments, the metal atoms may be lanthanides.

In some embodiments, the metal atoms may be actinides.

In some embodiments, the metal atoms may be transition metals.

15 In some embodiments, the metal atoms may be poor metals.

In some embodiments, the metal atoms may be gold atoms, bismuth atoms, tantalum atoms, and gadolinium atoms.

In some embodiments, the metal atoms may be metals with an atomic number of 53 (i.e. iodine) to 83 (i.e. bismuth).

20 In some embodiments, the metal atoms may be atoms suitable for magnetic resonance imaging.

The metal atoms may be metal ions in the form of +1, +2, or +3 oxidation states, such as Ba^{2+} , Bi^{3+} , Cs^+ , Ca^{2+} , Cr^{2+} , Cr^{3+} , Cr^{6+} , Co^{2+} , Co^{3+} , Cu^+ , Cu^{2+} , Cu^{3+} , Ga^{3+} , Gd^{3+} , Au^+ , Au^{3+} , Fe^{2+} , Fe^{3+} , F^{3+} , Pb^{2+} , Mn^{2+} , Mn^{3+} , Mn^{4+} , Mn^{7+} , Hg^{2+} , Ni^{2+} , Ni^{3+} , Ag^+ , Sr^{2+} , Sn^{2+} , Sn^{4+} , and Zn^{2+} . The metal atoms may comprise a metal oxide, such as iron oxide, manganese oxide, or gadolinium oxide.

25 Suitable dyes include any commercially available dyes such as, for example, 5(6)-carboxyfluorescein, IRDye 680RD maleimide or IRDye 800CW, ruthenium polypyridyl dyes, and the like.

Suitable fluorophores are fluorescein isothiocyanate (FITC), fluorescein thiosemicarbazide, rhodamine, Texas Red, CyDyes (e.g., Cy3, Cy5, Cy5.5), Alexa Fluors (e.g., Alexa488, Alexa555, Alexa594; Alexa647), near infrared (NIR) (700-900 nm) fluorescent dyes, and carbocyanine and aminostyryl dyes.

30 The antigen binding domain that binds HLA-G conjugated to a detectable label may be used as an imaging agent.

The protein comprising an antigen binding domain that binds HLA-G conjugated to a detectable label may be used as an imaging agent.

The multispecific protein comprising an antigen binding domain that binds HLA-G conjugated to a detectable label may be used as an imaging agent.

5 In some embodiments, the cytotoxic agent is a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

In some embodiments, the cytotoxic agent is daunomycin, doxorubicin, methotrexate, vindesine, bacterial toxins such as diphtheria toxin, ricin, geldanamycin, maytansinoids or calicheamicin. The
10 cytotoxic agent may elicit their cytotoxic and cytostatic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition.

In some embodiments, the cytotoxic agent is an enzymatically active toxin such as diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modecein A chain, alpha-sarcin, *Aleurites fordii* proteins,
15 dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *momordica charantia* inhibitor, curcin, crotin, *sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

In some embodiments, the cytotoxic agent is a radionuclide, such as ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

20 In some embodiments, the cytotoxic agent is dolastatins or dolostatin peptidic analogs and derivatives, auristatin or monomethyl auristatin phenylalanine. Exemplary molecules are disclosed in U.S. Pat No. 5,635,483 and 5,780,588. Dolastatins and auristatins have been shown to interfere with microtubule dynamics, GTP hydrolysis, and nuclear and cellular division (Woyke et al (2001) Antimicrob Agents and Chemother. 45(12):3580-3584) and have anticancer and antifungal activity. The dolastatin or
25 auristatin drug moiety may be attached to the antibody of the invention through the N (amino) terminus or the C (carboxyl) terminus of the peptidic drug moiety (WO02/088172), or via any cysteine engineered into the antibody.

The HLA-G binding proteins of the disclosure may be conjugated to a detectable label using known methods.

30 In some embodiments, the detectable label is complexed with a chelating agent.

In some embodiments, the detectable label is conjugated to the HLA-G binding proteins of the disclosure via a linker.

The detectable label or the cytotoxic moiety may be linked directly, or indirectly, to the HLA-G binding proteins of the disclosure using known methods. Suitable linkers are known in the art and

include, for example, prosthetic groups, non-phenolic linkers (derivatives of N-succinimidyl-benzoates; dodecaborate), chelating moieties of both macrocyclics and acyclic chelators, such as derivatives of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), derivatives of diethylenetriaminepentaacetic acid (DTPA), derivatives of S-2-(4-Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and derivatives of 1,4,8,11-tetraazacyclododecane-1,4,8,11-tetraacetic acid (TETA), N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis-(p-azidobenzoyl)hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene) and other chelating moieties. Suitable peptide linkers are well known.

In some embodiments, the HLA-G binding proteins of the disclosure is removed from the blood via renal clearance.

15

Kits

The invention also provides a kit comprising the antigen binding domain that binds HLA-G.

The invention also provides a kit comprising the protein comprising an antigen binding domain that binds HLA-G.

20 The invention also provides a kit comprising the multispecific protein comprising an antigen binding domain that binds HLA-G.

The kit may be used for therapeutic uses and as diagnostic kits.

The kit may be used to detect the presence of HLA-G in a sample.

25 In some embodiments, the kit comprises the HLA-G binding protein of the disclosure and reagents for detecting the HLA-G binding protein. The kit can include one or more other elements including: instructions for use; other reagents, e.g., a label, a therapeutic agent, or an agent useful for chelating, or otherwise coupling, an antibody to a label or therapeutic agent, or a radioprotective composition; devices or other materials for preparing the antibody for administration; pharmaceutically acceptable carriers; and devices or other materials for administration to a subject.

30 In some embodiments, the kit comprises the antigen binding domain that binds HLA-G in a container and instructions for use of the kit.

In some embodiments, the kit comprises the protein comprising an antigen binding domain that binds HLA-G in a container and instructions for use of the kit.

In some embodiments, the kit comprises the multispecific protein comprising an antigen binding domain that binds HLA-G in a container and instructions for use of the kit.

In some embodiments, the antigen binding domain that binds HLA-G in the kit is labeled.

In some embodiments, the protein comprising an antigen binding domain that binds HLA-G in the kit is labeled.

In some embodiments, the multispecific protein comprising an antigen binding domain that binds HLA-G in the kit is labeled.

In some embodiments, the kit comprises the antigen binding domain that binds HLA-G comprising

- 10 the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
15 the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

- 20 In some embodiments, the kit comprises the antigen binding domain that binds HLA-G comprising SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

Methods of detecting HLA-G

- 25 The invention also provides a method of detecting HLA-G in a sample, comprising obtaining the sample, contacting the sample with the antigen binding domain that binds HLA-G of the disclosure and detecting the bound HLA-G in the sample.

- In some embodiments, the sample may be derived from urine, blood, serum, plasma, saliva, ascites, circulating cells, synovial fluid, circulating cells, cells that are not tissue associated (*i.e.*, free cells), tissues (*e.g.*, surgically resected tissue, biopsies, including fine needle aspiration), histological preparations, and the like.

The antigen binding domain that binds HLA-G of the disclosure may be detected using known methods. Exemplary methods include direct labeling of the antibodies using fluorescent or chemiluminescent labels, or radiolabels, or attaching to the antibodies of the invention a moiety which is

readily detectable, such as biotin, enzymes or epitope tags. Exemplary labels and moieties are ruthenium, ^{111}In -DOTA, ^{111}In - diethylenetriaminepentaacetic acid (DTPA), horseradish peroxidase, alkaline phosphatase and beta-galactosidase, poly-histidine (HIS tag), acridine dyes, cyanine dyes, fluorone dyes, oxazin dyes, phenanthridine dyes, rhodamine dyes and Alexafluor® dyes.

5 The antigen binding domain that binds HLA-G of the disclosure may be used in a variety of assays to detect HLA-G in the sample. Exemplary assays are western blot analysis, radioimmunoassay, surface plasmon resonance, immunoprecipitation, equilibrium dialysis, immunodiffusion, electrochemiluminescence (ECL) immunoassay, immunohistochemistry, fluorescence-activated cell sorting (FACS) or ELISA assay.

10

Polynucleotides, vectors, host cells

 The disclosure also provides an isolated polynucleotide encoding any of the HLA-G binding proteins of the disclosure. The HLA-G binding protein includes the antigen binding domains that bind HLA-G, the proteins comprising the antigen binding domains that bind HLA-G, the multispecific proteins
15 that comprise the antigen binding domains that bind HLA-G of the disclosure.

 The invention also provides an isolated polynucleotide encoding any of HLA-G binding proteins or fragments thereof.

 The invention also provides an isolated polynucleotide encoding the VH of SEQ ID NO: 50.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 51.
20 The invention also provides an isolated polynucleotide encoding the VH of SEQ ID NO: 52.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 53.
 The invention also provides an isolated polynucleotide encoding the VH of SEQ ID NO: 54.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 55.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 56.
25 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 57.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 58.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 59.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 60.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 61.
30 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 62.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 63.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 64.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 65.
 The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 66.

The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 67.

The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 68.

The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NO: 69.

5 The invention also provides an isolated polynucleotide encoding the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68.

The invention also provides an isolated polynucleotide encoding the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

The invention also provides an isolated polynucleotide encoding the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

10 The invention also provides for an isolated polynucleotide encoding

the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;

the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;

the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;

the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;

15 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;

the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;

the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;

the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;

the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or

20 the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NOs: SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

25 The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO: 248.

The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO: 249.

The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO: 250.

30 The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO: 251.

The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO: 252.

253. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
254. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
5 255. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
256. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
10 257. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
258. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
259. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
15 260. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
261. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
20 262. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
263. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
264. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
25 265. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
266. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
267. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
30 268. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:
269. The invention also provides an isolated polynucleotide encoding the polypeptide of SEQ ID NO:

Some embodiments of the disclosure also provide an isolated or purified nucleic acid comprising a polynucleotide which is complementary to the polynucleotides encoding the HLA-G binding proteins of the disclosure or polynucleotides which hybridize under stringent conditions to the polynucleotides encoding the HLA-G binding proteins of the disclosure.

5 The polynucleotides which hybridize under stringent conditions may hybridize under high stringency conditions. By "high stringency conditions" is meant that the polynucleotide specifically hybridizes to a target sequence (the nucleotide sequence of any of the nucleic acids described herein) in an amount that is detectably stronger than non-specific hybridization. High stringency conditions include conditions which would distinguish a polynucleotide with an exact complementary sequence, or one
10 containing only a few scattered mismatches from a random sequence that happened to have a few small regions (e.g., 3-12 bases) that matched the nucleotide sequence. Such small regions of complementarity are more easily melted than a full-length complement of 14-17 or more bases, and high stringency hybridization makes them easily distinguishable. Relatively high stringency conditions would include, for example, low salt and/or high temperature conditions, such as provided by about 0.02-0.1 M NaCl or the
15 equivalent, at temperatures of about 50-70° C. Such high stringency conditions tolerate little, if any, mismatch between the nucleotide sequence and the template or target strand. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

The polynucleotide sequences of the disclosure may be operably linked to one or more regulatory elements, such as a promoter or enhancer, that allow expression of the nucleotide sequence in the
20 intended host cell. The polynucleotide may be a cDNA. The promoter may be a strong, weak, tissue-specific, inducible or developmental-specific promoter. Exemplary promoters that may be used are hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin, human myosin, human hemoglobin, human muscle creatine, and others. In addition, many viral promoters function constitutively in eukaryotic cells and are suitable for use with the described
25 embodiments. Such viral promoters include Cytomegalovirus (CMV) immediate early promoter, the early and late promoters of SV40, the Mouse Mammary Tumor Virus (MMTV) promoter, the long terminal repeats (LTRs) of Moloney leukemia virus, Human Immunodeficiency Virus (HIV), Epstein Barr Virus (EBV), Rous Sarcoma Virus (RSV), and other retroviruses, and the thymidine kinase promoter of Herpes Simplex Virus. Inducible promoters such as the metallothionein promoter, tetracycline-
30 inducible promoter, doxycycline-inducible promoter, promoters that contain one or more interferon-stimulated response elements (ISRE) such as protein kinase R 2',5'-oligoadenylate synthetases, Mx genes, ADAR1, and the like may also be used.

The invention also provides a vector comprising the polynucleotide of the invention. The disclosure also provide an expression vector comprising the polynucleotide of the invention. Such

vectors may be plasmid vectors, viral vectors, vectors for baculovirus expression, transposon based vectors or any other vector suitable for introduction of the synthetic polynucleotide of the invention into a given organism or genetic background by any means. Polynucleotides encoding the HLA-G binding proteins of the disclosure may be operably linked to control sequences in the expression vector(s) that ensure the expression of the HLA-G binding proteins. Such regulatory elements may include a transcriptional promoter, sequences encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. Expression vectors may also include one or more nontranscribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, other 5' or 3' flanking nontranscribed sequences, 5' or 3' nontranslated sequences (such as necessary ribosome binding sites), a polyadenylation site, splice donor and acceptor sites, or transcriptional termination sequences. An origin of replication that confers the ability to replicate in a host may also be incorporated.

The expression vectors can comprise naturally-occurring or non-naturally-occurring internucleotide linkages, or both types of linkages. The non-naturally occurring or altered nucleotides or internucleotide linkages do not hinder the transcription or replication of the vector.

Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the HLA-G binding proteins of the disclosure encoded by the incorporated polynucleotides. The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. Exemplary vectors may be constructed as described by Okayama and Berg, 3 *Mol. Cell. Biol.* 280 (1983).

Vectors of the disclosure may also contain one or more Internal Ribosome Entry Site(s) (IRES). Inclusion of an IRES sequence into fusion vectors may be beneficial for enhancing expression of some proteins. In some embodiments, the vector system will include one or more polyadenylation sites (e.g., SV40), which may be upstream or downstream of any of the aforementioned nucleic acid sequences. Vector components may be contiguously linked or arranged in a manner that provides optimal spacing for expressing the gene products (i.e., by the introduction of "spacer" nucleotides between the ORFs) or positioned in another way. Regulatory elements, such as the IRES motif, may also be arranged to provide optimal spacing for expression.

Vectors of the disclosure may be circular or linear. They may be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, e.g., from ColE1, SV40, 2 μ plasmid, λ , bovine papilloma virus, and the like.

The recombinant expression vectors can be designed for either transient expression, for stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression.

Further, the recombinant expression vectors can be made to include a suicide gene. As used herein, the term “suicide gene” refers to a gene that causes the cell expressing the suicide gene to die. The suicide gene can be a gene that confers sensitivity to an agent, e.g., a drug, upon the cell in which the gene is expressed, and causes the cell to die when the cell is contacted with or exposed to the agent. Suicide genes are known in the art and include, for example, the Herpes Simplex Virus (HSV) thymidine kinase (TK) gene, cytosine deaminase, purine nucleoside phosphorylase, and nitroreductase.

The vectors may also comprise selection markers, which are well known in the art. Selection markers include positive and negative selection marker. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host to provide prototrophy, and the like. Exemplary marker genes include antibiotic resistance genes (e.g., neomycin resistance gene, a hygromycin resistance gene, a kanamycin resistance gene, a tetracycline resistance gene, a penicillin resistance gene, histidinol resistance gene, histidinol x resistance gene), glutamine synthase genes, HSV-TK, HSV-TK derivatives for ganciclovir selection, or bacterial purine nucleoside phosphorylase gene for 6-methylpurine selection (Gadi et al., 7 *Gene Ther.* 1738-1743 (2000)). A nucleic acid sequence encoding a selection marker or the cloning site may be upstream or downstream of a nucleic acid sequence encoding a polypeptide of interest or cloning site.

Exemplary vectors that may be used are Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene, La Jolla, Calif., USA); pTrec99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia, Uppsala, Sweden). Eukaryotic: pWLneo, pSV2cat, pOG44, PXR1, pSG (Stratagene) pSVK3, pBPV, pMSG and pSVL (Pharmacia), pEE6.4 (Lonza) and pEE12.4 (Lonza). Additional vectors include the pUC series (Fermentas Life Sciences, Glen Burnie, Md.), the pBluescript series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as λ GT10, λ GT11, λ EMBL4, and λ NM1149, λ ZapII (Stratagene) can be used. Exemplary plant expression vectors include pBI01, pBI01.2, pBI121, pBI101.3, and pBIN19 (Clontech). Exemplary animal expression vectors include pEUK-CI, pMAM, and pMAMneo (Clontech). The expression vector may be a viral vector, e.g., a retroviral vector, e.g., a gamma retroviral vector.

In some embodiments, the vector comprises the polynucleotide encoding the VH of SEQ ID NO: 50.

In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO: 51.

In some embodiments, the vector comprises the polynucleotide encoding the VH of SEQ ID NO: 52.

53. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
54. In some embodiments, the vector comprises the polynucleotide encoding the VH of SEQ ID NO:
- 5 55. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
56. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
- 10 57. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
58. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
59. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
- 15 60. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
61. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
- 20 62. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
63. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
64. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
- 25 65. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
66. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
- 30 67. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
68. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:
69. In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NO:

In some embodiments, the vector comprises the polynucleotide encoding VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68.

In some embodiments, the vector comprises the polynucleotide encoding the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

5 In some embodiments, the vector comprises the polynucleotide encoding the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.

In some embodiments, the vector comprises the polynucleotide encoding
the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
10 the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
15 the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

In some embodiments, the vector comprises the polynucleotide encoding polypeptide of SEQ ID
20 NOs: SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264,
265, 266, 267, 268, or 269.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
ID NO: 248.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
25 ID NO: 249.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
ID NO: 250.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
ID NO: 251.

30 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
ID NO: 252.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ
ID NO: 253.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 254.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 255.

5 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 256.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 257.

10 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 258.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 259.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 260.

15 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 261.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 262.

20 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 263.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 264.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 265.

25 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 266.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 267.

30 In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 268.

In some embodiments, the vector comprises the polynucleotide encoding the polypeptide of SEQ ID NO: 269.

The invention also provides for a host cell comprising one or more vectors of the invention.

"Host cell" refers to a cell into which a vector has been introduced. It is understood that the term host cell is intended to refer not only to the particular subject cell but to the progeny of such a cell, and also to a stable cell line generated from the particular subject cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein. Such host cells may be eukaryotic cells, prokaryotic cells, plant cells or archeal cells. *Escherichia coli*, bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as *Salmonella*, *Serratia*, and various *Pseudomonas* species are examples of prokaryotic host cells. Other microbes, such as yeast, are also useful for expression. *Saccharomyces* (e.g., *S. cerevisiae*) and *Pichia* are examples of suitable yeast host cells. Exemplary eukaryotic cells may be of mammalian, insect, avian or other animal origins.

Mammalian eukaryotic cells include immortalized cell lines such as hybridomas or myeloma cell lines such as SP2/0 (American Type Culture Collection (ATCC), Manassas, VA, CRL-1581), NS0 (European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, ECACC No. 85110503), FO (ATCC CRL-1646) and Ag653 (ATCC CRL-1580) murine cell lines. An exemplary human myeloma cell line is U266 (ATCC CRL-TIB-196). Other useful cell lines include those derived from Chinese Hamster Ovary (CHO) cells such as CHO-K1SV (Lonza Biologics, Walkersville, MD), CHO-K1 (ATCC CRL-61) or DG44.

The disclosure also provides a method of producing the HLA-G binding protein of the disclosure comprising culturing the host cell of the disclosure in conditions that the K2 binding protein is expressed, and recovering the HLA-G binding protein produced by the host cell. Methods of making proteins and purifying them are known. Once synthesized (either chemically or recombinantly), the HLA-G binding proteins may be purified according to standard procedures, including ammonium sulfate precipitation, affinity columns, column chromatography, high performance liquid chromatography (HPLC) purification, gel electrophoresis, and the like (see generally Scopes, Protein Purification (Springer- Verlag, N.Y., (1982)). A subject protein may be substantially pure, e.g., at least about 80% to 85% pure, at least about 85% to 90% pure, at least about 90% to 95% pure, or at least about 98% to 99%, or more, pure, e.g., free from contaminants such as cell debris, macromolecules, etc. other than the subject protein.

The polynucleotides encoding the HLA-G binding proteins of the disclosure may be incorporated into vectors using standard molecular biology methods. Host cell transformation, culture, antibody expression and purification are done using well known methods.

Modified nucleotides may be used to generate the polynucleotides of the disclosure. Exemplary modified nucleotides are 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, carboxymethylaminomethyl-2-thiouridine,

5-carboxymethylaminomethyluracil, dihydrouracil, N⁶-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5''-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N⁶-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutosine, pseudouracil, queuosine, beta-D-galactosylqueosine, inosine, N⁶-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl)uracil, and 2,6-diaminopurine.

10 **Pharmaceutical Compositions/Administration**

The disclosure also provides a pharmaceutical composition comprising the HLA-G binding protein of the disclosure and a pharmaceutically acceptable carrier.

The disclosure also provides a pharmaceutical composition comprising the antigen binding domain that binds HLA-G of the disclosure and a pharmaceutically acceptable carrier.

15 The disclosure also provides a pharmaceutical composition comprising the protein comprising the antigen binding domain that binds HLA-G of the disclosure and a pharmaceutically acceptable carrier.

The disclosure also provides a pharmaceutical composition comprising the multispecific protein comprising the antigen binding domain that binds HLA-G of the disclosure and a pharmaceutically acceptable carrier.

20 The disclosure also provides a pharmaceutical composition comprising the multispecific protein comprising the antigen binding domain that binds HLA-G and an antigen binding domain that binds a tumor antigen other than HLA-G and a pharmaceutically acceptable carrier.

The HLA-G binding protein of the disclosure may be prepared as pharmaceutical compositions containing an effective amount of the antibody as an active ingredient in a pharmaceutically acceptable carrier. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc.

30 The term "pharmaceutically acceptable," as used herein with regard to pharmaceutical compositions, means 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/or in humans.

METHODS OF TREATMENT AND USES

The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in therapy.

5 The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in treating a cell proliferative disorder.

10 The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in treating cancer.

The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in the manufacture of a medicament for use in therapy.

15 The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in the manufacture of a medicament for use in treating a cell proliferative disorder.

20 The disclosure also provides the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure for use in the manufacture of a medicament for treating cancer.

25 The disclosure also provides a method of treating cancer in a subject, comprising administering a therapeutically effective amount of the multispecific protein comprising the antigen binding domain that binds HLA-G to the subject to treat the cancer, wherein the antigen binding domain that bind HLA-G comprises

the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
30 the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or

the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.

The disclosure also provides a method of treating cancer in a subject, comprising administering a therapeutically effective amount of the multispecific protein comprising the antigen binding domain that binds HLA-G to the subject to treat the cancer, wherein the antigen binding domain that binds HLA-G
5 comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

A further aspect of the disclosure is a method of treating a cell proliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of
10 the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure. In other embodiments, the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure, is administered to the subject.

15 In any of the preceding uses or methods, the cell proliferative disorder is cancer. In other embodiments, the cancer is selected from the group consisting of a lung cancer, a pancreatic cancer, a renal cancer, a head and neck cancer, an ovarian cancer, an esophageal cancer, a breast cancer, a uterine cancer, a melanoma, a neuroblastoma, a glioblastoma, a colorectal cancer, a gastric cancer, a parathyroid cancer, a bladder cancer, a liver cancer, a hepatocellular carcinoma, a pleural mesothelioma, a prostate
20 cancer, a cholangiocarcinoma, a thyroid cancer, an embryonal carcinoma, a seminoma, a uveal melanoma, a pheochromocytoma, a teratoma, a thymoma, an adrenocortical carcinoma, an astrocytoma, a synovial sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia (AML), a Hodgkin lymphoma, a multiple myeloma (MM), a non-Hodgkin's lymphoma, and a B-cell chronic lymphoid leukemia.

25 In other embodiments, the cancer is lung cancer. In other embodiments, the lung cancer is non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) or lung adenocarcinoma. In other embodiments, the cancer is pancreatic cancer. In other embodiments, the cancer is an adenocarcinoma, for example, a metastatic adenocarcinoma (e.g., a lung adenocarcinoma, a gastric adenocarcinoma, or a pancreatic adenocarcinoma).

30 In other embodiments, the renal cancer is Clear Cell Renal Cell Carcinoma (CCRCC).

In other embodiments, the renal cancer is papillary type.

In other embodiments, the ovarian cancer is high grade serous cancer of the ovary, peritoneum, or fallopian tube.

In other embodiments, the ovarian cancer has an elevated blood marker (e.g., CA 125) or cancer related fluid that can be monitored.

In other embodiments, the breast cancer is triple-negative breast cancer (TNBC).

In another aspect, the disclosure features a kit comprising: (a) a composition comprising any one
5 of the preceding the bispecific or multispecific protein comprising a first antigen binding domain that specifically binds HLA-G and a second antigen binding domain that specifically binds a second antigen of the disclosure and (b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a cell proliferative disorder.

In any of the preceding uses or methods, the subject can be a human.

10

EMBODIMENTS:

The invention provides the following non-limiting embodiments.

- 1) An isolated protein comprising an antigen binding domain that binds human leukocyte antigen G
15 (HLA-G), wherein the antigen binding domain that binds HLA-G comprises
- a) a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or
 - 20 b) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or
 - c) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or
 - d) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the
25 LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or
 - e) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or
 - f) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or
 - 30 g) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or
 - h) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or

- i) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or
 - j) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.
- 5 2) The isolated protein of Embodiment 1, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
- a) SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
 - b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
 - c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
 - 10 d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
 - e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
 - f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
 - g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
 - h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
 - 15 i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.
- 3) The isolated protein of Embodiment 1 or 2, wherein the antigen binding domain that binds HLA-G is a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.
- 4) The isolated protein of Embodiment 3, wherein the antigen binding domain that binds HLA-G is the Fab.
- 20 5) The isolated protein of Embodiment 3, wherein the antigen binding domain that binds HLA-G is the scFv.
- 6) The isolated protein of Embodiment 5, wherein the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).
- 7) The isolated protein of Embodiment 6, wherein the L1 comprises
- 25 a) about 5-50 amino acids;
 - b) about 5-40 amino acids;
 - c) about 10-30 amino acids; or
 - d) about 10-20 amino acids.
- 8) The isolated protein of Embodiment 6, wherein the L1 comprises an amino acid sequence of SEQ ID
- 30 NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 9) The isolated protein of Embodiment 8 wherein the L1 comprises the amino acid sequence of SEQ ID NO: 8.

- 10) The isolated protein of any one of Embodiments 1-9, wherein the antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.
- 11) The isolated protein of Embodiment 10, wherein the antigen binding domain that binds HLA-G comprises:
- 5 a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
- b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
- c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
- d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
- 10 e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
- f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
- g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
- h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
- i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
- 15 j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69;
- 12) The isolated protein of any one of Embodiments 1-11, wherein the antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.
- 13) The isolated protein of any one of Embodiments 1-12, wherein the protein is conjugated to a half-life extending moiety.
- 20 14) The isolated protein of Embodiment 13, wherein the half-life extending moiety is an immunoglobulin (Ig), a fragment of the Ig, an Ig constant region, a fragment of the Ig constant region, a Fc region, transferrin, albumin, an albumin binding domain or polyethylene glycol.
- 15) The isolated protein of any one of Embodiments 1-14, wherein the isolated protein is a monospecific protein.
- 25 16) The isolated protein of any one of Embodiments 1-14, wherein the isolated protein is a multispecific protein.
- 17) The isolated protein of Embodiment 16, wherein the multispecific protein is a bispecific protein.
- 18) The isolated protein of Embodiment 16, wherein the multispecific protein is a trispecific protein.
- 30 19) The isolated protein of any one of Embodiments 1-18, further comprising an immunoglobulin (Ig) constant region or a fragment of the Ig constant region thereof.
- 20) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises a Fc region.

- 21) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises a CH2 domain.
- 22) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises a CH3 domain.
- 5 23) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises the CH2 domain and the CH3 domain.
- 24) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises at least portion of a hinge, the CH2 domain and the CH3 domain.
- 25) The isolated protein of Embodiment 19, wherein the fragment of the Ig constant region comprises a hinge, the CH2 domain and the CH3 domain.
- 10 26) The isolated protein of any one of Embodiments 19-25, wherein the antigen binding domain that binds HLA-G is conjugated to the N-terminus of the Ig constant region or the fragment of the Ig constant region.
- 27) The isolated protein of any one of Embodiments 19-25, wherein the antigen binding domain that binds HLA-G is conjugated to the C-terminus of the Ig constant region or the fragment of the Ig constant region.
- 15 28) The isolated protein of any one of Embodiments 19-27, wherein the antigen binding domain that binds HLA-G is conjugated to the Ig constant region or the fragment of the Ig constant region via a second linker (L2).
- 20 29) The isolated protein of Embodiment 41, wherein the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 30) The isolated protein of any one of Embodiments 16-29, wherein the multispecific protein comprises an antigen binding domain that binds an antigen on a lymphocyte.
- 25 31) The isolated protein of Embodiment 30, wherein the lymphocyte is a T cell.
- 32) The isolated protein of Embodiment 30, wherein the T cell is a CD8⁺ T cell
- 33) The isolated protein of Embodiment 30, wherein the lymphocyte is a natural killer (NK) cell.
- 34) The isolated protein of any one of Embodiments 16-33, wherein the multispecific protein comprises an antigen binding domain that binds CD3, CD3 epsilon (CD3ε), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.
- 30 35) The isolated protein of Embodiment 34, wherein the multispecific protein comprises an antigen binding domain that binds CD3ε.
- 36) The isolated protein of Embodiment 48, wherein the antigen binding domain that binds CD3ε comprises:

- a) a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 361, a HCDR2 of SEQ ID NO: 362, a HCDR3 of SEQ ID NO: 363, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 367, a LCDR2 of SEQ ID NO: 368 and a LCDR3 of SEQ ID NO: 369;
- 5 b) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;
- c) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;
- d) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
- 10 e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
- f) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
- g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344;
- h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345;
- i) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
- 15 j) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347; or
- k) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349.
- 37) The isolated protein of any one of Embodiments 19-36, wherein the Ig constant region or the fragment of the Ig constant region is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.
- 20 38) The isolated protein of any one of Embodiments 19-37, wherein the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in reduced binding of the protein to a Fc γ receptor (Fc γ R).
- 39) The isolated protein of Embodiment 38, wherein the at least one mutation that results in reduced binding of the protein to the Fc γ R is selected from the group consisting of L235A/D265S, F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A, V234A/G237A, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index.
- 25
- 30

- 40) The isolated protein of any one of Embodiments 19-37, wherein the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in enhanced binding of the protein to the Fc γ R.
- 41) The isolated protein of Embodiment 40, wherein the at least one mutation that results in enhanced binding of the protein to the Fc γ R is selected from the group consisting of S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.
- 42) The isolated protein of any one of Embodiments 38-41, wherein the Fc γ R is Fc γ RI, Fc γ RIIA, Fc γ RIIB or Fc γ RIII, or any combination thereof.
- 43) The isolated protein of any one of Embodiments 19-42, wherein the Ig constant region of the fragment of the Ig constant region comprises at least one mutation that modulates a half-life of the protein.
- 44) The isolated protein of Embodiment 43, wherein the at least one mutation that modulates the half-life of the protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.
- 45) The isolated protein of any one of the Embodiments 19-44, wherein the protein comprises at least one mutation in a CH3 domain of the Ig constant region.
- 46) The isolated protein of Embodiment 45, wherein the at least one mutation in the CH3 domain of the Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.
- 47) An isolated multispecific protein comprising a first antigen binding domain that binds HLA-G and a second antigen binding domain that binds a lymphocyte antigen.
- 48) The isolated multispecific protein of Embodiment 47, wherein the lymphocyte antigen is a T cell antigen.
- 49) The isolated multispecific protein of Embodiment 47, wherein the T cell antigen is a CD8⁺ T cell antigen.
- 50) The isolated multispecific protein of Embodiment 47, wherein the lymphocyte antigen is a NK cell antigen.

- 51) The isolated multispecific protein of any one of Embodiments 47-50, wherein the lymphocyte antigen is CD3, CD3 epsilon (CD3ε), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.
- 52) The isolated multispecific protein of Embodiment 51, wherein the lymphocyte antigen is CD3ε.
- 53) The isolated multispecific protein of any one of Embodiments 47-52, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.
- 54) The isolated multispecific protein of Embodiment 53, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fab.
- 55) The isolated multispecific protein of Embodiment 53, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the scFv.
- 56) The isolated multispecific protein of Embodiment 55, wherein the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).
- 57) The isolated multispecific protein of Embodiment 56, wherein the L1 comprises
- about 5-50 amino acids;
 - about 5-40 amino acids;
 - about 10-30 amino acids; or
 - about 10-20 amino acids.
- 58) The isolated multispecific protein of Embodiment 57, wherein the L1 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 59) The isolated multispecific protein of Embodiment 58, wherein the L1 comprises the amino acid sequence of SEQ ID NO: 8.
- 60) The isolated multispecific protein of any one of Embodiments 47-59, wherein the first antigen binding domain that binds HLA-G comprises the HCDR1 of SEQ ID NOs: 70, 73, 75, 78, 81, or 85, the HCDR2 of SEQ ID NOs: 71, 76, 79, 82, or 86, the HCDR3 of SEQ ID NOs: 72, 74, 77, 80, 83, 84, or 87, the LCDR1 of SEQ ID NOs: 88, 91, 93, 95, 97, 99, 101, or 102, the LCDR2 of SEQ ID NOs: 89 or 103, and the LCDR3 of SEQ ID NOs: 90, 92, 94, 96, 98, 100, or 104.
- 61) The isolated multispecific protein of any one of Embodiments 47-60, wherein the first antigen binding domain that binds HLA-G comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
- SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;

- b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
 - c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
 - d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
 - e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
 - 5 f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
 - g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
 - h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
 - i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.
- 62) The isolated multispecific protein of any one of Embodiments 47-61, wherein the first antigen
- 10 binding domain that binds HLA-G comprises
- a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
 - b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
 - c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
 - d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
 - 15 e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
 - f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
 - g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
 - h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
 - i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
 - 20 j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 63) The isolated multispecific protein of any one of Embodiments 47-61, wherein the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68, and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.
- 64) The isolated multispecific protein of any one of Embodiments 47-63, wherein the first antigen
- 25 binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.
- 65) The isolated multispecific protein of any one of Embodiments 47-56, wherein the second antigen binding domain that binds the lymphocyte antigen comprises
- a) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 369;
 - 30 b) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;

- c) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;
- d) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
- 5 e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
- f) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
- g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344;
- h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345;
- i) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
- 10 j) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347; or
- k) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349.
- 66) The isolated multispecific protein of any one of Embodiments 47-65, wherein the first antigen binding domain that binds HLA-G is conjugated to a first immunoglobulin (Ig) constant region or a fragment of the first Ig constant region and/or the second antigen binding domain that binds the lymphocyte antigen is conjugated to a second immunoglobulin (Ig) constant region or a fragment of the second Ig constant region.
- 15 67) The isolated multispecific protein of Embodiment 66, further comprising a second linker (L2) between the first antigen binding domain that binds HLA-G and the first Ig constant region or the fragment of the first Ig constant region and the second antigen binding domain that binds the lymphocyte antigen and the second Ig constant region or the fragment of the second Ig constant region.
- 20 68) The isolated multispecific protein of Embodiment 67, wherein the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 25 69) The isolated multispecific protein of any one of Embodiments 66-68, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.
- 30 70) The isolated multispecific protein of Embodiment 66-69, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in reduced binding of the multispecific protein to a FcγR.

- 71) The isolated multispecific protein of Embodiment 70, wherein the at least one mutation that results in reduced binding of the multispecific protein to the FcγR is selected from the group consisting of L235A/D265S, F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A,
5 V234A/G237A, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index.
- 10 72) The isolated multispecific protein of any one of Embodiments 66-69, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in enhanced binding of the multispecific protein to a Fcγ receptor (FcγR).
- 73) The isolated multispecific protein of Embodiment 72, wherein the at least one mutation that results in
15 enhanced binding of the multispecific protein to the FcγR is selected from the group consisting of S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.
- 74) The isolated multispecific protein of any one of Embodiments 70-73, wherein the FcγR is FcγRI,
20 FcγRIIA, FcγRIIB or FcγRIII, or any combination thereof.
- 75) The isolated multispecific protein of any one of Embodiments 66-74, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that modulates a half-life of the multispecific protein.
- 25 76) The isolated multispecific protein of Embodiment 75, wherein the at least one mutation that modulates the half-life of the multispecific protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.
- 77) The isolated multispecific protein of any one of the Embodiments 66-76, comprising at least one
30 mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region.
- 78) The isolated multispecific protein of Embodiment 77, wherein the at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant

- region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V,
- 5 T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.
- 79) The isolated multispecific protein of any one of Embodiments 66-78, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the
- 10 fragment of the second Ig constant region comprise the following mutations:
- a) L235A_D265S_T350V_L351Y_F405A_Y407V in the first Ig constant region and L235A_D265S_T350V_T366L_K392L_T394W in the second Ig constant region; or
- b) L235A_D265S_T350V_T366L_K392L_T394W in the first Ig constant region and L235A_D265S_T350V_L351Y_F405A_Y407V in the second Ig constant region.
- 15
- 80) An immunoconjugate comprising the isolated protein of any one of Embodiments 1-46 conjugated to a therapeutic agent or an imaging agent.
- 81) A pharmaceutical composition comprising the isolated protein of any one of Embodiments 1-46 and a pharmaceutically acceptable carrier.
- 20 82) A polynucleotide encoding the isolated protein of any one of Embodiments 1-46.
- 83) A vector comprising the polynucleotide of Embodiment 82.
- 84) A host cell comprising the vector of Embodiment 83.
- 85) A method of producing the isolated protein of any one of Embodiments 1-46, comprising culturing the host cell of Embodiment 84 in conditions that the protein is expressed, and recovering the protein
- 25 produced by the host cell.
- 86) An immunoconjugate comprising the isolated multispecific protein of any one of Embodiments 47-79 conjugated to a therapeutic agent or an imaging agent.
- 87) A pharmaceutical composition comprising the isolated multispecific protein of any one of Embodiments 47-79 and a pharmaceutically acceptable carrier.
- 30 88) A polynucleotide encoding the isolated multispecific protein of any one of Embodiments 47-79.
- 89) A vector comprising the polynucleotide of Embodiment 88.
- 90) A host cell comprising the vector of Embodiment 89.

- 91) A method of producing the isolated multispecific protein of any one of Embodiments 47-79, comprising culturing the host cell of Embodiment 90 in conditions that the multispecific protein is expressed, and recovering the multispecific protein produced by the host cell.
- 5 92) A method of treating a HLA-G expressing cancer in a subject, comprising administering a therapeutically effective amount of the isolated protein of any one of Embodiments 1-46, the isolated multispecific protein of any one of Embodiments 47-79, the immunoconjugate of Embodiment 80 or 86, or the pharmaceutical composition of Embodiment 81 or 87 to the subject for a time sufficient to treat the HLA-G expressing cancer.
- 10 93) A method of reducing the amount of HLA-G expressing tumor cells in a subject, comprising administering the isolated protein of any one of Embodiments 1-46, the isolated multispecific protein of any one of Embodiments 47-79, the immunoconjugate of Embodiment 80 or 86, or the pharmaceutical composition of Embodiment 81 or 87 to the subject for a time sufficient to reduce the amount of HLA-G expressing tumor cells.
- 15 94) The method of any one of Embodiments 92-93, wherein the HLA-G expressing cancer is a lung cancer, a pancreatic cancer, a renal cancer, a head and neck cancer, an ovarian cancer, an esophageal cancer, or a breast cancer.
- 95) The method of any one of Embodiments 92-94, wherein the isolated protein or the isolated multispecific protein is administered in combination with a second therapeutic agent.
- 20 96) The method of Embodiment 95, wherein the second therapeutic agent is surgery, chemotherapy, or radiation, or any combination thereof.
- 97) A method of detecting the presence of cancer in a subject, comprising administering the immunoconjugate of Embodiment 80 or 86 to a subject suspected to have cancer and visualizing the biological structures to which the immunoconjugate is bound, thereby detecting the presence of
- 25 cancer.
- 98) A kit comprising the isolated protein of any one of Embodiments 1-46, the isolated multispecific protein of any one of Embodiments 47-79, the immunoconjugate of Embodiment 80 or 86, or the pharmaceutical composition of Embodiment 81 or 87.
- 99) An anti-idiotypic antibody binding to the isolated protein of any one of Embodiments 1-46.
- 30 100) An isolated protein comprising an antigen binding domain that binds to an epitope on HLA-G, wherein the epitope is a discontinuous epitope comprising the amino acid sequences of HHPVFDYE (SEQ ID NO: 485) and VPS.
- 101) An isolated protein comprising an amino acid sequence of SEQ ID NOs: 478 or 479.
- 102) An isolated protein comprising an amino acid sequence of SEQ ID NOs: 478.

- 103) An isolated protein comprising an amino acid sequence of SEQ ID NOs: 479.
- 104) The isolated protein of Embodiment 102 comprising an amino acid sequence of SEQ ID NO: 490.
- 105) The isolated protein of Embodiments 102 or 104 further comprising amino acid sequences of SEQ ID NOs: 489 and 447.
- 5 106) The isolated protein of Embodiments 105 further comprising an amino acid sequence of SEQ ID NO: 439.
- 107) An isolated protein comprising amino acid sequences of SEQ ID NOs: 465 and 468.
- 108) An isolated protein comprising amino acid sequences of SEQ ID NOs: 466 and 469.
- 109) An isolated protein comprising amino acid sequences of SEQ ID NOs: 467 and 470.

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The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

EXAMPLES

15 Example 1. Generation of HLA-G cell line.

K562 chronic myelogenous leukemia cell line (ATCC, CCL-243) lacking expression of all HLAs, including the MHC class I proteins: HLA-A (Uniprot P01892), HLA-B (Uniprot P18464), HLA-C (Uniprot P30508), and HLA-E (Uniprot P13747) (therefore suitable for NK cell based killing), was transduced using a pCDH lentiviral vector to express HLA-G1 – IRES (internal ribosome entry site) – β -2-microglobulin (β 2M, LPP-CS-Z7412-I0035-02-200, Genecopoeia) or the human HLA-G (C42S) - IRES - β 2M (LPP-CS-Z7412-I0035-01-200, Genecopoeia) in lentiviral particles (Genecopoeia) and cultured in IMDM, 10% FBS. At passage one, selection with 10 μ g/ml puromycin (Gibco, A1113803) to ensure stable HLA-G expression. Cells were split 1:10 when density reached $\sim 3 \times 10^6$ cells/ml, approximately every 3-4 days.

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Example 2: Generation of HLA-G antibodies.

Anti-HLA-G antibodies were generated using OmniRat® transgenic humanized rats. The OmniRat® contains a chimeric human/rat IgH locus (comprising 22 human V_{HS} , all human D and J_H segments in natural configuration linked to the rat C_H locus) together with fully human IgL loci (12 V_{KS} linked to J_K-C_K and 16 V_{λ} s linked to $J_{\lambda}-C_{\lambda}$). (see e.g., Osborn, et al. (2013) J Immunol 190(4): 1481-1490). Accordingly, the rats exhibit reduced expression of rat immunoglobulin, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully

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human variable regions. The preparation and use of OmniRat®, and the genomic modifications carried by such rats, is described in WO14/093908.

OmniRat® rats were immunized using a construct comprising α subunit of either recombinant human HLA-G1 or recombinant human HLA-G5, a soluble isoform of HLA-G containing the $\alpha 1$, $\alpha 2$, and $\alpha 3$ domains but lacking the transmembrane region, fused to the $\beta 2m$ subunit and histone H2A, K562 cells expressing HLA-G1, or DNA encoding HLA-G1 extracellular domain with C42S mutation (Table 1). In some cases the histone H2A peptide was fused to the antigen for enhanced stability. Table 4 shows the sequences of the antigens. The immunizations of OmniRat® rats were carried out in Belgium.

Table 4. Sequences of antigens used to generate antibodies.

10 H2A peptide is underlined. The $\beta 2M$ subunit is highlighted bold. His, Avi-, and Gly-Ser tags are italicized.

Campaign	Protein AA ID	Sequence	SEQ ID NO:
HYB:420, Hybridoma, OMT rats	MHGW8 (B2m-(3(G4S)-HLA-G1-G4S-Avi)	MIQRTPKIQVYSRHPAENGKSNFLNCYVSGFHPSDIEV DLLKNGERIEKVEHSDLSFSKDWSEFYLLYYTEFTPTEK DEYACRVNHVTL SQPKIVKWDRDMGGGGSGGGSGG GSGSGSHSMRYFSAAVSRPGRGEPRFIAMGYVDDTQFV RFDSDSASPRMEPRAPWVEQEGPEYWEETRNKKAHA QTDRMNLQTLRGYYNQSEASSHTLQWMIGCDLGS DGR LLRGYEQYAYDGKDYALNEDLRSWTAADTAAQISK RK CEAANVAEQRRAYLEGTCVEWLHRYLENGKEM LQ RAD PPKTHVTHHPVFDYEATLRCWALGFYPAEII LTWQRDGE DQTQDVELVETRPAGDGTQKWA AVVPSGEEQRYTCHVQHEGLPEPLMLRWKQSSLPTIPIGGGGSG LNDIFEAQ KIEWHE	41
HYB:420, Hybridoma, OMT rats	MHGW2 (H2A-2(G4S)-b2m-3(G4S)-HLA-G5-G4S-His-Avi)	RIIPRHLQLGGGGSGGGSGGGSIQRTPKIQVYSRHPAENGK SNFLNCYVSGFHPSDIEVDLLKNGERIEKVEHSDLSFSK DWSFYLLYYTEFTPTEKDEYACRVNHVTL SQPKIVKWDRDMGGGGSGGGSGGGSGSGSHSMRYFSAAVSRPGR GEPRFIAMGYVDDTQFVRFDSDSASPRMEPRAPWVEQ EGPEYWEETRNKKAHAQTDRMNLQTLRGYYNQSEAS SHTLQWMIGCDLGS DGR LLRGYEQYAYDGKDYALNE DLRSWTAADTAAQISK RKCEAANVAEQRRAYLEGTCVE WLHRYLENGKEM LQ RAD PPKTHVTHHPVFDYEATLRC WALGFYPAEII LTWQRDGEDQTQDVELVETRPAGDGTQ KWA AVVPSGEEQRYTCHVQHEGLPEPLMLRWSKE GDG GIMSVRESRSLSEDLGGGGSHHHHHHGSGLNDIFE AQ KIEWHE	42
HYB:420, Hybridoma, OMT rats	<u>FL</u> HLA-G1	GSHSMRYFSAAVSRPGRGEPRFIAMGYVDDTQFVRFD SDSACPRMEPRAPWVEQEGPEYWEETRNKKAHAQT DRMNLQTLRGYYNQSEASSHTLQWMIGCDLGS DGR LL RGYEQYAYDGKDYALNEDLRSWTAADTAAQISK RKCE AANVAEQRRAYLEGTCVEWLHRYLENGKEM LQ RADPP KTHVTHHPVFDYEATLRCWALGFYPAEII LTWQRDGED QTQDVELVETRPAGDGTQKWA AVVPSGEEQRYTCH VQHEGLPEPLMLRWKQSSLPTIPIMGIVAGLVVLA AVVT GA AVA AVLWRKKSSD	43

HYB:423, Hybridoma, OMT rats	pDR000057441 (H2A-3(G4S)- b2m-3G4S- HLA-G1-C42S)	DNA sequence, primary transcript: ATGGCTTGGGTGTGGACATTGTTGTTTCTGATGGCTG CTGCTCAATCTATTCAAGCTAGGATCATTCTAGACAT CTGCAACTCGGAGGCGGAGGCAGCGGAGGAGGAGG ATCTGGAGGAGGAGGATCTATTAGAGGACACCTAA GATTCAAGTGTACTCTAGACATCCTGCTGAGAACGGC AAGAGCAACTTTCTGAACTGCTATGTGAGCGGCTTTC ATCCTAGCGATATTGAAGTGGATCTGCTGAAAAACGG CGAACGTATTGAAAAAGTGGAAACATAGCGATCTGAGC TTTAGCAAAGATTGGAGCTTTTATCTGCTGTATTATAC CGAATTTACCCCTACCGAAAAAGATGAATATGCCTGC AGAGTGAACCATGTGACCCTGAGCCAGCCTAAGATTG TGAAATGGGATAGAGATATGGGAGGAGGAGGCTCT GAGGAGGAGGATCTGGAGGCGGAGGCAGCGGCTCT CATAGCATGAGATATTTTAGCGCTGCAGTGAGCCGTC CTGGACGTGGAGAACCTAGGTTTATTGCTATGGGCTA TGTGGATGATACCCAGTTTGTGAGGTTTGATAGCGAT AGCGCCTCTCCTAGGATGGAACCTAGAGCTCCCTGG GTGGAACAGGAAGGCCAGAAATATTGGGAAGAAGAA ACCAGGAACACCAAAGCACATGCTCAGACCGATCGTA TGAACCTGCAGACCCTGAGAGGCTATTATAACCAGAG CGAAGCATCTAGCCATACCCTGCAGTGGATGATTGGC TGCGATCTGGGCAGCGATGGCAGACTGCTGAGAGGC TATGAACAGTATGCATATGATGGCAAAGATTATCTGG CACTGAACGAAGATCTGAGGAGCTGGACCGCTGCTG ATACCGCTGCTCAGATTAGCAAGAGGAAGTGCGAAG CTGCTAACGTGGCTGAACAGAGACGCGCATATCTGG AAGGCACCTGCGTGAATGGCTGCATAGGTATCTGG AAAACGGCAAAGAAATGCTGCAGAGAGCTGATCCCTCC TAAACCCATGTGACCCATCATCCTGTGTTTGATTATG AAGCTACCCTGAGGTGCTGGGCTCTGGGCTTCTATC CTGCTGAGATTATTCTGACCTGGCAGAGAGATGGAGA AGATCAGACTCAAGATGTCGAGTTGGTCGAGACTAGA CCTGCTGGAGATGGCACCTTTCAGAAAGTGGGCAGCT GTTGTCGTGCCTAGCGGAGAAAGACAGAGATATACCT GCCATGTGCAGCATGAAGGCCTGCCTGAACCTCTGA TGCTGAGGTGGAACAGAGCAGCTTGCTACTATTCC TATTGGAGGAGGAGGATCTCACCATCATCATCAC TGA Mature Protein sequence: QARIIPRHLQLGGGSGGGSGGGSGGGSGSHSMRYFS HPAENGKSNFLNCYVSGFHPSDIEVDLLKNGERIEKVE HSDLFSKDWFSFYLLYTEFTPTEKDEYACRVNHVTL QPKIVKWDRDMGGGSGGGSGGGSGGGSGSHSMRYFS AAVSRPGRGEPFIAMGYVDDTQFVRFDSDSASPRME PRAPWVEQEGPEYWEETRNTKAHAQTDRMNLQTLR GYYNQSEASSHTLQWMIGCDLGSDGRLLRGYEQYAYD GKDYALNEDLRSWTAADTAAQISKRKCEANVAEQRR AYLEGTCEVWLHRYLENGKEMLQRADPPKTHVTHHPV FDYEATLRCWALGFYPAEIIITWQRDGEDQTQDVELVE TRPAGDGTQKWAAVVPSGEEQRYTCHVQHEGLPEP LMLRWKQSSLPTIPIGGGSHHHHHH	44
		DNA sequence, primary transcript:	45
			46

HYB:421, Hybridoma, OMT rats		ATGGCTTGGGTGTGGACATTGTTGTTTCTGATGGCTG CTGCTCAATCTATTCAAGCTAGGATCATTCCCTAGACAT CTGCAACTCGGAGGCGGAGGCAGCGGAGGAGGAGG ATCTGGAGGAGGAGGATCTATTCAGAGGACACCTAA GATTCAAGTGTA CTCTAGACATCCTGCTGAGAACGGC AAGAGCAACTTTCTGAACTGCTATGTGAGCGGCTTTC ATCCTAGCGATATTGAAGTGGATCTGCTGAAAAACGG CGAACGTATTGAAAAAGTGAACATAGCGATCTGAGC TTTAGCAAAGATTGGAGCTTTTATCTGCTGTATTATAC CGAATTTACCCCTACCGAAAAAGATGAATATGCCTGC AGAGTGAACCATGTGACCCTGAGCCAGCCTAAGATTG TGAAATGGGATAGAGATATGGGAGGAGGAGGCTCTG GAGGAGGAGGATCTGGAGGCGGAGGCAGCGGCTCT CATAGCATGAGATATTTTAGCGCTGCAGTGAGCCGTC CTGGACGTGGAGAACCTAGGTTTATTGCTATGGGCTA TGTGGATGATACCCAGTTTGTGAGGTTTGATAGCGAT AGCGCCTCTCCTAGGATGGAACCTAGAGCTCCCTGG GTGGAACAGGAAGGCCAGAAATATTGGGAAGAAGAA ACCAGGAACACCAAAGCACATGCTCAGACCGATCGTA TGAACCTGCAGACCCTGAGAGGCTATTATAACCAGAG CGAAGCATCTAGCCATACCCTGCAGTGGATGATTGGC TGCGATCTGGGCAGCGATGGCAGACTGCTGAGAGGC TATGAACAGTATGCATATGATGGCAAAGATTATCTGG CACTGAACGAAGATCTGAGGAGCTGGACCGCTGCTG ATACCGCTGCTCAGATTAGCAAGAGGAAGTGCGAAG CTGCTAACGTGGCTGAACAGAGACGCGCATATCTGG AAGGCACCTGCGTGGAAATGGCTGCATAGGTATCTGG AAAACGGCAAAGAAATGCTGCAGAGAGCTGATCCCTCC TAAACCCATGTGACCCATCATCCTGTGTTTGATTATG AAGCTACCCTGAGGTGCTGGGCTCTGGGCTTCTATC CTGCTGAGATTATTCTGACCTGGCAGAGAGATGGAGA AGATCAGACTCAAGATGTCGAGTTGGTCGAGACTAGA CCTGCTGGAGATGGCACCTTTCAGAAAGTGGGCAGCT GTTGTCGTGCCTAGCGGAGAAGAACAGAGATATACCT GCCATGTGCAGCATGAAGGCCTGCCTGAACCTCTGA TGCTGAGGTGGAAACAGAGCAGCTTGCTACTATTCC TATTGGAGGAGGAGGATCTCACCATCATCATCAC TGA	
		Mature Protein sequence: RIIPRHLQLGGGGSGGGSGGGSGGGSGSHSMRYFSAA AENGKSNFLNCYVSGFHPSDIEVDLLKNGERIEKVEHS DLSFSKDWSFYLLYYTEFTPTEKDEYACRVNHVTL SQP KIVKWDRDMGGGGSGGGSGGGSGGGSGSHSMRYFSAA VSRPGRGEPRIAMGYVDDTQFVRFDSDSASPRMEPR APWWEQEGPEYWEEETRNKKAHAQTDRMNLQTLRGYY NQSEASSHTLQWMIGCDLGS DGRLLRGYEQYAYDGKD YLALNEDLRSWTAADTAAQISKRKCEANVAEQRRAYL EGTCVEVLHRYLENGKEMLRADPPKTHVTHHPVFDY EATLRCWALGFYPAEILTWQRDGEDQTQDVELVETRP AGDGTQKWA VVPSGEEQRYTCHVQHEGLPEPLML RWKQSSLPTIPGGGGSHHHHHH	47
HYB:420, Hybridoma, OMT rats	<u>pDR00006641</u> <u>3</u> (Mafa-AG- ECD-G4S-	GSHSMRYFYTAVSRPGRGQPRFIAGYVDDTQFVRFD SDAESPRMEPRAPWWEQEGPEYWDRETQNMKTATQT YQANLRTLRYYNQSEAGSHTFQKMYGCDLGP DGRLL RGYEQFAYDGRDYIILNEDLRSWTAADMAAQNTQRKW EAAGAAEQHRTYLEGECLEWLRRYLENGKETLQRADP	48

	6XHis-GS-Avi T) <u>pDR00004770</u> 3 (Cynomolgus monkey beta 2- microglobulin (b2M))	PKTNVTHHPVSDYEATLRCWALGFYPAEITLTWQRDGE EQTEDTELVEPTRPTGDGTFQKWAAVVVPSEGEQRYTC HVQHEGLPKPLTLRWEPSSQSTILIGGGGSHHHHHHGS GLNDIFEAQKIEWHE IQRTPKIQVYSRHPENGKPNFLNCYVSGFHPSDIEVDL LKNGEKMGKVEHSDLSFSKDWSFYLLYYTEFTPNEKDE YACRVNHVTLSGPRTVKWDRDM	49
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For HYB:420, OmniRats were immunized twice weekly for a total of 12 immunization boosts by following a Repetitive Immunizations Multiple Sites (RIMMS) protocol with recombinant human HLA-G1, human HLA-G5 and cynomolgus monkey Mafa-AG (homolog of HLA-G1) proteins. A final cell boost was performed using a hHLA-G1 K562 expressing cell line derived from K562 cells (ATCC® CCL-243™). Sera titers were determined via a solid phase ELISA with immunogen being coated on the plate. Draining lymph nodes were harvested for lymphocytes fusion with FO myeloma cells (ATCC® CRL-1646™) for hybridoma generation.

For HYB:423, OmniRats were immunized with human HLA-G pDNA (pDR000057441 (Table 3); C>S variant) via the tibialis muscle immediately followed by in vivo electroporation multiple times. Rats received a final boost of a combination of both human and cyno HLA-G over expressing cells. Draining lymph nodes were collected and fused with FO myeloma cells for hybridoma generation.

For HYB:421, OmniRats were immunized with human HLA-G pDNA into each tibialis muscle followed by in-vivo electroporation. Titers were assessed and ranged from 0-800 at Day 25. Rats were rested for several months and then further immunized with pDNA followed by a final boost with K562 cells exogenously overexpressing human HLA-G. Lower draining lymph nodes were used in downstream hybridoma generation.

To select antibody clones for downstream screening, hybridoma supernatants were screened for their abilities to bind cells expressing human HLA-G only and not to cells exogenously expressing HLA-A, HLA-B, and HLA-C, or wild type K562 cells, which do not express cell surface MHC class I antigens. Supernatants which displayed > 20-fold higher binding to K562-HLA-G and 10-fold lower binding to K562-HLA-A/B/C (compared to isotype control) were selected for v-region sequencing and cloning. Monoclonal antibodies were generated in both silent format – lacking effector function (IgG4 PAA or IgG1 AAS, where “PAA” indicates P228S, L234A, L235A and “AAS” indicates mutation of L234A, L235A, D265S in EU numbering) and in active format – having normal effector function (IgG1).

Antibodies were expressed in the supernatant from CHO cells and isolated by protein A affinity chromatography. Recombinant antibodies were then re-screened (as described above) for selectivity to HLA-G expressing cells as well as for their abilities to bind recombinant HLA-G (MHGW2). From these analyses, a panel of 48 unique v-regions was identified and 8 unique v-regions were selected for further analysis. Two of these 8 v-regions, derived from MHGB688 and MHGB694 were germline-optimized to result in MHGB738 and MHGB737, respectively.

Example 3. Structural characterization of anti HLA-G antibodies

Variable domains of the select anti-HLA-G antibodies were expressed in a Fab format, a scFv format in the VH-linker-VL orientation or a scFv format in VL-linker-VH orientation.

Variable domains VH, VL and CDRs

Table 5 shows the VH and VL amino acid sequences of selected anti-HLA-G antibodies. **Table 6** shows the Kabat HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies. **Table 7** shows the Kabat LCDR1, LCDR2 and LCDR3 of the selected anti- HLA-G antibodies. **Table 8** shows the Chothia HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies. **Table 9** shows the Chothia LCDR1, LCDR2 and LCDR3 of the anti- HLA-G. **Table 10** shows the IMGT HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies. **Table 11** shows the IMGT LCDR1, LCDR2 and LCDR3 of the anti- HLA-G. **Table 12** shows the AbM HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies. **Table 13** shows the AbM LCDR1, LCDR2 and LCDR3 of the anti- HLA-G.

Table 5. Variable region sequences of selected anti-HLA-G antibodies.

Antibody	VH	SEQ ID No:	VL	SEQ ID No:
MHGB665 MHGB732	QVQLQQSGPGLVKPSQTLSTL CAISGDSVSSNSAAWNWIRQS PSRGGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQISL QLNSVTPEDTAVYYCAGDRR YGIVGLPFAYWGQGLTVTVSS	50	DIVMTQSPDSLAVSLGERATI NCKSSQSVLHSSNNKNYLTW FQKKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISL QAEDVAVYYCHQYYSTPPTF GQGTVKVEIK	51
MHGB668	QVQLQQSGPGLVKPSQTLSTL CAISGDSVSSNSAAWNWIRQS	52	DIVMTQSPDSLAVSLGERATI NCKSSQSVLYSSKNKNYLAW	53

	PSRGLEWLGRITYYRSKWYND YAVSVKSRITINPDTSKNQFSL QLNSVTPEDTAVYYCARYGSG TLLFDYWQGGLTVTVSS		YQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQYYSTFPYT FGQGTKLEIK	
MHGB669	QVQLQQSGPGLVRPSQTLSVT CAISGDSVSSNSASWNWIRQSP SRGLEWLGRITYYRSEWFNDY AVSVKSRVTINPDTSKNQLSL QLNSVIPEDTAVYYCAREARI GVAGKGFQDYWGQGLTVTVSS	54	DIVMTQSPDSLAVSLGERATI NCKSSQSVLFSSNNKNYLAW FQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQYYSTPRTF GQGTKVEIK	55
MHGB672	QVQLQQSGPGLVKPSQTLSLT CAISGDSVSSNRAAWNWIQT PSRGLEWLGRITYYRSEWYND YAVSVKSRITINPDTSKNQFSL QLNSVTPEDTAVYYCARVRA AVPFQDYWGQGLTVTVSS	56	DIVMTQSPDSLAVSLGERATI NCKSSQSVLFSSNNKNYLAW YQQKPGQPPNLLIYWASTRES GVPDRFSGSVSGTDFTLTISSL QAEDVAIYYCQYHSTPWF GQGTKVEIK	57
MHGB687	QLQLQESGPGLVKPSETLSLM CTVSGGSITSSSYWGWIQPP GKGLEWIGNIYSGTTYNNPS LKSRVTISVDTSKNQFSLKLSS VTAADTAVYYCAAGARDFDS WGQGS�TVTVSS	58	DIVMTQSPDSLAVSLGERATI NCKSSQSVLYSSSNKSYLAW YQQRPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQYYSTPRM YTFGQGTKLEIK	59
MHGB688	EVQLLESGPGLVKPSQTLSLTC VISGDSVSSNRAAWNWIQSP SRGLEWLGRITYYRSKWYNDY AVSVKSRITINSDTSKNQISLQL NSVTPEDTAVYYCARVRPGIP FDYWQGQTPVTVSS	60	DIVMTQSPDSLAVSLGERATI NCKSSQSVLFSSNNKNYLAW YQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCQYNSTPWT FGQGTKVEIK	61
MHGB689	QVQLQQSGPGLVKPSQTLSLT CVISGDSVSSNRAAWNWIQSP PSRGLEWLGRITYYRSKWYND YAVSVKSRITINSDTSKNQISL	62	DIQMTQSPDSLAVSLGERATI NCESSQSVLFSSNNKNYLAW YQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTINR	63

	QLNSVTPEDTAVYYCARVRPG IPFDYWGQGTTVTVSS		LQAEDVAVYYCQQYNSTPW TFGQGTKVEIK	
MHGB694	EVQLLESGGGLVQPGGSLRLS CAASGFTFSSYAMHWVRQAP GKGLDWVSGISGSGFSTYYVD SVKGRFTISRDNKHTLYLQM NSLRAEDTAVYYCAKDNLVA GTVFDYWGQGTLLTVSS	64	DIQMTQSPSTLSASVGDRVIT TCRASQSISSWLAWYQQKPG KAPKLLIYKASSLESGVPSRFS GSGSGTEFTLTISSLQPDDFAT YYCQQYNSYSLTFGGGTKVD IK	65
MHGB737 (GL- optimized B694)	EVQLLESGGGLVQPGGSLRLS CAASGFTFSSYAMHWVRQAP GKGLEWVSGISGSGFSTYYVD SVKGRFTISRDNKNTLYLQM NSLRAEDTAVYYCAKDNLVA GTVFDYWGQGTLLTVSS	66	DIQMTQSPSTLSASVGDRVIT TCRASQSISSWLAWYQQKPG KAPKLLIYKASSLESGVPSRFS GSGSGTEFTLTISSLQPDDFAT YYCQQYNSYSLTFGGGTKVD IK	67
MHGB738 (GL optimized B688)	QVQLQQSGPGLVKPSQTLST CAISGDSVSSNRAAWNWRQS PSRGLEWLGRITYYRSKWYND YAVSVKSRITINPDTSKNQISL QLNSVTPEDTAVYYCARVRPG IPFDYWGQGTPVTVSS	68	DIVMTQSPDSLAVSLGERATI NCKSSQSVLFSSNNKNYLAW YQQKPGQPPKLLIYWASTRES GVPDRFSGSVSGTDFTLTISL QAEDVAVYYCQQYHSTPWT FGQGTKVEIK	69

Table 6. Kabat HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G selected antibodies.

	Kabat HCDR1		Kabat HCDR2		Kabat HCDR3	
mAb name	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	SNSAAWN	70	RTYYRSKWYNDYAVSVKS	71	DRRYGIVGLPFAY	72
MHGB668	NNSAAWN	73	RTYYRSKWYNDYAVSVKS	71	YSGTLLFDY	74
MHGB669	SNSASWN	75	RTYYRSEWFNDYAVSVKS	76	EARIGVAGKGFY	77
MHGB672	SNRAAWN	78	RTYYRSEWYNDYAVSVKS	79	VRAAVPFY	80
MHGB687	SSSYWYG	81	NIYSGTTYNPSLKS	82	GARDFDS	83
MHGB688	SNRAAWN	78	RTYYRSKWYNDYAVSVKS	71	VRPGIPFY	84
MHGB689	SNRAAWN	78	RTYYRSKWYNDYAVSVKS	71	VRPGIPFY	84
MHGB694	SYAMH	85	GISGSGFSTYYVDSVKG	86	DNLVAGTVFY	87

MHGB732	SNSAAWN	70	RTYYRSKWYNDYAVSVKS	71	DRRYGIVGLPFAY	72
MHGB737	SYAMH	85	GISGSGFSTYYVDSVKG	86	DNLVAGTVFDY	87
MHGB738	SNRAAWN	78	RTYYRSKWYNDYAVSVKS	71	VRPGIPFDY	84

Table 7. Kabat LCDR1, LCDR2 and LCDR3 of the selected anti- HLA-G antibodies.

mAb name	Kabat LCDR1		Kabat LCDR2		Kabat LCDR3	
	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	KSSQSVLHSSNNKNYLT	88	WASTRES	89	HQYYSTPPT	90
MHGB668	KSSQSVLYSSKNKNYLA	91	WASTRES	89	QQYYSTFPYT	92
MHGB669	KSSQSVLFRSNNKNYLA	93	WASTRES	89	QQYYSTPRT	94
MHGB672	KSSQSVLFSSNNKNYLA	95	WASTRES	89	QQYHSTPWT	96
MHGB687	KSSQSVLYSSSNKSYLA	97	WASTRES	89	QQYYSTPRMYT	98
MHGB688	KSSQSVLFSSNNKNYLA	99	WASTRES	89	QQYNSTPWT	100
MHGB689	ESSQSVLFSSNNKNYLA	101	WASTRES	89	QQYNSTPWT	100
MHGB694	RASQSISSWLA	102	KASSLES	103	QQYNSYSLT	104
MHGB732	KSSQSVLHSSNNKNYLT	88	WASTRES	89	HQYYSTPPT	90
MHGB737	RASQSISSWLA	102	KASSLES	103	QQYNSYSLT	104
MHGB738	KSSQSVLFSSNNKNYLA	95	WASTRES	89	QQYHSTPWT	96

5 **Table 8. Chothia HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies.**

mAb name	Chothia HCDR1		Chothia HCDR2		Chothia HCDR3	
	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	GDSVSSNSA	105	YYRSKWY	106	DRRYGIVGLPFA	107
MHGB668	GDSVSNNNSA	108	YYRSKWY	106	YGSGLLLFD	109
MHGB669	GDSVSSNSA	105	YYRSEWF	110	EARIGVAGKGFD	111
MHGB672	GDSVSSNRA	112	YYRSEWY	113	VRAAVPFD	114
MHGB687	GGITSSSY	115	YYSGT	116	GARDFD	117
MHGB688	GDSVSSNRA	112	YYRSKWY	106	VRPGIPFD	118
MHGB689	GDSVSSNRA	112	YYRSKWY	106	VRPGIPFD	118
MHGB694	GFTFSSY	119	SGSGFS	120	DNLVAGTVFD	121

MHGB732	GDSVSSNSA	105	YYRSKWY	106	DRRYGIVGLPFA	107
MHGB737	GFTFSSY	119	SGSGFS	120	DNLVAGTVFD	121
MHGB738	GDSVSSNRA	112	YYRSKWY	106	VRPGIPFD	118

Table 9. Chothia LCDR1, LCDR2 and LCDR3 of the anti-HLA-G antibodies.

	Chothia LCDR1		Chothia LCDR2		Chothia LCDR3	
mAb name	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	SQSVLHSSNNKNY	122	WAS	123	YYSTPP	124
MHGB668	SQSVLYSSKNKNY	125	WAS	123	YYSTFPY	126
MHGB669	SQSVLFRSNNKNY	127	WAS	123	YYSTPR	128
MHGB672	SQSVLFSSNNKNY	129	WAS	123	YHSTPW	130
MHGB687	SQSVLYSSSNKSY	131	WAS	123	YYSTPRMY	496
MHGB688	SQSVLFSSNNKNY	132	WAS	123	YNSTPW	133
MHGB689	SQSVLFSSNNKNY	132	WAS	123	YNSTPW	133
MHGB694	SQSISSW	134	KAS	135	YNSYSL	136
MHGB732	SQSVLHSSNNKNY	122	WAS	123	YYSTPP	124
MHGB737	SQSISSW	134	KAS	135	YNSYSL	136
MHGB738	SQSVLFSSNNKNY	129	WAS	123	YHSTPW	130

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Table 10. IMGT HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies.

	IMGT HCDR1		IMGT HCDR2		IMGT HCDR3	
mAb name	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	GDSVSSNSAA	137	TYRSKWYN	138	AGDRRYGIVGLPFAY	139
MHGB668	GDSVSSNSAA	140	TYRSKWYN	138	ARYGSGTLLFDY	141
MHGB669	GDSVSSNSAS	142	TYRSEWFN	143	AREARIGVAGKGFY	144
MHGB672	GDSVSSNRAA	145	TYRSEWYN	146	ARVRAAVPFY	147
MHGB687	GGSITSSSY	148	IYSGTT	149	AAGARDFDS	150

MHGB688	GDSVSSNRAA	145	TYRSKWYN	138	ARVRPGIPFDY	151
MHGB689	GDSVSSNRAA	145	TYRSKWYN	138	ARVRPGIPFDY	151
MHGB694	GFTFSSYA	152	ISGSGFST	153	AKDNLVAGTVFDY	154
MHGB732	GDSVSSNSAA	137	TYRSKWYN	138	AGDRRYGIVGLPFAY	139
MHGB737	GFTFSSYA	152	ISGSGFST	153	AKDNLVAGTVFDY	154
MHGB738	GDSVSSNRAA	145	TYRSKWYN	138	ARVRPGIPFDY	151

Table 11. IMGT LCDR1, LCDR2 and LCDR3 of the anti-HLA-G antibodies.

	IMGT LCDR1		IMGT LCDR2		IMGT LCDR3	
mAb name	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	QSVLHSSNNKNY	155	WAS	123	HQYYSTPPT	156
MHGB668	QSVLYSSKNKNY	157	WAS	123	QQYYSTFPYT	92
MHGB669	QSVLFSSNNKNY	159	WAS	123	QQYYSTPRT	160
MHGB672	QSVLFSSNNKNY	161	WAS	123	QQYHSTPWT	162
MHGB687	QSVLYSSSNKSY	163	WAS	123	QQYYSTPRMYT	164
MHGB688	QSVLFSSNNKNY	165	WAS	123	QQYNSTPWT	166
MHGB689	QSVLFSSNNKNY	165	WAS	123	QQYNSTPWT	166
MHGB694	QSISSW	167	KAS	135	QQYNSYSLT	168
MHGB732	QSVLHSSNNKNY	155	WAS	123	HQYYSTPPT	156
MHGB737	QSISSW	167	KAS	135	QQYNSYSLT	168
MHGB738	QSVLFSSNNKNY	161	WAS	123	QQYHSTPWT	162

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Table 12. AbM HCDR1, HCDR2 and HCDR3 of selected anti- HLA-G antibodies.

	AbM HCDR1		AbM HCDR2		AbM HCDR3	
mAb name	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	GDSVSSNSAAWN	169	RTYYRSKWYND	170	DRRYGIVGLPFAY	171

MHGB668	GDSVSNNSAAWN	172	RTYYRSKWYND	170	YSGTLLFDY	173
MHGB669	GDSVSSNSASWN	174	RTYYRSEWFND	175	EARIGVAGKGFY	176
MHGB672	GDSVSSNRAAWN	177	RTYYRSEWYND	178	VRAAVPFY	179
MHGB687	GGSTITSSYYWG	180	NIYYSGTTY	181	GARDFDS	182
MHGB688	GDSVSSNRAAWN	177	RTYYRSKWYND	170	VRPGIPFDY	183
MHGB689	GDSVSSNRAAWN	177	RTYYRSKWYND	170	VRPGIPFDY	183
MHGB694	GFTFSSYAMH	184	GISGSGFSTY	185	DNLVAGTVFDY	186
MHGB732	GDSVSSNSAAWN	169	RTYYRSKWYND	170	DRRYGIVGLPFAY	171
MHGB737	GFTFSSYAMH	184	GISGSGFSTY	185	DNLVAGTVFDY	186
MHGB738	GDSVSSNRAAWN	177	RTYYRSKWYND	170	VRPGIPFDY	183

Table 13. AbM LCDR1, LCDR2 and LCDR3 of the anti-HLA-G antibodies.

mAb name	AbM LCDR1		AbM LCDR2		AbM LCDR3	
	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
MHGB665	KSSQSVLHSSNNKNYLT	187	WASTRES	188	HQYYSTPPT	189
MHGB668	KSSQSVLYSSKNKNYLA	190	WASTRES	188	QQYYSTFPYT	191
MHGB669	KSSQSVLFRSNNKNYLA	192	WASTRES	188	QQYYSTPRT	193
MHGB672	KSSQSVLFSSNNKNYLA	194	WASTRES	188	QQYHSTPWT	195
MHGB687	KSSQSVLYSSSNKSYLA	196	WASTRES	188	QQYYSTPRMYT	197
MHGB688	KSSQSVLFSSNNKNYLA	198	WASTRES	188	QQYNSTPWT	199
MHGB689	ESSQSVLFSSNNKNYLA	200	WASTRES	188	QQYNSTPWT	199
MHGB694	RASQSISSWLA	201	KASSLES	202	QQYNSYSLT	203
MHGB732	KSSQSVLHSSNNKNYLT	187	WASTRES	188	HQYYSTPPT	189
MHGB737	RASQSISSWLA	201	KASSLES	202	QQYNSYSLT	203
MHGB738	KSSQSVLFSSNNKNYLA	194	WASTRES	188	QQYHSTPWT	195

Germline optimization

The v-region sequences of the antibodies were analyzed for risks of potential post-translational modifications, for germline fitness, and for their abilities to format as scFv. Two antibodies, MHGB694 and MHGB688 were germline-optimized. The v-region of MHGB694 contained two germline mutations (E46D and N77H), and this v-region was thus optimized by back-mutation of these residues to the germline sequence at those sites to generate MHGB737 variable region by mutation of D46E and H77N in the VH domain. The v-region of MHGB688 was similarly optimized by mutation of E1Q, L5Q, E6Q, and S71P in the VH domain and by mutation of K30E, G66V in the VL. We found that MHGB688 also contained an "NS" motif at position 92-93 (Kabat) which presents a risk for deamidation. Since the VL of MHGB672 had identical LC-CDRs except that it contained "HS" at positions 92-93, we mutated N92H. This combination of changes resulted in MHGB738.

Fab-Fc and scFvs

The HLA-G specific VH/VL domains were engineered to be expressed either in an antibody format, or as an scFv, or as an arm of a bi-specific (as either Fab-Fc or scFv-Fc). The antibody format and the Fab-Fc bi-specific arm format included a heavy chain as VH-CH1-hinge-CH2-CH3 and the light chain as VL-CL and expressed as IgG2 or IgG4. The scFv-Fc format included either the VH-Linker-VL-Fc or VL-linker-VH-Fc orientations. The linker that is used in the scFv was the linker of SEQ ID NO: 8 described above. The scFv-Fc and Fab-Fc were used to generate bispecific antibodies as described in Example 10.

Table 14 shows the HC amino acid sequences of selected anti-HLA-G antibodies. **Table 15** shows the LC amino acid sequences of selected anti-HLA-G antibodies. **Table 16** summarizes the HC and LC DNA SEQ ID NOs of selected anti-HLA-G antibodies. **Table 17** shows the amino acid sequences of selected scFvs in VH-linker-VL or VL-linker-VH orientation. **Table 18** shows the amino acid sequences of selected scFv-Fc. **Table 19** shows the scFv and scFv-Fc DNA SEQ ID NOs of selected anti-HLA-G antibodies in the scFv-Fc format.

Table 14. Amino acid sequence of the HC (VH-CH1-hinge-CH2-CH3) of selected anti-HLA-G antibodies in a mAb format.

HLA-G HEAVY CHAIN	SEQ ID NO:	AMINO ACID SEQUENCE
MHGB665 HC	204	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRT YYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGIV

		GLPFAYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
MHGB668 HC	205	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWRQSPSRGLEWLGR YYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARYGSGTL LFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
MHGB669 HC	206	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSASAWNWRQSPSRGLEWLGR YYRSEWFNDYAVSVKSRITINPDTSKNQFSLQLNSVIPEDTAVYYCAREARIGV AGKGFYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
MHGB672 HC	207	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWRQTPSRGLEWLGR YYRSEWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARVRAAVP FDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
MHGB687 HC	208	QLQLQESGPGLVKPSETLSLMCTVSGGSITSSSYWGWIRQPPGKGLEWIGNIY YSGTTYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCAAGARDFDSWG QGS�TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSH DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK KVSNAKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
MHGB688 HC	209	EVQLLESGPGLVKPSQTLSTLCVISGDSVSSNSAAWNWRQSPSRGLEWLGR YYRSKWYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIF DYWGQGTPTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
MHGB689 HC	210	QVQLQQSGPGLVKPSQTLSTLCVISGDSVSSNSAAWNWRQSPSRGLEWLGR YYRSKWYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIF DYWGQGTPTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK

		DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK
MHGB694 HC	211	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWWRQAPGKGLDWWSGISGSGFSTYYVDSVKGRFTISRDNKHTLYLQMNSLRAEDTAVYYCAKDNLVAGTVFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK
MHGB732 HC	212	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPG
MHGB737 HC	213	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWWRQAPGKGLEWWSGISGSGFSTYYVDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDNLVAGTVFDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPG
MHGB738 HC	214	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNRAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCARVRPGIPFDYWGQGTPTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPG

Table 15. Amino acid sequences of the LC (VL-CL) of selected anti-HLA-G antibodies in a mAb (Fab-Fc) format.

HLA-G LIGHT CHAIN	SEQ ID NO:	AMINO ACID SEQUENCE
MHGB665	215	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQKQPGQP PKLLIYWASTRESGVDPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYY TPPTFGQGKTVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA

		KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB668	216	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSKNKNYLAWYQQKPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYS TFPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNREGC
MHGB669	217	DIVMTQSPDSLAVSLGERATINCKSSQSVLFRSNNKNYLAWFQQKPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYS TPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB672	218	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQP PNLLIYWASTRESGVPDRFSGSVSGTDFTLTISSLQAEDVAIYYCQQYHST PWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB687	219	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKSYLAWYQQRPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYS TPRMYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNREGC
MHGB688	220	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPP KLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYNST PWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB689	221	DIQMTQSPDSLAVSLGERATINCESSQSVLFSSNNKNYLAWYQQKPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTINRLQAEDVAVYYCQQYNS TPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB694	222	DIQMTQSPSTLSASVGDRVITITCRASQSISSWLAWYQQKPGKAPKLLIYKA SSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYSLTFGGG TKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNREGC
MHGB732	223	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYS TPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
MHGB737	224	DIQMTQSPSTLSASVGDRVITITCRASQSISSWLAWYQQKPGKAPKLLIYKA SSLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYSLTFGGG TKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNREGC
MHGB738	225	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQP PKLLIYWASTRESGVPDRFSGSVSGTDFTLTISSLQAEDVAVYYCQQYHS TPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC

Table 16. SEQ ID Nos of the cDNA sequences of HC and LC of selected HLA-G antibodies

Antibody	HC cDNA SEQ ID NO:	LC cDNA SEQ ID NO:
MHGB665	226	227
MHGB668	228	229
MHGB669	230	231
MHGB672	232	233
MHGB687	234	235
MHGB688	236	237
MHGB689	238	239
MHGB694	240	241
MHGB732	242	243
MHGB737	244	245
MHGB738	246	247

SEQ ID NO: 226

5 CAGGTGCAGCTGCAGCAGAGCGGCCCTGGACTGGTGAAGCCCAGCCAGACCCTGAG
 CCTGACCTGCGCTATCAGCGGCGATAGCGTGAGCTCCAACAGCGCCGCTGGAACCTGGATCA
 GGCAGAGCCCTAGCAGGGGCTGGAATGGCTGGGCAGGACCTACTACAGGAGCAAGTGGTA
 CAACGACTACGCCGTGTCCGTGAAGAGCAGGATCACCATCAACCCCGACACCAGCAAGAAC
 CAGATCAGCCTGCAGCTGAACAGCGTGACCCCGAGGACACCGCCGTGTACTACTGCGCCG
 10 GCGACAGAAGGTACGGCATCGTGGGCTGCCTTTTCGCCTACTGGGGCCAGGGAACCCTGGT
 GACCGTGAGCAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGA
 GCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG
 ACGGTGTGCTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGTGTCTTACA
 GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCC
 15 AGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGA
 GCCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCCAGCACCTGAACTCCTGGGGG
 GACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCT
 GAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGT
 ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACA
 20 GCACGTACCGTGTGGTCAGCGTCTCACCCTGCACCAGGACTGGCTGAATGGCAAGGAG
 TACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAG
 CCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGAC
 CAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGG
 AGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGTGGACTC

CGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCT
CTCCCTGTCTCCGGGTAAA

SEQ ID NO: 227

5 GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGAGAGC
CACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGCACAGCAGCAACAACAAGAACTACCTG
ACCTGGTTCCAGCAGAAGCCCGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCTAGCACCAG
AGAGTCCGGCGTGCTGACAGGTTACAGCGGAAGCGGCAGCGGCACCGACTTCACCCTGACC
ATCAGCAGCCTGCAGGCCGAGGACGTGGCCGTGTAATACTGCCACCAGTACTACAGCACCCC
10 CCCTACCTTTGGCCAGGGCACCAAGGTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCT
TCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGTGA
ATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCGGG
TAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC
15 ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 228

CAGGTGCAGCTGCAGCAGAGCGGACCCGGCCTGGTGAAACCCAGCCAGACCCTGAG
CCTGACCTGCGCCATCAGCGGCGACAGCGTGAGCAACAACAGCGCCGCCTGGAAGTGGATC
AGGCAGAGCCCCAGCAGAGGCCTGGAATGGCTGGGCAGGACCTACTACAGGAGCAAGTGGT
20 ACAACGACTACGCCGTGAGCGTGAAGAGCAGGATCACCATCAACCCCGACACCTCCAAGAA
CCAGTTCAGCCTGCAGCTGAACAGCGTGACCCCGAGGACACCGCCGTGTACTACTGCGCCA
GGTATGGCAGCGGCACCCTGCTGTTGACTACTGGGGCCAGGGCACCCCTGGTGACAGTGAG
CAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTG
GGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTC
25 GTGGAAGTCAAGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAG
GACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAAT
CTTGTGACAAAACCTCACACATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGGACCGTCA
GTCTTCCTCTTCCCCC AAAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTAC
30 ATGCGTGGTGGTGGACGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC
GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC
CGTGTGGTCAGCGTCCTACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
CAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGG
CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACC

AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT
CCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC
TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTC
5 TCCGGGTAAA

SEQ ID NO: 229

GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGAGAGAGGGC
CACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTACAGCAGCAAGAACAAGAACTACCTG
GCCTGGTACCAGCAGAAACCCGGCCAGCCCCCAAGCTGCTGATCTACTGGGCCAGCACAA
10 GGGAAAGCGGCGTGCCCGACAGATTCAGCGGAAGCGGCAGCGGCACCGACTTCACCCTGAC
CATCAGCAGCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCT
TCCCCTACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGCGTACGGTGGCTGCACCATCT
GTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTG
CTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAAT
15 CGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAG
CAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCTGCGAAGTC
ACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 230

CAGGTGCAGCTGCAGCAGAGCGGACCCGGACTGGTGAGACCCAGCCAGACCCTGAG
20 CGTGACCTGCGCCATCAGCGGCGACAGCGTGAGCAGCAACAGCGCCAGCTGGAAGTGGATC
AGGCAGAGCCCCAGCAGAGGCCTGGAGTGGCTGGGAAGGACATACTACAGGAGCGAGTGG
TTCAACGACTACGCCGTGAGCGTGAAGAGCAGGGTGACCATCAACCCCGACACCAGCAAGA
ACCAGCTGAGCCTGCAGCTGAACAGCGTGATCCCCGAGGACACCGCCGTGTACTACTGCGCC
AGAGAGGCCAGAATCGGCGTGCCCGGCAAAGGCTTCGACTACTGGGGCCAGGGCACCCCTGG
25 TGACAGTGTCCAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAG
AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT
GACGGTGTCTGGAAGTCAAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACC
CAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTG
30 AGCCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCCAGCACCTGAACTCCTGGGG
GGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC
TGAGGTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGG
TACGTGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGA

GTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAA
GCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGA
CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
GAGTGGGAGAGCAATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCGTGGTGGACT
5 CCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGG
GAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCC
TCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 231

GACATCGTGATGACCCAGAGCCCTGACTCCCTGGCTGTGAGCCTGGGCGAGAGAGCC
10 ACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTCAGGAGCAACAACAAGAACTACCTGG
CCTGGTTCCAGCAGAAGCCCGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCCAGCACCAGA
GAGAGCGGCGTGCCCCGATAGATTTAGCGGCAGCGGCAGCGGCACCGACTTTACCCTGACCA
TCAGTCCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCC
AGAACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTT
15 CATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAA
TAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGT
AACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCA
CCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCCA
TCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

20 SEQ ID NO: 232

CAGGTGCAGCTGCAGCAGAGCGGACCTGGCCTGGTGAAGCCCAGCCAGACCCTGAG
CCTGACATGCGCCATCAGCGGCGACAGCGTGAGCAGCAATAGGGCCGCCTGGAAGTGGATC
AGGCAGACCCCTAGCAGGGGCCTGGAATGGCTGGGCAGGACATACTACAGGAGCGAGTGGT
ACAACGACTACGCCGTGTCCGTGAAGAGCAGGATCACCATCAACCCCGACACCAGCAAGAA
25 CCAGTTCAGCCTGCAGCTGAACAGCGTGACCCCCGAGGACACCGCCGTGTACTACTGCGCCA
GAGTGAGAGCCGCCGTGCCTTTCGACTACTGGGGCCAGGGCACCCCTGGTGACAGTGAGCAG
CGCCTCCACCAAGGGGCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGG
GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGG
AACTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT
30 CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT
GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTG
TGACAAAACCTCACACATGCCCACCGTGCCAGCACCTGAAGTCTTGGGGGGACCGTCAGTCT
TCCTCTTCCCCCAAACCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGC
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCG

TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAG
GTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
CCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
5 CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA
ATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTC
TTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA

10 SEQ ID NO: 233

GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGAGGGC
CACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTTCCAGCAACAACAAGAACTACCTG
GCCTGGTACCAGCAGAAACCCGGCCAGCCCCCAACCTGCTGATCTACTGGGCCAGCACCA
GAGAAAGCGGCGTGCCCGACAGGTTTAGCGGCAGCGTGAGCGGCACCGACTTCACCCTGAC
15 CATCAGCAGCCTGCAGGCCGAGGACGTGGCCATCTACTACTGCCAGCAGTACCACAGCACC
CCCTGGACATTTCGGCCAGGGCACCAAGGTGGAGATCAAGCGTACGGTGGCTGCACCATCTG
TCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGC
TGAATAACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATC
GGGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGC
20 AGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCA
CCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 234

CAGCTGCAGCTGCAGGAGAGCGGCCCTGGACTGGTGAAGCCCAGCGAGACCCTGAG
CCTGATGTGCACCGTGAGCGGCGGCAGCATCACCAGCAGCAGCTACTACTGGGGATGGATC
25 AGACAGCCCCCTGGCAAGGGCCTGGAGTGGATCGGCAACATCTACTACAGCGGCACCACCT
ACTACAACCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGGACACCAGCAAGAACCAGTT
CAGCCTGAAGCTGAGCAGCGTGACAGCTGCCGACACCGCCGTGTACTACTGTGCCGCCGGA
GCCAGAGACTTCGACAGCTGGGGACAGGGCAGCCTGGTGACCGTGTCCAGCGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCC
30 CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCAGGCGC
CCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT
CACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTC
ACACATGCCACCGTGCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCTCTTCCCC

CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGGA
CGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCC
TCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAA
5 AGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCA
CAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCT
GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC
GGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACA
GCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT
10 GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 235

GACATCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCCTGGGAGAGAGAGC
CACCATCAACTGCAAGTCCTCCCAGAGCGTGCTGTACAGCTCCAGCAACAAGAGCTACCTGG
CCTGGTACCAGCAGAGGCCCGGACAGCCTCCCAAGCTGCTGATCTACTGGGCCAGCACCAG
15 AGAGAGCGGCGTGCCTGACAGGTTTAGCGGCTCCGGCTCCGGCACCGACTTTACCCTGACCA
TCAGCAGCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCC
AGGATGTACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGCGTACGGTGGCTGCACCAT
CTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCC
TGCTGAATAAATTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCA
20 ATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAG
TCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 236

GAGGTGCAGCTGTTGGAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCA
25 CTCACCTGTGTATCTCCGGGGACAGTGTCTCTAGCAACAGAGCTGCTTGGAAGTGGATCAG
GCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTAT
AATGATTATGCAGTATCTGTGAAAAGTCGAATAACCATCAATTCAGACACATCCAAGAACCA
GATCTCCCTGCAGTTGAACTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAG
TGAGACCGGGGATCCCATTTGACTACTGGGGCCAGGGAACCCCGGTCACCGTCTCCTCAGCC
30 TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAT
CAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAA
CGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGAC

AAAAC TCACACATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCT
CTTCCCCCAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGG
TGGTGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT
5 AGCGTCCTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCT
CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG
AGAACCACAGGTGTACACCCTGCCCCCATCCCGGAGGAGATGACCAAGAACCAGGTCAGC
CTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG
GCAGCCGGAGAACAATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
10 TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA
AA

SEQ ID NO: 237

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCC
15 ACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATTAGCTCCAACAAAAAGAACTACTTAGC
TTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCTGCTCATTTACTGGGCATCTACCCGGG
AATCCGGGGTCCCTGACCGATTAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATC
AGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATAATAGTACTCCGTG
GACGTTCCGCCAAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTC
20 ATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAAT
AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTA
ACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT
CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

25 SEQ ID NO: 238

CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCA
CTCACCTGTGTATCTCCGGGGACAGTGTCTTAGCAACAGAGCTGCCTGGAACCTGGATCAG
GCAGTCCCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTAT
AATGATTATGCAGTTTCTGTGAAAAGTCGAATAACCATCAATTCAGACACATCCAAGAACCA
30 GATCTCCCTGCAGTTGAACTCTGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAG
TGAGACCGGGGATCCCTTTTACTACTGGGGCCAGGGAACACGGTCACCGTCTCCTCAGCC
TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAACT
CAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTAC

TCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAA
CGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGAC
AAAACCTCACACATGCCCACCGTGCCAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCT
CTTCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGG
5 TGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCT
CCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG
AGAACCACAGGTGTACACCCTGCCCCCATCCCGGAGGAGATGACCAAGAACCAGGTACAGC
10 CTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG
GCAGCCGGAGAACAATAACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCC
TCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC
CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA
AA

15 SEQ ID NO: 239

GACATCCAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCC
ACCATCAACTGCGAGTCCAGCCAGAGTGTTTTATTAGCTCCAACAAAAAGAACTACTTAGC
TTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCTGCTCATTTACTGGGCATCTACCCGGG
AATCCGGGGTCCCTGACCGATTAGTGGCAGCGGGTCTGGGACAGATTTACTCTCACCATC
20 AACCGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATAATAGTACTCCGTG
GACGTTCCGCCAAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATCTGTCTTC
ATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAAT
AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTA
ACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
25 CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT
CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 240

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGCACTGGGTCCGCCAGGC
30 CCCAGGGAAGGGGCTGGACTGGGTCTCAGGTATTAGTGGTAGTGGCTTTAGCACATACTATG
TAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGCACACGCTGTATCTG
CAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGATAATTTAG
TGGCTGGTACCGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGCACAGC

GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAG
GCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCC
CTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA
5 ACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTT
CCCCCAAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGG
TGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC
GTCCTCACCGTCTGACACAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCA
10 ACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTG
ACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGAGAACTACAAGACCACGCTCCCGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGTGGT
TACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG
15 TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 241

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCCTGGTATCAGCAGAAACC
AGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCTAGTTTAGAAAGTGGGGTCCCATCAA
20 GGTTACGCGCAGTGGATCTGGGACAGAATTCATCTCACCATCAGCAGCCTGCAGCCTGAT
GATTTTGCAACTTATTACTGCCAACAGTATAATAGTTATTCGCTCACTTTCGGCGGAGGGACC
AAGGTGGATATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGG
CCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTAC
25 AGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCA
GACTACGAGAAACACAAAGTCTACGCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCCG
TCACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 242

CAAGTACAACCTGCAACAAAGTGGTCTGGGCTCGTGAAGCCTTCCCAGACTCTCAGC
30 CTCACATGCGCTATAAGTGGGGATTCTGTTTCTCAAATTCAGCAGCCTGGAATTGGATACG
ACAGTCTCCATCCCGTGGCCTTGAGTGGCTTGGTAGAACTTATTACCGATCCAAGTGGTACA
ATGATTACGCCGTTTCAGTGAAGTCCCGCATTACTATTAATCCCGACACATCTAAGAATCAA
ATTTCAATTGCAACTGAATAGCGTAACACCCGAAGATACAGCAGTTTATTATTGTGCAGGTGA
TCGACGCTACGGCATAGTGGGACTTCCTTTCGCCTATTGGGGCCAAGGGACACTGGTCACTG

TGTCATCCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCT
CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGT
GTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTTACAGTCCT
CAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACC
5 TACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGTCCACCGTGCCAGCACCTGAACTGCTGGGGGGACCG
TCAGTCTTCTCTTCCCCC AAAACCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTC
ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCACGT
10 ACCGTGTGGTCAGCGTCTCACCCTGCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAA
GTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAA
GGGCAGCCCCGAGAACCACAGGTGTACACCCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG
GAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACG
15 GCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGT
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT
GTCTCCGGGT

SEQ ID NO: 243

GACATCGTAATGACACAGTCACCAGATTCAATTGGCAGTTAGTCTGGGTGAAAGGGCA
20 ACAATCAACTGCAAGTCTTCTCAGAGTGTACTGCATAGTTCTAACAATAAGAACTACCTTAC
CTGGTTTCAACAGAAACCAGGTCAGCCCCCAAGTTGCTGATTTACTGGGCAAGCACCCGCG
AATCCGGCGTTCCCGATCGATTTTCAGGTTCCGGGAGTGGGACCGACTTTACCTTGACCATCT
CTTCCTTGAGGCCGAAGATGTAGCCGTCTATTACTGCCATCAGTATTACTCTACTCCCCCA
CATTCGGTCAAGGTACAAAAGTTGAGATAAAACGGACAGTGGCCGCTCCTTCCGTGTTTCATC
25 TTCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTGAACAA
CTTCTACCCTCGGGAAGCCAAGGTGCAGTGAAGGTGGACAATGCCCTGCAGTCCGGCAAC
TCCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCTCCACACT
GACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGGTGTACGCCTGCGAAGTGACCCATCAG
GGCCTGTCTAGCCCTGTGACCAAGTCTTTCAACCGGGGCGAGTGT

30 SEQ ID NO: 244

GAGGTGCAACTCCTTGAATCAGGCGGAGGACTCGTCCAACCTGGAGGGAGTCTTAGG
CTTAGCTGTGCAGCCAGTGGCTTTACTTTTAGCAGCTATGCAATGCACTGGGTGAGGCAGGC
TCCTGGTAAGGGGCTCGAATGGGTGAGCGGCATATCCGGGTGAGTTTCTCTACATATTATG
TCGATTCTGTAAAAGGACGATTACCATATCCAGAGACAATTCTAAAAATACCTTGTATCTC

CAGATGAACAGCCTGAGAGCAGAAGATACCGCAGTTTATTACTGTGCAAAGGATAATCTGG
TTGCCGGGACAGTTTTTTGATTATTGGGGGCAAGGCACCCTCGTCACAGTATCCAGTGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGC
GGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACTCAG
5 GCGCCCTGACCAGCGGCGTGCACACCTTCCCCGGCTGTCTACAGTCCTCAGGACTCTACTCC
CTCAGCAGCGTGGTGACCGTGGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT
GAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA
ACTCACACATGTCCACCGTGCCAGCACCTGAAGTGTGGGGGGACCGTCAGTCTTCCTCTT
CCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGG
10 TGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
GCATAATGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC
GTCCTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCA
ACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTG
15 ACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGGAGAACAATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGT
GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO: 245

20 GATATTGATGACTCAATCACCTTCAACCCCTTAGCGCCTCCGTTGGAGATCGCGTTA
CCATTACCTGCCGAGCCTCCCAAAGTATCAGCTCATGGTTGGCATGGTATCAACAGAAGCCT
GGAAAGGCACCCAACTTCTGATTTACAAAGCCAGCTCCTTGGAGTCAGGAGTCCCAAGCC
GGTTCAGCGGATCTGGGTGAGGGACAGAATTTACCCTGACCATATCTTCCCTTCAGCCCCGAC
GACTTCGCCACTTACTATTGTCAGCAATACAACCTCCTATTCCCTGACTTTCGGCGGTGGCACA
25 AAGGTTGACATCAAGCGGACAGTGGCCGCTCCTTCCGTGTTTATCTTCCACCTTCCGACGA
GCAGCTGAAGTCCGGCACAGCTTCTGTCTGTGCTGCTGAACAACCTTACCCCTCGGGAAG
CCAAGGTGACGTGGAAGGTGGACAATGCCCTGCAGTCCGGCAACTCCCAAGAGTCTGTGAC
CGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCTCCCACTGACCCTGTCCAAGGCCG
ACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGT
30 GACCAAGTCTTTCAACCGGGGCGAGTGT

SEQ ID NO: 246

CAGGTGCAGCTTCAACAGAGCGGACCTGGTCTGGTTAAGCCTTCCCAAACCTGAGC
CTGACTTGTGCTATTTCCGGGGATAGTGTTAGCTCCAATAGGGCAGCATGGAAGTGGATCAG
ACAGTCCCCAAGCCGTGGACTTGAGTGGCTTGGACGTACTTATTACAGGAGTAAATGGTACA

ATGATTATGCCGTTTCTGTGAAGAGCCGTATTACTATAAACCCAGATACTTCTAAAAATCAA
ATTTCCCTTCAGCTCAACTCAGTTACACCAGAGGATACTGCAGTCTATTATTGCGCAAGAGTT
CGACCTGGCATTCCCTTCGATTATTGGGGGCAGGGGACACCCGTTACTGTGTCCTCAGCCTC
CACCAAGGGCCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAG
5 CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTA
GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTC
CCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACG
TGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAA
AACTCACACATGTCCACCGTGCCAGCACCTGAACTGCTGGGGGGACCGTCAGTCTTCTCTCT
10 TCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTG
GTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGG
TGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG
CGTCCTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCA
ACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
15 ACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACGCCTG
ACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGT
GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT
20 SEQ ID NO: 247
GATATTGTTATGACACAGTCCCCAGATTTCATTGGCAGTAAGCCTCGGTGAACGGGCT
ACTATTAAGTGTAAAGTCTTCCCAGAGTGTATTGTTCTCTTCAAATAACAAAAACTACCTGGCA
TGGTATCAGCAAAAAGCCTGGTCAACCCCTAACTTCTCATATACTGGGCATCCACTCGGGA
GAGCGGTGTGCCAGACCGTTTCTCAGGGAGTGTGTCAGGTACAGATTTTACACTCACAATTT
25 CCAGCCTCCAAGCCGAAGACGTTGCAGTATATTATTGCCAACAATATCACTCTACACCTTGG
ACATTTGGTCAAGGTACTAAAGTCGAAATCAAACGGACAGTGGCCGCTCCTTCCGTGTTTCAT
CTTCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCGTGTGCCTGCTGAACA
ACTTCTACCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGTCCGGCAA
CTCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCCTCCACAC
30 TGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCCAAGTGACCCATCA
GGGCCTGTCTAGCCCTGTGACCAAGTCTTTCAACCGGGGCGAGTGT

Table 17. Amino acid sequences of the anti-HLA-G scFvs in VH-linker-VL (HL) or in VL-linker-VH (LH) format.

Acronym	Amino acid sequence of scFv	SEQ ID NO:
MHGB665-HL	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGR TYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGI VGLPFAYWGQGTTLTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSL GERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLIWASTRESGVPDRF SGSGSGTDFTLTISLQAEDVAVYYCHQYYSTPPTFGQGTKEIK	248
MHGB665-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCHQYYSTPPTFGQGT KVEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDSVS SNSAAWNWIRQSPSRGLEWLGRTYRSKWYNDYAVSVKSRITINPDTSKNQIS LQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTTLTVSS	249
MHGB668-HL	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGR TYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARYGSGT LLFDYWGGQGTTLTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGE RATINCKSSQSVLYSSKNKNYLAWYQQKPGQPPKLLIWASTRESGVPDRFSGS GSGTDFTLTISLQAEDVAVYYCQQYYSTFPYTFGQGTKEIK	250
MHGB668-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSKNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQYYSTFPYTFGQG TKLEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDSV SNSAAWNWIRQSPSRGLEWLGRTYRSKWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARYGSGTLLFDYWGGQGTTLTVSS	251
MHGB669-HL	QVQLQQSGPGLVRPSQTLSTCAISGDSVSSNSASWNWIRQSPSRGLEWLGR TYRSEWFNDYAVSVKSRVTINPDTSKNQSLQLNSVIPEDTAVYYCAREARIG VAGKGFYWGQGTTLTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAV SLGERATINCKSSQSVLFRSNNKNYLAWFQQKPGQPPKLLIWASTRESGVPD RFSGSGSGTDFTLTISLQAEDVAVYYCQQYYSTPRTFGQGTKEIK	252
MHGB669-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLFRSNNKNYLAWFQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQQYYSTPRTFGQGT KVEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVRPSQTLSTCAISGDSV SSNSASWNWIRQSPSRGLEWLGRTYRSEWFNDYAVSVKSRVTINPDTSKNQ LSLQLNSVIPEDTAVYYCAREARIGVAGKGFYWGQGTTLTVSS	253
MHGB672-HL	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNRAAWNWRQTPSRGLEWLGR TYRSEWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARVRAAV PFDYWGGQGTTLTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGER ATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPNLLIWASTRESGVPDRFSGS VSGTDFTLTISLQAEDVAIYYCQQYHSTPWTFGQGTKEIK	254
MHGB672-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPNLLI YWASTRESGVPDRFSGSVSGTDFTLTISLQAEDVAIYYCQQYHSTPWTFGQG TKVEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDS VSSNRAAWNWRQTPSRGLEWLGRTYRSEWYNDYAVSVKSRITINPDTSKN QFSLQLNSVTPEDTAVYYCARVRAAVPFDYWGGQGTTLTVSS	255
MHGB687-HL	QLQLQESGPGLVKPSETLSLMCTVSGGSITSSSYWGWIRPPGKLEWIGNIY YSGTTYNPSPKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAAGARDFDSWG	256

	QGS LVT VSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGERATINCKSSQSVLYSSSNKSYLAWYQQRPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQYYSTPRMYTFGQGTKEIK	
MHGB687-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSSNKSYLAWYQQRPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQYYSTPRMYTFGQGTKEIKGGSEGKSSGSGSESKSTGGSQLQLQESGPGLVKPSQETLSLMCTVSGGSITSSSYWGWIRQPPGKLEWIGNIYSGTTYNNPSLKSRTISVDTSKNQFSLKLSVTAADTAVYYCAAGARDFDSWGQGS LVT VSS	257
MHGB688-HL	EVQLLES GPGLVKPSQTLSTLCVISGDSVSSNRAAWNWI RQSPSRGLEWLGRTYYRSK WYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGTPTVT VSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNKKNYLAWYQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQYNSTPWTFGQGTKEIK	258
MHGB688-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNKKNYLAWYQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQYNSTPWTFGQGTKEIKGGSEGKSSGSGSESKSTGGSEVQLLES GPGLVKPSQTLSTLCVISGDSVSSNRAAWNWI RQSPSRGLEWLGRTYYRSK WYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGTPTVT VSS	259
MHGB689-HL	QVQLQQSGPGLVKPSQTLSTLCVISGDSVSSNRAAWNWI RQSPSRGLEWLGRTYYRSK WYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGTPTVT VSSGGSEGKSSGSGSESKSTGGSDI QMTQSPDSLAVSLGERATINCESSQSVLFSSNKKNYLAWYQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTINRLQAEDVAVYYCQYNSTPWTFGQGTKEIK	260
MHGB689-LH	DIQMTQSPDSLAVSLGERATINCESSQSVLFSSNKKNYLAWYQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTINRLQAEDVAVYYCQYNSTPWTFGQGTKEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTLCVISGDSVSSNRAAWNWI RQSPSRGLEWLGRTYYRSK WYNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGTPTVT VSS	261
MHGB694-HL	EVQLLES GGLVQPGGSLRLS CAASGFTFSSYAMHWVRQAPGKGLDWVSGISGSGFSTYYVDSVKGRFTISRDN SKHTLYLQMNSLRAEDTAVYYCAKDNLVAGTVFDYWGGQTLVT VSSGGSEGKSSGSGSESKSTGGSDI QMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQKPGKAPKLLIYKASSLES GVP SRFSGSGSGTEFTLTISSLQPD FATYYCQYNSYS LTFGGGT KVDIK	262
MHGB694-LH	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQKPGKAPKLLIYKASSLES GVP SRFSGSGSGTEFTLTISSLQPD FATYYCQYNSYS LTFGGGT KVDIKGGSEGKSSGSGSESKSTGGSEVQLLES GGLVQPGGSLRLS CAASGFTFSSYAMHWVRQAPGKGLDWVSGISGSGFSTYYVDSVKGRFTISRDN SKHTLYLQMNSLRAEDTAVYYCAKDNLVAGTVFDYWGGQTLVT VSS	263
MHGB732-HL	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWI RQSPSRGLEWLGRTYYRSK WYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGGQTLVT VSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPPTFGQGTKEIK	264
MHGB732-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPPTFGQGTKEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTLCAISGDSVSS	265

	SNSAAWNWIRQSPSRGLEWLGRITYYRSKWYNDYAVSVKSRITINPDTSKNQIS LQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTSLTVSS	
MHGB737-HL	EVQLLESGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVSGIS SGSFSTYYVDSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKDNLVAGT VFDYWGGQTLTVSSGGSEKSSGSGSESKSTGGSDIQMTQSPSTLSASVGDR VTITCRASQSISSWLAWYQQKPKAPKLLIYKASLESQVPSRFSGSGSGTEFTL TISSLQPDFFATYYCQYNSYSLTFGGGTKVDIK	266
MHGB737-LH	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPKAPKLLIYKASSL ESQVPSRFSGSGSGTEFTLTISLQPDFFATYYCQYNSYSLTFGGGTKVDIKGG SEKSSGSGSESKSTGGSEVQLLESGLVQPGGSLRLSCAASGFTFSSYAMH WVRQAPGKLEWVSGISGSGSFSTYYVDSVKGRFTISRDN SKNTLYLQMNSLRA EDTAVYYCAKDNLVAGTVFDYWGGQTLTVSS	267
MHGB738-HL	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNRAAWN WIRQSPSRGLEWLGR ITYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCARVRPGIP FDYWGGQTPVTVSSGGSEKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGERA TINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSVS GTDFTLTISLQAEDVAVYYCQYHSTPWTFGQGTKEIK	268
MHGB738-LH	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSVSGTDFTLTISLQAEDVAVYYCQYHSTPWTFGQG TKVEIKGGSEKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDS VSSNRAAWN WIRQSPSRGLEWLGRITYYRSKWYNDYAVSVKSRITINPDTSKN QISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGQTPVTVSS	269

Table 18. Amino acid sequences of the scFv-Fcs.

Acronym	Amino acid sequence of scFv	SEQ ID NO:
MHGB665-HL-Fc	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGR ITYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGI VGLPFAYWGQGTSLTVSSGGSEKSSGSGSESKSTGGSDIVMTQSPDSLAVSL GERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTISLQAEDVAVYYCHQYYSTPPTFGQGTKEIKEPKSSDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPI EKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFPYPSDIAVEWESNGQ PENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ KSLSLSPGK	270
MHGB665-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCHQYYSTPPTFGQGT KVEIKGGSEKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDSVS SNSAAWNWIRQSPSRGLEWLGRITYYRSKWYNDYAVSVKSRITINPDTSKNQIS LQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTSLTVSSSEPKSSDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIE KTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFPYPSDIAVEWESNGQP	271

	ENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	
MHGB668-HL-Fc	QVQLQQSGPGLVKPSQTLSTCAISGDSVSNNSAAWNWIRQSPSRGLEWLGR TYYSKWKYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARYGSGT LLFDYWGGQTLTVTSVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGER ATINCKSSQSVLYSSKNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGS GSGTDFTLTISSLQAEDVAVYYCQQYYSTFPYTFGQGTKEIKEPKSSDKHTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFPYSDIAVEWESNGQP ENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	272
MHGB668-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSKNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTFPYTFGQG TKLEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTCAISGDSV SNNSAAWNWIRQSPSRGLEWLGRYYYSKWKYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARYGSGTLLFDYWGGQTLTVTSSEPKSSDKHTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE TISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFPYSDIAVEWESNGQPE NNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	273
MHGB669-HL-Fc	QVQLQQSGPGLVRPSQTLSTCAISGDSVSSNSASWNWIRQSPSRGLEWLGR TYRSEWFNDYAVSVKSRVTINPDTSKNQSLQLNSVIPEDTAVYYCAREARIGV AGKGFYWGQGTTLTVTSVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSL GERATINCKSSQSVLFRSNNKNYLAWFQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPRTFGQGTKEIKEPKSSDKHTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFPYSDIAVEWESNGQ PENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	274
MHGB669-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLFRSNNKNYLAWFQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPRTFGQGT KVEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVRPSQTLSTCAISGDSV SSNSASWNWIRQSPSRGLEWLGRYYRSEWFNDYAVSVKSRVTINPDTSKNQ LSLQLNSVIPEDTAVYYCAREARIGVAGKGFYWGQGTTLTVTSSEPKSSDKHTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFPYSDIAVEWESNGQ PENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	275
MHGB672-HL-Fc	QVQLQQSGPGLVKPSQTLSTCAISGDSVSNRAAWNWIRQTPSRGLEWLGR TYRSEWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARVRAAV PFDYWGGQTLTVTSVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGER ATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPNLLIYWASTRESGVPDRFSGS VSGTDFTLTISSLQAEDVAIYYCQQYHSTPWFQGTKEIKEPKSSDKHTHTCPP	276

	CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEK TISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPE NNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	
MHGB672-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPNLLI YWASTRESGVPDRFSGSVSGTDFTLTISSLQAEDVAIYYCQYHSTPWFQGG TKVEIKGGSEGKSSGSGSEKSTGGSQVQLQSGPGLVKPSQTLSTCAISGDSV SSNRAAWNWRQTSPRGLEWLGRYYRSEWYNDYAVSVKSRITINPDTSKNQ FSLQLNSVTPEDTAVYYCARVRAAVPFDYWGQGLTVTSSEPKSSDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEK TISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPE NNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	277
MHGB687-HL-Fc	QLQLQESGPGLVKPSSETLSLMCTVSGGSITSSSYWGWIRQPPGKGLEWIGNIY YSGTTYNPSPKSRVTISVDTSKNQFSLKSSVTAADTAVYYCAAGARDFDSWG QGSLVTVSSGGSEGKSSGSGSEKSTGGSDIVMTQSPDSLAVSLGERATINCKSS QSVLYSSNKNYLAWYQQRPQPPLLIYWASTRESGVPDRFSGSGSDFTLT ISSLQAEDVAIYYCQYYSTPRMYTFGQGTKEIKEPKSSDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKG QPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLT WPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK	278
MHGB687-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNKNYLAWYQQRPQPPLLIY WASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQYYSTPRMYTFGQ GTKEIKGGSEGKSSGSGSEKSTGGSQLQLQESGPGLVKPSSETLSLMCTVSGGS ITSSSYWGWIRQPPGKGLEWIGNIYSGTTYNPSPKSRVTISVDTSKNQFSLK LSSVTAADTAVYYCAAGARDFDSWGQGSLVTVSSEPKSSDKTHTCPPCPAPEA AGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKG QPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLT WPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK	279
MHGB688-HL-Fc	EVQLLESQGLVKPSQTLSTLCVIGDSVSSNRAAWNWRQSPSRGLEWLGR YYRSKWNNDYAVSVKSRITINSDTSKNQISLQLNSVTPEDTAVYYCARVRPGIF DYWGQGPVTVSSGGSEGKSSGSGSEKSTGGSDIVMTQSPDSLAVSLGERAT INCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGS GTDFTLTISSLQAEDVAIYYCQYNSTPWFQGTKEIKEPKSSDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDG EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKT ISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPE NNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK	280
MHGB688-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAIYYCQYNSTPWFQGG	281

	TKVEIKGGSEKSSGSGSESKSTGGSEVQLLESGPGLVKPSQTLSTLCVISGDSVS SNRAAWNWIWQSPSRGLEWLGRYYRSKWYNDYAVSVKSRITINSKTNQIS LQLNSVTPEDTAVYYCARVRPGIPFDYWGGQTPVTVSSEPKSSDKTHTCPPCP APEAAGGSPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPEN NYLTWPPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSL SLSPGK	
MHGB689-HL-Fc	QVQLQQSGPGLVKPSQTLSTLCVISGDSVSSNRAAWNWIWQSPSRGLEWLGR YYRSKWYNDYAVSVKSRITINSKTNQISLQLNSVTPEDTAVYYCARVRPGIP FDYWGGQTTVTVSSGGSEKSSGSGSESKSTGGSDIQTQSPDSLAVSLGERA TINCESSQSVLFSSNKKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGS GTDFTLTINRLQAEDVAVYYCQYNSPTWTFGQGTKEIKEPKSSDKTHTCPPC PAPEAAGGSPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDG EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPEN NYLTWPPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSL SLSPGK	282
MHGB689-LH-Fc	DIQMTQSPDSLAVSLGERATINCESSQSVLFSSNKKNYLAWYQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTINRLQAEDVAVYYCQYNSPTWTFGQ GTKEIKGGSEKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTLCVISGD SVSSNRAAWNWIWQSPSRGLEWLGRYYRSKWYNDYAVSVKSRITINSKTN QISLQLNSVTPEDTAVYYCARVRPGIPFDYWGGQTTVTVSSEPKSSDKTHTCPP CPAPEAAGGSPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPE NNYLTWPPVLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKS LSLSPGK	283
MHGB694-HL-Fc	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKGLDWSGIS GSGFSTYYVDSVKGRFTISRDNKHTLYLQMNSLRAEDTAVYYCAKDNLVAGT VFDYWGGQTLTVTVSSGGSEKSSGSGSESKSTGGSDIQTQSPSTLSASVGDR VTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSGSGSGTEFTLT ISSLQPDDEFATYYCQYNSYSLTFGGGTKVDIKEPKSSDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLTWPP VLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK	284
MHGB694-LH-Fc	DIQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSL ESGVPSRFSGSGSGTEFTLTISLQPDDEFATYYCQYNSYSLTFGGGTKVDIKGG SEKSSGSGSESKSTGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMH WVRQAPGKGLDWSGISGSGFSTYYVDSVKGRFTISRDNKHTLYLQMNSLR AEDTAVYYCAKDNLVAGTVFDYWGGQTLTVTVSSEPKSSDKTHTCPPCPAPEAA GGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYVLPSPREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLTWPP VLDSDGSEFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK	285

MHGB732-HL-Fc	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWIRQSPSRGLEWLGR TYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGI VGLPFAYWGQGTTLVTSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSL GERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPTFGQGTKEIKEPKSSDKTHT CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYV DGEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPI EKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFYPSDIAVEWESNGQ PENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQ KSLSLSPGK	286
MHGB732-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQQKPGQPPKLLI YWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPTFGQGT KVEIKGGSEGKSSGSGSESKSTGGSQVQLQQSGPGLVKPSQTLSTLCAISGDSVS SNSAAWNWIRQSPSRGLEWLGRTYRSKWYNDYAVSVKSRITINPDTSKNQIS LQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTTLVTSSSEPKSSDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIE KTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFYPSDIAVEWESNGQP ENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK SLSLSPGK	287
MHGB737-HL-Fc	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMHWVRQAPGKGLEWVSGIS GSGFSTYYVDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDNLVAGT VFDYWGQGTTLVTSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSTLSASVGDR VTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSGSGSGTEFTLT ISLQPDFFATYYCQQYNYSYSLTFGGGTQVDIKEPKSSDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVDGVEVHNAK TPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ PREPQVYVLPSSREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLTWPP VLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK	288
MHGB737-LH-Fc	DIQMTQSPSTLSASVGDRTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSL ESQVPSRFSGSGSGTEFTLTISLQPDFFATYYCQQYNYSYSLTFGGGTQVDIKG SEGKSSGSGSESKSTGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMH WVRQAPGKGLEWVSGISGSGFSTYYVDSVKGRFTISRDNKNTLYLQMNSLRA EDTAVYYCAKDNLVAGTVFDYWGQGTTLVTSSSEPKSSDKTHTCPPCPAPEAAG GPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVDGVEVHNAK TPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQ PREPQVYVLPSSREEMTKNQVSLCLVKGFYPSDIAVEWESNGQPENNYLTWPP VLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK	289
MHGB738-HL-Fc	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNRAAWNWIRQSPSRGLEWLGR TYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCARVRP FDYWGQGTPTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPDSLAVSLGERA TINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSV GTDFTLTISSLQAEDVAVYYCQYHSTPWFQGTKEIKEPKSSDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVSVSHPEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIE KTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFYPSDIAVEWESNGQP ENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK SLSLSPGK	290

MHGB738-LH-Fc	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGVPDFSGSVSGTDFTLTISSLQAEDVAVYYCQQYHSTPWTFGQG TKVEIKGGSEGKSSGSGSEKSTGGSQVQLQQSGPGLVKPSQTLSTLCAISGDSV SSNRAAWNWIRQSPSRGLEWLGRITYYRSKWNNDYAVSVKSRITINPDTSKNQI SLQLNSVTPEDTAVYYCARVRPGIPFDYWGGQTPVTVSSEPKSSDKHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYVLPSPREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSL SLSPGK	291
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Table 19. cDNA sequences of anti-HLA-G scFvs and scFv-Fcs.

scFv or scFv- Fc	cDNA SEQ ID NO:	cDNA
MHG B665- HL	292	CAGGTGCAGCTGCAGCAGAGCGGCCCTGGACTGGTGAAGCCCAGCCAGACCC TGAGCCTGACCTGCGCTATCAGCGGCGATAGCGTGAGCTCCAACAGCGCCGC CTGGAACCTGGATCAGGCAGAGCCCTAGCAGGGGCTGGAATGGCTGGGCAGG ACCTACTACAGGAGCAAGTGGTACAACGACTACGCCGTGTCCGTGAAGAGCA GGATCACCATCAACCCCCGACACCAGCAAGAACCAGATCAGCCTGCAGCTGAA CAGCGTGACCCCCGAGGACACCGCCGTGTACTACTGCGCCGGCGACAGAAGG TACGGCATCGTGCGCCTGCCTTTCGCCTACTGGGGCCAGGGAACCCCTGGTGAC CGTGAGCAGCGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAG CAAGTCCACCGGCGGAAGCGACATCGTGATGACCCAGAGCCCCGATAGCCTG GCTGTGAGCCTGGGCGAGAGAGCCACCATCAACTGCAAGAGCAGCCAGAGCG TGCTGCACAGCAGCAACAACAAGAACTACCTGACCTGGTTCCAGCAGAAGCC CGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCTAGCACCAGAGAGTCCGGC GTGCCTGACAGGTTTCAGCGGAAGCGGCAGCGGCACCGACTTCACCCTGACCA TCAGCAGCCTGCAGGCCGAGGACGTGGCCGTGTACTACTGCCACCAGTACTA CAGCACCCCCCTACCTTTGGCCAGGGCACCAAGGTGGAGATCAAG
MHG B665- LH	293	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGA GAGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGCACAGCAGCAACAA CAAGAACTACCTGACCTGGTTCCAGCAGAAGCCCGGCCAGCCTCCCAAGCTG CTGATCTACTGGGCTAGCACCAGAGAGTCCGGCGTGCTGACAGGTTACGCG GAAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGGCCGA GGACGTGGCCGTGTACTACTGCCACCAGTACTACAGCACCCCCCTACCTTTG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCG GCTCCGCGCAGCGAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCAGCA GAGCGGCCCTGGACTGGTGAAGCCCAGCCAGACCCTGAGCCTGACCTGCGCT ATCAGCGCGATAGCGTGAGCTCCAACAGCGCCGCTGGAACCTGGATCAGGC AGAGCCCTAGCAGGGGCTGGAATGGCTGGGCAGGACCTACTACAGGAGCAA GTGGTACAACGACTACGCCGTGTCCGTGAAGAGCAGGATCACCATCAACCCC GACACCAGCAAGAACCAGATCAGCCTGCAGCTGAACAGCGTGACCCCCGAGG ACACCGCGTGTAATACTGCGCCGGCGACAGAAGGTACGGCATCGTGGGCCT GCCTTTCGCCTACTGGGGCCAGGGAACCCCTGGTGACCGTGAGCAGC
MHG B668- HL	294	CAGGTGCAGCTGCAGCAGAGCGGACCCGGCCTGGTGAACCCAGCCAGACCC TGAGCCTGACCTGCGCCATCAGCGGCGACAGCGTGAGCAACAACAGCGCCGC CTGGAACCTGGATCAGGCAGAGCCCCAGCAGAGGCCTGGAATGGCTGGGCAGG ACCTACTACAGGAGCAAGTGGTACAACGACTACGCCGTGAGCGTGAAGAGCA

		GGATCACCATCAACCCCGACACCTCCAAGAACCAGTTCAGCCTGCAGCTGAA CAGCGTGACCCCGGAGGACACCGCCGTGTACTACTGCGCCAGGTATGGCAGC GGCACCTGCTGTTTCGACTACTGGGGCCAGGGCACCTGGTGACAGTGAGCA GCGGCGGATCTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAAAGCAAGTCCAC CGGCGGAAGCGACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGC CTGGGAGAGAGGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTACA GCAGCAAGAACAAGAACTACCTGGCCTGGTACCAGCAGAAAACCCGGCCAGCC CCCCAAGCTGCTGATCTACTGGGCCAGCACAAAGGGAAAAGCGGCGTGCCCGAC AGATTACGCGGAAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCC TGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCTTC CCCTACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG
MHG B668- LH	295	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGAGAGA GGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGTGTACAGAGCAAGAA CAAGAACTACCTGGCCTGGTACCAGCAGAAAACCCGGCCAGCCCCCAAGCTG CTGATCTACTGGGCCAGCACAAAGGGAAAAGCGGCGTGCCCGACAGATTACAGC GAAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGGCCGA GGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCTTCCTTACACCT TCGGCCAGGGCACCAAGCTGGAGATCAAGGGCGGATCTGAGGGAAAAGTCCA GCGGCTCCGGCAGCGAAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCA GCAGAGCGGACCCGGCCTGGTGAAACCCAGCCAGACCCTGAGCCTGACCTGC GCCATCAGCGGCGACAGCGTGAGCAACAACAGCGCCGCTGGAAGTGGATCA GGCAGAGCCCCAGCAGAGGCCCTGGAATGGCTGGGCAGGACCTACTACAGGA GCAAGTGGTACAACGACTACGCCGTGAGCGTGAAGAGCAGGATCACCATCAA CCCCGACACCTCCAAGAACCAGTTCAGCCTGCAGCTGAACAGCGTGACCCCC GAGGACACCGCCGTGTACTACTGCGCCAGGTATGGCAGCGGCACCCCTGCTGT TCGACTACTGGGGCCAGGGCACCTGGTGACAGTGAGCAGC
MHG B669- HL	296	CAGGTGCAGCTGCAGCAGAGCGGACCCGGACTGGTGAGACCCAGCCAGACCC TGAGCGTGACCTGCGCCATCAGCGCGCAGAGCGTGAGCAGCAACAGCGCCAG CTGGAAGTGGATCAGGCAGAGCCCCAGCAGAGGCCTGGAGTGGCTGGGAAG GACATACTACAGGAGCGAGTGGTTCAACGACTACGCCGTGAGCGTGAAGAGC AGGGTGACCATCAACCCCGACACCAAGCAAGAACCAAGCTGAGCCTGCAGCTGA ACAGCGTGATCCCCGAGGACACCGCCGTGTACTACTGCGCCAGAGAGGCCAG AATCGGCGTGCGCCGCAAGGGCTTCGACTACTGGGGCCAGGGCACCTGGTG ACAGTGTCCAGCGGCGGATCTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAA GCAAGTCCACCGGCGGAAGCGACATCGTGATGACCCAGAGCCCTGACTCCCT GGCTGTGAGCCTGGGCGAGAGAGCCACCATCAACTGCAAGAGCAGCCAGAGC GTGCTGTTCAGGAGCAACAACAAGAACTACCTGGCCTGGTTCAGCAGAAAGC CCGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCCAGCACCAAGAGAGAGCGG CGTGCCCGATAGATTTAGCGGCAGCGGCAGCGGCACCGACTTTACCCTGACC ATCAGCTCCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTA CAGCACCCCCAGAACCTTCGGCCAGGGCACCAAGGTGGAGATCAAG
MHG B669- LH	297	GACATCGTGATGACCCAGAGCCCTGACTCCCTGGCTGTGAGCCTGGGCGAGA GAGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTCAGGAGCAACAA CAAGAACTACCTGGCCTGGTTCAGCAGAAAGCCGGCCAGCCTCCCAAGCTG CTGATCTACTGGGCCAGCACCAAGAGAGAGCGGCGTGCCCGATAGATTTAGCG GCAGCGGCAGCGGCACCGACTTTACCCTGACCATCAGCTCCCTGCAGGCCGA GGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCCAGAACCTTCG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAAAGTCCAGCG GCTCCGGCAGCGAAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCAGCA GAGCGGACCCGGACTGGTGAGACCCAGCCAGACCCTGAGCGTGACCTGCGCC ATCAGCGGCGACAGCGTGAGCAGCAACAGCGCCAGCTGGAAGTGGATCAGCG AGAGCCCCAGCAGAGGCCTGGAGTGGCTGGGAAGGACATACTACAGGAGCG AGTGGTTCAACGACTACGCCGTGAGCGTGAAGAGCAGGGTGACCATCAACCC CGACACCAGCAAGAACCAGCTGAGCCTGCAGCTGAACAGCGTGATCCCCGAG GACACCGCCGTGTACTACTGCGCCAGAGAGGCCAGAATCGGCGTGCCCGGCA AAGGCTTCGACTACTGGGGCCAGGGCACCTGGTGACAGTGTCAGC

MHG B672- HL	298	CAGGTGCAGCTGCAGCAGAGCGGACCTGGCCTGGTGAAGCCCAGCCAGACCC TGAGCCTGACATGCGCCATCAGCGGCGACAGCGTGAGCAGCAATAGGGCCGC CTGGAATGGATCAGGCAGACCCCTAGCAGGGGCTGGAATGGCTGGGCAGG ACATACTACAGGAGCGAGTGGTACAACGACTACGCCGTGTCCGTGAAGAGCA GGATCACCATCAACCCCCGACACCAGCAAGAACCAGTTCAGCCTGCAGCTGAA CAGCGTGACCCCCGAGGACACCGCCGTGTACTACTGCCCCAGAGTGAGAGCC GCCGTGCCTTTCTGACTACTGGGGCCAGGGCACCCCTGGTGACAGTGAGCAGCG GCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGG CGGAAGCGACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTG GGCGAGAGGGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTTCCA GCAACAACAAGAACTACCTGGCCTGGTACCAGCAGAAACCCGGCCAGCCCC CAACCTGCTGATCTACTGGGCCAGCACCAGAGAAAGCGGCGTGCCCGCAGG TTTAGCGGCAGCGTGAGCGGCACCGACTTCACCCCTGACCATCAGCAGCCTGC AGGCCGAGGACGTGGCCATCTACTACTGCCAGCAGTACCACAGCACCCCTG GACATTCCGGCCAGGGCACCAAGGTGGAGATCAAG
MHG B672- LH	299	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGA GGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTTCCAGCAACAA CAAGAACTACCTGGCCTGGTACCAGCAGAAACCCGGCCAGCCCCCAACCTG CTGATCTACTGGGCCAGCACCAGAGAAAGCGGCGTGCCCGACAGGTTTAGCG GCAGCGTGAGCGGCACCGACTTCACCCCTGACCATCAGCAGCCTGCAGGGCCA GGACGTGGCCATCTACTACTGCCAGCAGTACCACAGCACCCCTGGACATTCTG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCG GCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCCAGGTGCAGCTGCAGCA GAGCGGACCTGGCCTGGTGAAGCCCAGCCAGACCCCTGAGCCTGACATGCGCC ATCAGCGGCGACAGCGTGAGCAGCAATAGGGCCGCTGGAAGTGGATCAGGC AGACCCCTAGCAGGGGCTGGAATGGCTGGGCAGGACATACTACAGGAGCGA GTGGTACAACGACTACGCCGTGTCCGTGAAGAGCAGGATCACCATCAACCCC GACACCAGCAAGAACAGTTTACGCTGCAGCTGAACAGCGTGACCCCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGAGAGCCCGCCGTGCCTTTCTGACTAC TGGGGCCAGGGCACCCCTGGTGACAGTGAGCAGC
MHG B687- HL	300	CAGCTGCAGCTGCAGGAGAGCGGCCCTGGACTGGTGAAGCCCAGCGAGACCC TGAGCCTGATGTGCACCGTGAGCGGCGGCAGCATCACCAGCAGCAGCTACTA CTGGGGATGGATCAGACAGCCCCCTGGCAAGGGCCTGGAGTGGATCGGCAAC ATCTACTACAGCGGCACCACCTACTACAACCCAGCCTGAAGAGCAGGGGTGA CCATCAGCGTGGACACCAGCAAGAACCAGTTTACGCTGAAGCTGAGCAGCGT GACAGCTGCCGACACCGCCGTGTACTACTGTGCCGCCGGAGCCAGAGACTTC GACAGCTGGGGACAGGGCAGCCTGGTGACCGTGTCCAGCGGCGGATCTGAGG GAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACA TCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCCTGGGAGAGAGAGC CACCATCAACTGCAAGTCTCCAGAGCGTGCTGTACAGCTCCAGCAACAAG AGCTACCTGGCCTGGTACCAGCAGAGGCCCGGACAGCCTCCCAAGCTGCTGA TCTACTGGGCCAGCACCAGAGAGAGCGGCGTGCCTGACAGGTTTAGCGGCTC CGGCTCCGGCACCGACTTTACCCTGACCATCAGCAGCCTGCAGGCCGAGGAT GTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCCAGGATGTACACCTT CGGCCAGGGCACCAAGCTGGAGATCAAG
MHG B687- LH	301	GACATCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCCTGGGAGAGA GAGCCACCATCAACTGCAAGTCTCCAGAGCGTGCTGTACAGCTCCAGCAA CAAGAGCTACCTGGCCTGGTACCAGCAGAGGCCCGGACAGCCTCCCAAGCTG CTGATCTACTGGGCCAGCACCAGAGAGAGCGGCGTGCCTGACAGGTTTAGCG GCTCCGGCTCCGGCACCGACTTTACCCTGACCATCAGCAGCCTGCAGGCCGAG GATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCCAGGATGTACA CCTTCGGCCAGGGCACCAAGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTC CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCCAGCTGCAGCTG CAGGAGAGCGGCCCTGGACTGGTGAAGCCCAGCGAGACCCTGAGCCTGATGT GCACCGTGAGCGGCGGCAGCATCACCAGCAGCAGCTACTACTGGGGATGGAT CAGACAGCCCCCTGGCAAGGGCCTGGAGTGGATCGGCAACATCTACTACAGC

		GGCACCACCTACTACAACCCAGCCTGAAGAGCAGGGTGACCATCAGCGTGG ACACCAGCAAGAACAGTTCAGCCTGAAGCTGAGCAGCGTGACAGCTGCCGA CACCGCCGTGTACTACTGTGCCGCCGAGCCAGAGACTTCGACAGCTGGGGA CAGGGCAGCCTGGTGACCGTGTCCAGC
MHG B688- HL	302	GAGGTGCAGCTGTTGGAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCC TCTCACTCACCTGTGTCTATCTCCGGGGACAGTGTCTCTAGCAACAGAGCTGCT TGGAAGTGGATCAGGCAGTCCCCATCGAGAGGCCCTTGAGTGGCTGGGAAGGA CATACTACAGGTCCAAGTGGTATAATGATTATGCAGTATCTGTGAAAAGTCGA ATAACCATCAATTCAGACACATCCAAGAACCAGATCTCCCTGCAGTTGAACTC TGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGTGAGACCGGGG ATCCCATTTGACTACTGGGGCCAGGGAACCCCGGTACCGTCTCCTCAGGCGG ATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGGA AGCGACATCGTGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTTGGGCGA GAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATTAGCTCCAACA AAAAGAAGTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCT GCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGT GCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGA AGATGTGGCAGTTTATTACTGTGCAATATAATAGTACTCCGTGGACGTTTCG GCCAAGGGACCAAGGTGGAGATCAAA
MHG B688- LH	303	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAG GGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATTAGCTCCAACAAAA AGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCTGCT CATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGTGGA GCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGGCTGAAGA TGTGGCAGTTTATTACTGTGCAATATAATAGTACTCCGTGGACGTTCCGGC AAGGGACCAAGGTGGAGATCAAAGGCGGATCTGAGGGAAAGTCCAGCGGCT CCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGAGGTGCAGCTGTTGGAGTC AGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGTCTCT CCGGGGACAGTGTCTCTAGCAACAGAGCTGCTTGGAACTGGATCAGGCAGTC CCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGG TATAATGATTATGCAGTATCTGTGAAAAGTCGAATAACCATCAATTCAGACAC ATCCAAGAACCAGATCTCCCTGCAGTTGAACTCTGTGACTCCCGAGGACACG GCTGTGTATTACTGTGCAAGAGTGAGACCGGGGATCCCATTTGACTACTGGGG CCAGGGAACCCCGGTACCGTCTCCTCA
MHG B689- HL	304	CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCC TCTCACTCACCTGTGTCTATCTCCGGGGACAGTGTCTCTAGCAACAGAGCTGCC TGGAAGTGGATCAGGCAGTCCCCATCGAGAGGCCCTTGAGTGGCTGGGAAGGA CATACTACAGGTCCAAGTGGTATAATGATTATGCAGTTTCTGTGAAAAGTCGA ATAACCATCAATTCAGACACATCCAAGAACCAGATCTCCCTGCAGTTGAACTC TGTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGTGAGACCGGGG ATCCCTTTTACTACTGGGGCCAGGGAACACGGTACCGTCTCCTCAGGCGG ATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGGA AGCGACATCCAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGA GAGGGCCACCATCAACTGCGAGTCCAGCCAGAGTGTTTTATTAGCTCCAACA AAAAGAAGTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCT GCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGT GCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAACCGCCTGCAGGCTGA AGATGTGGCAGTTTATTACTGTGCAATATAATAGTACTCCGTGGACGTTTCG GCCAAGGGACCAAGGTGGAGATCAAA
MHG B689- LH	305	GACATCCAGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAGAG GGCCACCATCAACTGCGAGTCCAGCCAGAGTGTTTTATTAGCTCCAACAAAA AGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCCCCTAAGCTGCT CATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGATTCAAGTGGCA GCGGGTCTGGGACAGATTTCACTCTCACCATCAACCGCCTGCAGGCTGAAGAT GTGGCAGTTTATTACTGTGCAATATAATAGTACTCCGTGGACGTTTCGGCCA AGGGACCAAGGTGGAGATCAAAGGCGGATCTGAGGGAAAGTCCAGCGGCTC

		CGGCAGCGAAAGCAAGTCCACCGGCGGAAGCCAGGTACAGCTGCAGCAGTC AGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGTCATCT CCGGGGACAGTGTCTCTAGCAACAGAGCTGCCTGGAAGTGGATCAGGCAGTC CCCATCGAGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGG TATAATGATTATGCAGTTTCTGTGAAAAGTCGAATAACCATCAATTCAGACAC ATCCAAGAACAGATCTCCCTGCAGTTGAACTCTGTGACTCCCCAGGACACG GCTGTGTATTACTGTGCAAGAGTGAGACCGGGGATCCCTTTTACTACTGGGG CCAGGGAACCACGGTCACCGTCTCCTCA
MHG B694- HL	306	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGTCCC TGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGCAC TGGGTCCGCCAGGCCCCAGGGAAGGGGCTGGACTGGGTCTCAGGTATTAGTG GTAGTGGCTTTAGCACATACTATGTAGACTCCGTGAAGGGCCGGTTCACCATC TCCAGAGACAATTCCAAGCACACGCTGTATCTGCAAAATGAACAGCTGAGAG CCGAGGACACGGCCGTATATTACTGTGCGAAAGATAATTTAGTGGCTGGTAC CGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGCGGAT CTGAGGGAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAA GCGACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGAC AGAGTCAACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCCTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCT AGTTTAGAAAGTGGGGTCCCATCAAGGTTTACGCGGCAGTGGATCTGGGACAG AATTCATCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTAC TGCCAACAGTATAATAGTTATTCGCTCACTTTCGGCGGAGGGACCAAGGTGG ATATCAAA
MHG B694- LH	307	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCCTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCTAG TTTAGAAAGTGGGGTCCCATCAAGGTTTACGCGGCAGTGGATCTGGGACAGAA TTCATCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGC CAACAGTATAATAGTTATTCGCTCACTTTCGGCGGAGGGACCAAGGTGGATAT CAAAGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC CACC GGCGGAAGCGAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAG CCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAG CTATGCCATGCACTGGGTCCGCCAGGCCCCAGGGAAGGGGCTGGACTGGGTCT TCAGGTATTAGTGGTAGTGGCTTTAGCACATACTATGTAGACTCCGTGAAGGG CCGTTTACCATCTCCAGAGACAATTCCAAGCACACGCTGTATCTGCAAAATGA ACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGATAATTT AGTGGCTGGTACCGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCT CCTCA
MHG B732- HL	308	CAAGTACAACCTGCAACAAAGTGGTCTGGGCTCGTGAAGCCTTCCCAGACTCT CAGCCTCACATGCGCTATAAGTGGGGATTCTGTTTCTCAAATTCAGCAGCCT GGAATTGGATACGACAGTCTCCATCCCGTGGCCTTGAGTGGCTTGGTAGAACT TATTACCGATCCAAGTGGTACAATGATTACGCCGTTTCAGTGAAGTCCCGCAT TACTATTAATCCCGACACATCTAAGAATCAAATTTTATTGCAACTGAATAGCG TAACACCCGAAGATACAGCAGTTTATTATTGTGCAGGTGATCGACGCTACGGC ATAGTGGGACTTCTTTTCGCTATTGGGGCCAAGGGACACTGGTCACTGTGTCT ATCCGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCC ACCGGCGGAAGCGACATCGTAATGACACAGTCACCAGATTCAATGGCAGTTA GTCTGGGTGAAAGGGCAACAATCAACTGCAAGTCTTCTCAGAGTGTACTGCA TAGTTCTAACAAATAAGAACTACCTTACCTGGTTTCAACAGAAACCAGGTACAGC CCCCAAGTTGCTGATTTACTGGGCAAGCACCCGCGAATCCGGCGTTCCTCGAT CGATTTTCAGGTTCCGGGAGTGGGACCGACTTACCTTGACCATCTCTTCTCTIG CAGGCCGAAGATGTAGCCGTCTATTACTGCCATCAGTATTACTCTACTCCCC CACATTCGGTCAAGGTACAAAAGTTGAGATAAAA

MHG B732- LH	309	GACATCGTAATGACACAGTCACCAGATTCATTGGCAGTTAGTCTGGGTGAAA GGGCAACAATCAACTGCAAGTCTTCTCAGAGTGTACTGCATAGTTCTAAACAAT AAGAATACCTTACCTGGTTTCAACAGAAACCAGGTCAGCCCCCAAGTTGCT GATTTACTGGGCAAGCACCCGCGAATCCGGCGTTCCCGATCGATTTTCAGGTT CCGGGAGTGGGACCGACTTTACCTTGACCATCTCTTCTTGCAGGCCGAAGAT GTAGCCGTCTATTACTGCCATCAGTATTACTCTACTCCCCCACATTCGGTCAA GGTACAAAAGTTGAGATAAAAGGCGGATCTGAGGGAAAGTCCAGCGGCTCCG GCAGCGAAAAGCAAGTCCACCGCGGAAGCCAAGTACAACCTGCAACAAAAGTG GTCCTGGGCTCGTGAAGCCTTCCCAGACTCTCAGCCTCACATGCGCTATAAGT GGGGATTCTGTTTCTCAAATTCAGCAGCCTGGAATTGGATACGACAGTCTCC ATCCCGTGGCCTTGAGTGGCTTGGTAGAACTTATTACCGATCCAAGTGGTACA ATGATTACGCCGTTTCAGTGAAGTCCCGCATTACTATTAATCCCGACACATCT AAGAATCAAATTTTCATTGCAACTGAATAGCGTAACACCCGGAAGATCAGCAG TTTATTATTGTGCAGGTGATCGACGCTACGGCATAAGTGGGACTTCTTTTCGCC TATTGGGGCCAAGGGACACTGGTCACTGTGTCATCC
MHG B737- HL	310	GAGGTGCAACTCCTTGAATCAGGCGGAGGACTCGTCCAACCTGGAGGGAGTC TTAGGCTTAGCTGTGCAGCCAGTGGCTTTACTTTTAGCAGCTATGCAATGCAC TGGGTCAGGCAGGCTCCTGGTAAGGGGCTCGAATGGGTCAGCGGCATATCCG GGTCAGGTTTCTCTACATATTATGTCGATTCTGTAAAAGGACGATTCACCATA TCCAGAGACAATTCTAAAAATACCTTGTATCTCCAGATGAACAGCCTGAGAG CAGAAGATACCGCAGTTTATTACTGTGCAAAGGATAATCTGGTTGCCGGGAC AGTTTTTGATTATTGGGGGCAAGGCACCCTCGTCACAGTATCCAGTGGCGGAT CTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGCGAA GCGATATTCAGATGACTCAATCACCTTCAACCCTTAGCGCCTCCGTTGGAGAT CGCGTTACCATTAACCTGCCGAGCCTCCCAAAGTATCAGCTCATGGTTGGCATG GTATCAACAGAAAGCCTGGAAAGGCACCCAACTTCTGATTACAAAGCCAGC TCCTTGAGTCAAGGAGTCCCAAGCCGTTTCAGCGGATCTGGGTCAAGGACAG AATTTACCCTGACCATATCTTCCCTCAGCCCGACGACTTCGCCACTTACTATT GTCAGCAATACAACCTCTATTCCCTGACTTTCGGCGGTGGCACAAAGTTGAC ATCAAG
MHG B737- LH	311	GATATTCAGATGACTCAATCACCTTCAACCCTTAGCGCCTCCGTTGGAGATCG CGTTACCATTACCTGCCGAGCCTCCCAAAGTATCAGCTCATGGTTGGCATGGT ATCAACAGAAAGCCTGGAAAGGCACCCAACTTCTGATTACAAAGCCAGCTC CTTGAGTCAAGGAGTCCCAAGCCGGTTCAGCGGATCTGGGTCAAGGACAGAA TTTACCCTGACCATATCTTCCCTCAGCCCGACGACTTCGCCACTTACTATTGT CAGCAATACAACCTCTATTCCCTGACTTTTCGGCGGTGGCACAAAGGTTGACAT CAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC CACCGGCGGAAGCGAGGTGCAACTCCTTGAATCAGGCGGAGGACTCGTCCAA CCTGGAGGGAGTCTTAGGCTTAGCTGTGCAGCCAGTGGCTTTACTTTTAGCAG CTATGCAATGCACTGGGTCAAGCAGGCTCCTGGTAAGGGGCTCGAATGGGTC AGCGGCATATCCGGGTCAAGTTTCTCTACATATTATGTCGATTCTGTAAAAGG ACGATTACCATATCCAGAGACAATTCTAAAAATACCTTGTATCTCCAGATGA ACAGCCTGAGAGCAGAAGATACCGCAGTTTATTACTGTGCAAAGGATAATCT GGTTGCCGGGACAGTTTTTGATTATTGGGGGCAAGGCACCCTCGTCACAGTAT CCAGT
MHG B738- HL	312	CAGGTGCAGCTTCAACAGAGCGGACCTGGTCTGGTTAAGCCTTCCCAAACCT GAGCCTGACTTGTGCTATTTCCGGGGATAGTGTAGCTCCAATAGGGCAGCAT GGAATGGATCAGACAGTCCCCAAGCCGTGGACTTGAGTGGCTTGGACGTAC TTATTACAGGAGTAAATGGTACAATGATTATGCCGTTTCTGTGAAGAGCCGTA TTACTATAAACCCAGATACTTCTAAAAATCAAATTTCCCTTCAGCTCAACTCA GTIACACCAGAGGATACTGCAGTCTATTATTGCGCAAGAGTTCGACCTGGCAT TCCCTTCGATTATTGGGGGACAGGGACACCCGTTACTGTGTCCTCAGGCGGAT CTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGCGAA GCGATATTGTTATGACACAGTCCCCAGATTCAATTGGCAGTAAGCCTCGGTGAA CGGGCTACTATTAAGTGAAGTCTTCCAGAGTGTATTGTTCTCTTCAAATAA CAAAAACCTACCTGGCATGGTATCAGCAAAAAGCCTGGTCAACCCCTAAACTT

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MHG B738- LH	313	GATATTGTTATGACACAGTCCCCAGATTCTTGGCAGTAAGCCTCGGTGAACG GGCTACTATTAAGTGTAAAGTCTTCCCAGAGTGTATTGTTCTTCAAATAACA AAAAGTACCTGGCATGGTATCAGCAAAAAGCCTGGTCAACCCCTAAACTTCTC ATATACTGGGCATCCACTCGGGAGAGCGGTGTGCCAGACCGTTTCTCAGGGA GTGTGTCAAGGTACAGATTTTACACTCACAATTTCCAGCCTCCAAGCCGAAGAC GTTGCAGTATATTATTGCCAACAATATCACTCTACACCTTGGACATTTGGTCA AGGTAATAAGTCGAAATCAAAGGCGGATCTGAGGGAAAAGTCCAGCGGCTCC GGCAGCGAAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTTCAACAGAGC GGACCTGGTCTGGTTAAGCCTTCCCAAACCTGAGCCTGACTGTGCTATTTC CGGGGATAGTGTAGCTCCAATAGGGCAGCATGGAAGTGGATCAGACAGTCC CCAAGCCGTGGACTTGAGTGGCTTGGACGTACTTATTACAGGAGTAAATGGT ACAATGATTATGCCGTTTCTGTGAAGAGCCGTATTACTATAAACCAGATACT TCTAAAAATCAAAATTTCCCTTCAGCTCAACTCAGTTACACCAGAGGATATGC AGTCTATTATTGCGCAAGAGTTTCGACCTGGCATTCCCTTCGATTATTGGGGGC AGGGGACACCCGTTACTGTGTCCTCA
MHG B665- HL-Fc	314	CAGGTGCAGCTGCAGCAGAGCGGCCCTGGACTGGTGAAGCCCAGCCAGACCC TGAGCCTGACCTGCGCTATCAGCGGCGATAGCGTGAGCTCCAACAGCGCCGC CTGGAAGTGGATCAGGCAGAGCCCTAGCAGGGGCTGGAATGGCTGGGCAGG ACCTACTACAGGAGCAAGTGGTACAACGACTACGCCGTGTCCGTGAAGAGCA GGATCACCATCAACCCCGACACCAGCAAGAACCAGATCAGCCTGCAGCTGAA CAGCGTGACCCCCGAGGACACCGCGGTGTACTACTGCGCCGGCGCAGAGAAG TACGGCATCGTGGGCCTGCCTTTCGCCTACTGGGGCCAGGGAACCTGGTGAC CGTGAGCAGCGCGGATCTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAAAG CAAGTCCACCGCGGGAAGCGACATCGTGATGACCCAGAGCCCCGATAGCCTG GCTGTGAGCCTGGGCGAGAGAGCCACCATCAACTGCAAGAGCAGCCAGAGCG TGCTGCACAGCAGCAACAACAAGAACTACCTGACCTGGTTCCAGCAGAAGCC CGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCTAGCACCAAGAGAGTCCGGC GTGCCTGACAGGTTTCAGCGGAAGCGGCAGCGGCACCGACTTACCCTGACCA TCAGCAGCCTGCAGGCCGAGGACGTGGCCGTGTACTACTGCCACCAGTACTA CAGCACCCCCCTACCTTTGGCCAGGGCACCAAGGTGGAGATCAAGGAGCCC AAATCTAGCGACAAAACTCACACTTGTCACCGTGCCAGCACCTGAAGCAG CAGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCCTCATG ATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGTGAGCCACGAAG ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAG CGTCTCACCGTCTGCAACAGGACTGGCTGAATGGCAAGGAGTACAAGTGC AAGGTGTCCAACAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAG CCAAAGGGCAGCCCCGAGAACCACAGGTGTACGTGCTGCCCCATCCCGGGA GGAGATGACCAAGAACCAGGTGAGCCTGCTGTGCCTGGTCAAAGGCTTCTAT CCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGAGAGAACAAC TACCTCACCTGGCCTCCCGTGTGACTCCGACGGCTCCTTCTCTCTACAGC AAGCTCACCGTGGACAAGTCCAGATGGCAGCAGGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCAACAACCACTACACGCAGAAGTCTCTCCCTG TCTCCGGGAAAA
MHG B665- LH-Fc	315	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGA GAGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGTGACAGCAGCAACAA CAAGAACTACCTGACCTGGTTCCAGCAGAAGCCCGGCCAGCTCCCAAGCTG CTGATCTACTGGGCTAGCACCAAGAGAGTCCGGCGTGCCTGACAGGTTACGC GAAGCGGCAGCGCACCGACTTCACCTGACCATCAGCAGCCTGCAGGCCGA GGACGTGGCCGTGTACTACTGCCACCAAGTACTACAGCACCCCCCTACCTTTG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAAAGTCCAGCG GCTCCGCGACGCAAGCAAGTCCACCGCGGGAAGCCAGGTGCAGCTGCAGCA

		GAGCGGCCCTGGACTGGTGAAGCCCAGCCAGACCCTGAGCCTGACCTGCGCT ATCAGCGGCGATAGCGTGAGCTCCAACAGCGCCGCTGGAACCTGGATCAGGC AGAGCCCTAGCAGGGGCTGGAATGGCTGGGCAAGACCTACTACAGGAGCAA GTGGTACAACGACTACGCCGTGTCCGTGAAGAGCAGGATACCATCAACCCC GACACCAGCAAGAACCAGATCAGCCTGCAGCTGAACAGCGTGACCCCGAGG ACACCGCGGTGTACTACTGCGCCGGCGACAGAAGGTACGGCATCGTGGGCT GCCTTTCGCCTACTGGGGCCAGGGAACCTGGTGACCGTGAGCAGCgagcccaat ctagcgacaaaactcacactgtccaccgtgccagcacctgaagcagcagggggaccgtcagtccttcttcccccaaac ccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtgagcgtgagccacgaagacctgaggtcaag ttcaactgtacgtggacggcgtggaggtgcataatccaagacaaagccgggagggagcagtacaacagcacgtaccgtg tggtcagcgtcctcaccgtcctgaccagagactggctgaatggcaaggagtacaagtcaagggtgtccaacaaagccctcca gccccatcgagaaaaccatctccaagccaagggcagccccgagaaccacaggtgtacgtgtccccatcccggag gagatgaccaagaaccaggtcagcctgctgtgctgtgcaaggcttctatccagcgacatcgccgtggagtgaggagcaaa tgggcagccggagaacaactacacactggcctccgtgctggactccgacggctccttctctacagcaagtcaccgtg gacaagtcagatgcagcaggggaacgttctcatgctccgtgatcatgaggctctgcacaaccactacacgcagaagtc ctctcctgtctcgggaaaa
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MHG B668- LH-Fc	317	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGAGAGA GGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTACAGCAGCAAGAA CAAGAATACTTGGCCTGGTACCAGCAGAAACCCGGCCAGCCCCCAAGCTG CTGATCTACTGGGCCAGCACAAAGGGAAAGCGGCGTGCCCGACAGATTACGC GAAGCGGCAGCGGACCGGACTTCACCCTGACCATCAGCAGCCTGCAGGCCGA GGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCTTCCCCTACACCT TCGGCCAGGGCACCAAGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCA GCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCA GCAGAGCGGACCCGCTGGTGAAACCCAGCCAGACCTGAGCCTGACCTGC GCCATCAGCGGCGACAGCGTGAGCAACAACAGCGCCGCTGGAACCTGGATCA GGCAGAGCCCCAGCAGAGGCCTGGAATGGCTGGGCAAGACCTACTACAGGA GCAAGTGGTACAACGACTACGCCGTGAGCGTGAAGAGCAGGATCACCATCAA CCCCGACACCTCCAAGAACCAGTTACGCTGCAGCTGAACAGCGTGACCCCC GAGGACACCGCCGTGTACTACTGCGCCAGGTATGGCAGCGGCACCTGCTGT TCGACTACTGGGGCCAGGGCACCTGGTGACAGTGAGCAGCgagcccaatctagcgac aaaactcacactgtccaccgtgccagcacctgaagcagcagggggaccgtcagtccttcttcccccaaacccaagac

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MHG B669- HL-Fc	318	CAGGTGCAGCTGCAGCAGAGCGGACCCGGACTGGTGAGACCCAGCCAGACCC TGAGCGTGACCTGCGCCATCAGCGCGCAGACGCTGAGCAGCAACAGCGCCAG CTGGAATCTGGATCAGGCAGAGCCCCAGCAGAGGCCTGGAGTGGCTGGGAAG GACATACTACAGGAGCGAGTGGTTCAACGACTACGCCGTGAGCGTGAAAGAGC AGGGTGACCATCAACCCCGACACCCAGCAAGAACCAGCTGAGCCTGACGCTGA ACAGCGTGATCCCCGAGGACACCGCCGTGTACTACTGCGCCAGAGAGGCCAG AATCGGCGTGGCCGGCAAAGGCTTCGACTACTGGGGCCAGGGCACCTGGTG ACAGTGTCCAGCGGCGGATCTGAGGGAAGTCCAGCGGCTCCGGCAGCGAAA GCAAGTCCACCGCGGAAGCGACATCTGTGATGACCCAGAGCCCTGACTCACT GGCTGTGAGCCTGGGCGAGAGAGCCACCATCAACTGCAAGAGCAGCCAGAGC GTGCTGTTCAGGAGCAACAACAAGAACTACCTGGCCTGGTTCCAGCAGAAGC CCGGCCAGCCTCCCAAGCTGCTGATCTACTGGGCCAGCACCCAGAGAGAGCGG CGTGCCCGATAGATTTAGCGGCAGCGGCAGCGGCACCGACTTTACCTGACC ATCAGCTCCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCAGCAGTACTA CAGCACCCCCAGAACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGagcccaaa tctagcgacaaaactcacactgtccaccgtgcccagcacctgaagcagcaggggaccgtcagttcttcttcccccaaac ccaaggacacccatgatctcccgaccctgaggtcacatgcgtggtggtgagcgtgagccacgaagaccctgaggtcaag ttcaactggtacgtggacggcgtggaggtgcataatgccaaagacaagccgaggaggagcagtagacaacagcacgtaccgtg tggtcagcgtctcaccgtcctgaccaggactggctgaatggcaaggagtacaagtgaagggtgtccaacaagccctccca gccccatcgagaaaaccatctccaaagccaaaggcagccccgagaaccacaggtgtacgtgctgccccatccgggag gagatgaccaagaaccaggtcagcctgctgtgctggtcaaaaggcttctatcccagcgacatcgccgtggagtgggagagcaa tgggcagccggagagaacaactacctacctggcctccgtgctggactccgacggctccttctctctacagcaagctcaccgtg gacaagtcagatggcagcaggggaacgtcttctcatgctccgtgatgcatgaggtctgacacaaccactacacgcagaagctct ctctccctgtctccgggaaaa
MHG B669- LH-Fc	319	GACATCTGTGATGACCCAGAGCCCTGACTCCCTGGCTGTGAGCCTGGGCGAGA GAGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTCAGGAGCAACAA CAAGAACTACCTGGCCTGGTTCCAGCAGAAGCCCGCCAGCCTCCCAAGTG CTGATCTACTGGGCCAGCACCCAGAGAGAGCGGCGTGCCCGATAGATTTAGCG GCAGCGGCAGCGGCACCGACTTTACCTGACCATCAGTCCCTGCAGGCCGA GGATGTGGCCGTGTACTACTGCCAGCAGTACTACAGCACCCCCAGAACCTTCG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAGTCCAGCG GCTCCGGCAGCGAAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCAGCA GAGCGGACCCGACTGGTGAGACCCAGCCAGACCCTGAGCGTGACCTGCGCC ATCAGCGCGCAGAGCGTGAGCAGCAACAGCGCCAGCTGGAAGTGGATCAGGC AGAGCCCCAGCAGAGGCCTGGAGTGGCTGGGAAGGACATACTACAGGAGCG AGTGGTTCAACGACTACGCCGTGAGCGTGAAGAGCAGGGTGACCATCAACCC CGACACCAGCAAGAACCAGCTGAGCCTGCAGCTGAACAGCGTGATCCCCGAG GACACCGCCGTGTACTACTGCGCCAGAGAGGCCAGAATCGGCGTGGCCGGCA AAGGCTTCGACTACTGGGGCCAGGGCACCTGGTGACAGTGTCCAGCgagcccaa atctagcgacaaaactcacactgtccaccgtgcccagcacctgaagcagcaggggaccgtcagttcttcttcccccaaaa cccaaggacacccatgatctcccgaccctgaggtcacatgcgtggtggtgagcgtgagccacgaagaccctgaggtcaa gttcaactggtacgtggacggcgtggaggtgcataatgccaaagacaagccgaggaggagcagtagacaacagcacgtaccgt gtggtcagcgtctcaccgtcctgaccaggactggctgaatggcaaggagtacaagtgaagggtgtccaacaagccctccc agccccatcgagaaaaccatctccaaagccaaaggcagccccgagaaccacaggtgtacgtgctgccccatccgggag gagatgaccaagaaccaggtcagcctgctgtgctggtcaaaaggcttctatcccagcgacatcgccgtggagtgggagagcaa tgggcagccggagagaacaactacctacctggcctccgtgctggactccgacggctccttctctctacagcaagctcaccgtg gacaagtcagatggcagcaggggaacgtcttctcatgctccgtgatgcatgaggtctgacacaaccactacacgcagaagctct ctctccctgtctccgggaaaa

MHG B672- HL-Fc	320	CAGGTGCAGCTGCAGCAGAGCGGACCTGGCCTGGTGAAGCCCAGCCAGACCC TGAGCCTGACATGCGCCATCAGCGGCGACAGCGTGAGCAGCAATAGGGCCCG CTGGAACTGGATCAGGCAGACCCCTAGCAGGGGCTGGAATGGCTGGGCAGG ACATACTACAGGAGCGAGTGGTACAACGACTACGCCGTGTCCGTGAAGAGCA GGATCACCATCAACCCCGACACCAGCAAGAACCAGTTCAGCCTGCAGCTGAA CAGCGTGACCCCCGAGGACACCGCCGTGTACTACTGCGCCAGAGTGAGAGCC GCCGTGCCTTTCTGACTACTGGGGCCAGGGCACCCCTGGTGACAGTGAGCAGCG GCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGG CGGAAGCGACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTG GGCGAGAGGGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTTCCA GCAACAACAAGAACTACCTGGCCTGGTACCAGCAGAAACCCGGCCAGCCCC CAACCTGCTGATCTACTGGGCCAGCACCAGAGAAAGCGGCGTGCCCGACAGG TTTAGCGGCAGCGTGAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGGCCGAGGACGTGGCCATCTACTACTGCCAGCAGTACCACAGCACCCCCCTG GACATTTCGGCCAGGGCACCAAGGTGGAGATCAAGgagcccaaatctagcgacaaaactcaca ctgtccacogtgcacagcacctgaagcagcaggggacgtcagctctctctcccccaaaacccaagcacccctcatgat ctcccgagccctgaggtcacatgcgtggtggtgagcgtgagccacgaagacctgaggtcaagtcaactggtacgtggacg gcgtggaggtgcataatgccaagacaagcccgaggagagcagtagacaacagcacgtaccgtgtgtcagcgtctcaccgt cctgaccaggactgctgaatggcaaggagtacaagtgcaaggtgtccaacaaagccctccagcccccatcgagaaaaacc atctccaaagccaaagggcagccccgagaaccacaggtgtacgtgtgtcccccatcccgaggagatgaccaagaaccag gtcagcctgtgtgctgtgcaaaaggcttctatccagcgacatcgccgtggagtgaggagcaatggcgagccggagaacaa ctacctacctggcctccgtgctggactccgacggtcctctctctctacagcaagctaccgtggacaagtccagatggcag caggggaacgtctctcatgctccgtgatgatgaggtctgcacaaactacacgcagaagtctctctctctctccgtgtccggaaa a
MHG B672- LH-Fc	321	GACATCGTGATGACCCAGAGCCCCGATAGCCTGGCTGTGAGCCTGGGCGAGA GGGCCACCATCAACTGCAAGAGCAGCCAGAGCGTGCTGTTTTCCAGCAACAA CAAGAACTACCTGGCCTGGTACCAGCAGAAACCCGGCCAGCCCCCAACCTG CTGATCTACTGGGCCAGCACCAGAGAAAGCGGCGTGCCCGACAGGTTTAGCG GCAGCGTGAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGGCCGA GGACGTGGCCATCTACTACTGCCAGCAGTACCACAGCACCCCTGGACATTCTG GCCAGGGCACCAAGGTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCG GCTCCGGCAGCGAAAGCAAGTCCACCGCGGAAGCCAGGTGCAGCTGCAGCA GAGCGGACCTGGCCTGGTGAAGCCCAGCCAGACCCCTGAGCCTGACATGCGCC ATCAGCGGCGACAGCGTGAGCAGCAATAGGGCCGCTGGAAGTGGATCAGGC AGACCCCTAGCAGGGGCTGGAATGGCTGGGCAGGACATACTACAGAGCGA GTGGTACAACGACTACGCCGTGTCCGTGAAGAGCAGGATCACCATCAACCCC GACACCAGCAAGAACCAGTTCAGCCTGCAGCTGAACAGCGTGACCCCCGAGG ACACCGCCGTGTACTACTGCGCCAGAGTGAGAGCCCGCCGTGCCTTTCTGACTAC TGGGGCCAGGGCACCCCTGGTGACAGTGAGCAGCgagcccaaatctagcgacaaaactcacact gtccacogtgcacagcacctgaagcagcaggggacgtcagctctctctctcccccaaaacccaagcacccctcatgat cccggacccctgaggtcacatgcgtggtggtgagcgtgagccacgaagacctgaggtcaagtcaactggtacgtggacggc gtggaggtgcataatgccaagacaagcccgaggagagcagtagacaacagcacgtaccgtgtgtcagcgtctcaccgtcct gcaccaggactgctgaatggcaaggagtacaagtgcaaggtgtccaacaaagccctccagcccccatcgagaaaaaccatct ccaaagccaaaggcgagccccgagaaccacaggtgtacgtgtgtcccccatcccgaggagatgaccaagaaccagggtca gcctgtgtgctgtgcaaaaggcttctatccagcgacatcgccgtggagtgaggagcaatggcgagccggagaacaaactac ctcacctggcctccgtgctggactccgacggtcctctctctctacagcaagctaccgtggacaagtccagatggcagcagg ggaacgtctctcatgctccgtgatgatgaggtctgcacaaactacacgcagaagtctctctctctctccgtgtccggaaaaa
MHG B687- HL-Fc	322	CAGCTGCAGCTGCAGGAGAGCGGCCCTGGACTGGTGAAGCCCAGCGAGACCC TGAGCCTGATGTGCACCGTGAGCGGCGGCAGCATCACCAGCAGCAGCTACTA CTGGGGATGGATCAGACAGCCCCCTGGCAAGGGCCTGGAGTGGATCGGCAAC ATCTACTACAGCGGCACCACCTACTACAACCCAGCCTGAAGAGCAGGGTGA CCATCAGCGTGGAACACAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGT GACAGCTGCCGACACCGCCGTGTACTACTGTGCCGCCGAGCCAGACACTTC GACAGCTGGGGACAGGGCAGCCTGGTGACCGTGTCCAGCGGCGGATCTGAGG GAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACA TCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCCTGGGAGAGAGAGC

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MHG B694- HL-Fc	328	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGTCC TGAGACTCTCTGTGCAGCCTCTGGATTACCTTTAGCAGCTATGCCATGCAC TGGGTCCGCCAGGCCCCAGGGAAGGGGCTGGACTGGGTCTCAGGTATTAGTG GTAGTGGCTTTAGCACATACTATGTAGACTCCGTGAAGGGCCGGTTACCATC TCCAGAGACAATTCCAAGCACACGCTGTATCTGCAATGAACAGCCTGAGAG CCGAGGACACGGCCGTATATTACTGTGCGAAAGATAATTTAGTGGCTGGTAC CGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCAACGTCTCTCAGGCGGAT CTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAA GCGACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGAC AGAGTCAACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCCTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCT AGTTTAGAAAGTGGGGTCCCATCAAGGTTCAAGCGGCAGTGGATCTGGGACAG AATTCATCTCAACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTATTAC TGCCAAACAGTATAATAGTTATTGCTCACTTTGCGCGGAGGGACCAAGGTGG ATATCAAAGagcccaaatctagcgacaaaactcacactgtccaccgtgcccagcacctgaagcagcagggggaccgt cagcttctcttcccccaaaacccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtgagcgtgag ccaagaagacctgaggtcaagtcaactggtagcggcgtgaggtgcataatccaagacaagcccggggaggag cagtagaacagcagtagcgtgtgtcagcgtcctcaccgtcctgcaccaggaactggtgaatggcaaggagtagaagtgcaa gggtgtcaacaagccctccagccccatcgagaaaacctctcacaagcccaaggcgagccccgagaaaccacaggtgtac gtgctgccccatcccgaggagatgaccaagaaccaggtcagcctgctgtgcctgtgcaaggcttctatccagcgacatc gcccgtgagtgaggagcaatggcgagccggagaaactacactcacctggcctccgtgtgactccgacgctccttct cctctacagcaagctcaccgtggacaagtcagatggcagcaggggaacgtcttctatgctccgtgatgaggtcgtgcac aaccactacacgcagaagtctcttctcctgtctccgggaaaa
MHG B694- LH-Fc	329	GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAG AGTCAACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGCTGGTTGGCCTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCTAG TTTAGAAAGTGGGGTCCCATCAAGGTTCAAGCGGCAGTGGATCTGGGACAGAA TTCACTCTCAACATCAGCAGCCTGCAGCCTGATGATTTTGCAACTATTACTGC CAACAGTATAATAGTTATTGCTCACTTTGCGCGGAGGGACCAAGGTGGATAT CAAAGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC CACC GGCGGAAGCGAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTTGTACAG CCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTAGCAG CTATGCCATGCACTGGGTCCGCCAGGCCCCAGGGAAGGGGCTGGACTGGGTC TCAGGTATTAGTGGTAGTGGCTTTAGCACATACTATGTAGACTCCGTGAAGGG CCGGTTCACCATCTCCAGAGACAATTCCAAGCACACGCTGTATCTGCAAAATGA ACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAAAGATAATTT AGTGGCTGGTACCGTCTTTGACTACTGGGGCCAGGGAACCCTGGTCAACGTCT CCTCAgagcccaaatctagcgacaaaactcacactgtccaccgtgcccagcacctgaagcagcagggggaccgtcagtc tctcttcccccaaaacccaaggacacctcatgatctccggaccctgaggtcacatgcgtggtggtgagcgtgagccacg

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MHG B732- HL-Fc	330	CAAGTACAACCTGCAACAAAGTGGTCTCTGGGCTCGTGAAGCCTTCCCAGACTCT CAGCCTCATGCGCTATAAGTGGGAGTTCTGTTTCTCAAATTCAGCAGCCT GGAATTTGGATACGACAGATCTTCATCCCGTGGCCTTGAGTGGCTTGGTAGA ACTTATTACCGATCCAAGTGGTACAATGATTACGCCGTTTCAGTGAAGTCCCGCAT TACTATTAATCCCGACACATCTAAGAATCAAATTTTCATTGCAACTGAATAGCG TAACACCCGAAGATACAGCAGTTTATTATTGTGCAAGGTGATCGACGCTACGGC ATAGTGGGACTTCTTTCCGCTATTGGGGCCAAGGACACTGTCTCACTGTGTC ATCCGGCGGATCTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCC ACCGGGCGAAGCGACATCGTAATGACACAGTCAACGATTCATTGGCAGTTA GTCTGGGTGAAAGGGCAACAACTCAACTGCAAGTCTTCTCAGAGTGTACTGCA TAGTTCTAACAAATAAGAACTACCTTACCTGGTTTCAACAGAAACCAAGGTCA CCCCAAGTTGCTGATTACTGGGCAAGCAGCCGCAATCCGGCGTTCCCGAT CGATTTTCAGGTTCCGGGAGTGGGACCGACTTTACCTTGACCATCTCTTCCTG CAGGCCGAAGATGTAGCCGCTATTACTGCCATCAGTATTACTCTACTCCCC CATCTCGGTCAAGGTACAAAAGTTGAGATAAAAGagcccaaatctagcgacaaaactcac tgtccaccgtgccagcacctgaagcagcagggggaccgtcagttctctctcccccaaaagcaccctcatgatc tcccgaccctgaggtcagatcgctgtgtgtgagcgtgagccacgaagacctgagggtcaagttaactgtgtacgtggcgg cgtggaggtgcataatgccaaagcaaaagccgcgggaggagcagtacaacagcacgtaccgtgtgtgacgtctcaccgtc ctgcaccaggactgctgaatggcaaggaggtacaaggtgacaaagccctccagcccccatcgagaaaaccat ctccaaagccaaagggcagccccgagaaccacaggtgtacgtgtgtgtccccatccggggagatgaccaagaaccaggt cagcctgtgtgctgtgcaaaaggtctctatcccagcgacatcgccgtggagttgggagagcaatggcgagccggaacaact acctcacctggcctccgtgtgtgacgtccgagcgtctctctctctacagaagctcaccgtggacaagtcagatggcagca ggggagcgtctctctatgctccgtgatgatgaggtctgtcacaaccactacacgcagaagttctctctccctgtctccgggaaaa
MHG B732- LH-Fc	331	GACATCGTAATGACACAGTCAACGAGTTCATTGGCAGTTAGTCTGGGTGAAA GGGCAACAATCAACTGCAAGTCTTCTCAGTGTACTGCATAGTTCTATAACAAT AAGAATACTCTTACCTGGTTTCAACAGAAACCAAGGTACGCCCCCAAGTTGCT GATTTACTGGGCAGCACCCGCGAATCCGGCGTTCCTCGATCGATTTTCAGGTT CCGGGAGTGGGACCGACTTACCTTGACCATCTCTCTTCCAGGCGCCGAAGAT GTAGCGTCTATTACTGCCATAGTATTACTACTCTCCCCCAATCTTCGTTCAA GGTACAAAAGTTGAGATAAAAGCGGATCTGAGGGAAAAGTCCAGCGGCTCCG GCAGCGAAAGCAAGTCCACCGCGGAAGCCAAGTACAAGTCAACAAAGTG GTCCTGGGCTCGTGAAGCCTTCCAGACTCTCAGCCTCATATGCGCTATAAGT GGGAGTTCTGTTTCTCAAATTCAGACGCTGGAATTGGATACGACAGTCTCC ATCCGTTGGCCTTGAGTGCTTGGTGAAGCTTATTACGATCCAAAGTGGTACA ATGATTACGCCGTTTCAGTGAAGTCCCGCATTACTATTAATCCCGACACATCT AAGAATCAAATTTCAATTGCAACTGAATAGCGTAACACCCGAAGATACAGCAG TTTATTATTGTGCAAGTGATCGACGCTACGGCATAGTGGGACTTCTCTTCGCC TATTGGGGCCAAGGACACTGTGTCATCTGTCATCCagcccaaatctagcgacaaaactca cactgtccaccgtgccagcacctgaagcagcagggggaccgtcagttctctctcccccaaaagcaccctcat gatctccgggaccctgaggtcagatcgctgtgtgtgagcgtgagccacgaagacctgaggtcaagttaactggtagctgga cgcgctgtgaggtgcataatgccaaagcaaaagccgcgggaggagcagtacaacagcacgtaccgtgtgtgacgtctcacc gtctgcaccaggactggctgaatggcaaggaggtacaaggtgcaaaagccctccagcccccatcgagaaaac catctccaaagccaaagggcgcccccgagaaccacaggtgtacgtgtgtccccatcccgagagatgaccaagaacaa ggtagcctgtgtgctgtgcaaaaggtctctatcccagcgacatcgccgtggagttgggagagcaatggcgagccggagaaca actacctacgtggcctccgtgtgtgactccgacggcctctctctctacagaagctcaccgtggacaagtcagatggcagca gcaggggagcgtctctatgctccgtgatgatgaggtctgtcacaaccactacacgcagaagttctctctccctgtctccgggaa aa

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MHG B737- LH-Fc	333	GATATTAGATGACTCAATCACCTTCAACCTTAGCGCCTCCGTTGGAGATCG CGTTACCATTACCTGCCGAGCCTCCCAAAGTATCAGCTCATGGTTGGCATGGT ATCAACAGAAAGCCTGGAAAGGCACCCAACTTCTGATTTACAAAGCCAGCTC CTTGAGTCAGGAGTCCCAAGCCGGTTCAGCGGATCTGGGTGAGGGACAGAA TTTACCCTGACCATATCTTCCCTTCAGCCCGACGACTTCGCCACTTACTATTGT CAGCAATACAACCTCTATTCCCTGACTTTCGGCGGTGGCACAAAGTTGACAT CAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAAGCAAGTC CACCGGCGGAAAGCGAGGTGCAACTCCTTGAATCAGGCGGAGGACTCGTCCAA CCTGGAGGGAGTCTTAGGCTTAGCTGTGCAGCCAGTGGCTTTACTTTAGCAG CTATGCAATGCACTGGGTGAGCGAGGCTCCTGGTAAGGGGCTCGAATGGGTC AGCGGCATATCCGGGTGAGGTTTCTCTACATATTATGTCGATTCTGTAAAAGG ACGATTACCATATCCAGAGACAATTCTAAAAATACCTTGTATCTCCGAGATGA ACAGCCTGAGAGCAGAAGATACCGCAGTTTATTACTGTGCAAAGGATAATCT GGTTGCCGGGACAGTTTTTGATTATTGGGGGCAAGGCACCCTCGTCACAGTAT CCAGTgagcccaaatctagcgacaaaactcacactgtccaccgtgccagcacctgaagcagcaggggaccgtcagtc tctcttcccccaaaacccaaggacacctcatgatctcccgaccctgaggtcacatgcgtggtgagcgtgagccacg aagacctgaggtcaagttcaactgttagcgtggacggcgtggaggtgcataatgccaagacaaagccgaggagagcagta caacagcagtcacgtgtgtgtagcgtctcaccgtctgaccagagactggctgaatggcaaggagtagcaaggtgtc caacaaagccctccagccccatcgagaaaacatctccaagccaaaggcagccccgagaaccacaggtgtacgtgtg ccccatcccgaggagagatgaccaagaaccaggtgacgtgctgtgctgtgcaaaagcttctatccagcgacatcgccgt ggagtgaggagcaatgggcagcggagaaactacctcacctggcctccgtgctggactccgacggctcttctctc cagcaagctcaccgtggacaagtcagatggcagcaggggaacgtcttctcatgctccgtgatgcatgaggtctgcacaacca ctacacgcagaagtcctctcctgtctccgggaaaa
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Example 4. Biophysical characterization of anti-HLA-G antibodies

Thermal stability of anti-HLA-G antibodies.

- 5 The original and germline-optimized v-regions were screened for thermal stability in scFv format. Briefly, v-regions were cloned into scFv format and were expressed in *E. coli*. The culture supernatants were assessed by ELISA for their abilities to bind recombinant HLA-G. Supernatant samples were also heat shocked at either 55, 60, or 65 °C, and the binding of the heat-shocked samples was compared to the unheated samples. This analysis provided an estimate of the thermal stability of the v-regions when
- 10 formatted as scFv. Based on this analysis, MHGB732, MHGB737 and MHGB738, the germline-optimized versions of MHGB694 and MHGB688, respectively, were preferred.

Figure 1 and **Table 20** show the ability of v-regions to bind recombinant HLA-G after heat treatment when formatted as scFv. V-regions were expressed as scFv in the supernatant from *E. coli* and were analyzed for their ability to bind recombinant HLA-G by ELISA. Samples were tested at room temperature or after heat treatment for 10 min at 55, 60, or 65 °C. B23 was an isotype control.

5 **Table 20. Analysis of antigen binding after heat treatment by v-regions formatted as scFv.**

Antibody parent of scFv	Room temperature binding signal	% Binding retained		
		55 °C	60 °C	65 °C
MHGB665 / MHGB732	15215600	103	122	11
MHGB668	No binding			
MHGB669	No binding			
MHGB672	No binding			
MHGB687	No binding			
MHGB688	No binding			
MHGB689	3073733	2	3	4
MHGB694	3073733	85	9	4
MHGB737 (GL optimized B694)	2747333	84	80	48
MHGB738 (GL optimized B688)	5758400	14	2	1

Binding Specificity and Affinity

The v-regions in IgG1 mAb format were tested for their abilities to specifically bind cells expressing HLA-G but not other MHC class I molecules (**Table 21**). Briefly, 1.5×10^7 cells were washed 2 times with 1 X PBS and resuspended in 7 mL of 1 X PBS and incubated for 10 min. After incubation, 8 mL of fetal bovine serum (FBS) were added, cells were washed by centrifugation at 300 X g for 5 min and resuspended at 1×10^6 cells/mL in DMEM supplemented with 10 % FBS. Cells were then washed by centrifugation at 300 X g for 5 min and resuspended in staining buffer supplemented with goat anti-human Fc A647 (Jackson cat. # 109-606-098) and incubated for 30 min at 4 °C. After incubation, 150 µL of staining buffer were added and cells were washed by centrifugation at 300 X g for 5 min. Cells

were resuspended in 200 μ L of running buffer (staining buffer supplemented with 1 mM EDTA, 0.1 % (v/v) pluronic acid) and washed by centrifugation at 300 X g for 5 min. Cells were resuspended in 30 mL of running buffer and analyzed for antibody binding by flow cytometry.

5 **Table 21. Cell-based selectivity of anti-HLA-G antibodies. Geomean fluorescence signal reports maximum value for binding.**

Antibody	HLA-G	HLA-A	HLA-B	HLA-C
MHGB665 / MHGB732 GeoMean	631628	9956	10436	11586
MHGB668 GeoMean	590753	4574	6323	4941
MHGB669 GeoMean	616340	8142	8312	10950
MHGB672 GeoMean	522292	158	4263	2447
MHGB687 GeoMean	527964	28765	22936	35939
MHGB688 GeoMean	481619	2860	6290	2226
MHGB689 GeoMean	536504	2541	5787	266
MHGB694 GeoMean	472613	2874	4853	3974

Next, the v-regions were tested for their abilities to bind recombinant HLA-G as mAbs using surface plasmon resonance (SPR). SPR is a label-free technique to study the strength of an interaction between two binding partners by measuring the change in mass upon complex formation and dissociation. Briefly, antibodies were immobilized on a sensor chip, which was coupled with goat anti-human Fc. Soluble HLA-G1 extracellular domain (MHGW8) was flowed over the immobilized antibody and association / dissociation responses were monitored. Kinetic information (on-rate and off-rate constants) were extracted by fitting sensorgrams to the 1:1 Langmuir model. Binding affinity (K_D) were reported as

the ratio of rate constants (k_{off}/k_{on}). Antibody affinities (K_d) ranged from ~ 77 pM – 2.6 nM and are shown in Table 22.

Table 22. SPR-based affinity measurements of variable regions binding to HLA-G (MHGW8).

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)
MHGB665 / MHGB732	5.18E+05	4.00E-05	7.71E-11
MHGB669	3.15E+05	4.53E-04	1.44E-09
MHGB672	3.25E+06	1.79E-03	5.50E-10
MHGB687	1.89E+05	1.53E-04	8.09E-10
MHGB688	6.58E+05	2.63E-04	4.00E-10
MHGB694	2.08E+06	2.40E-03	1.15E-09
MHGB737	1.996E+5	3.103E-4	2.555E-9
MHGB738	2.03E+10	2.83E+00	1.39E-10

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Example 5. Ligand blocking

HLA-G is over-expressed on certain tumor types and can thus serve as a marker for tumor cells. Additionally, HLA-G binds to the ligands ILT2 and ILT4, which are expressed on immune effector cells such as NK cells^{4,5}. The interaction between HLA-G and ILT2 / ILT4 leads to inhibition of NK cell activity. Thus, we hypothesized that antibodies which bind to HLA-G competitively with ILT2/4 would prevent inhibitory interaction between tumor cells and NK cells and lead to increased NK mediated tumor cell killing. To address this hypothesis, we first assayed whether the antibodies could block interaction between HLA-G and ILT2/4 using a competition assay. Binding between the HLA-G-dextramer complex and HEK293T cells exogenously expressing ILT2 or ILT4 receptors results in a fluorescence signal. Addition of a mAb which competes with the interaction between HLA-G-dextramer and ILT-2/4 cells results in a decrease in fluorescence signal. The inverse of the fluorescence signal inhibition was related to the ligand blocking inhibition of the mAbs (Table 22). Briefly, recombinant biotinylated HLA-G1 (MHGW8) was bound up to a streptavidin APC-dextramer (Immudex cat. # DX01-APC) to a final ratio of approximately 4 HLA-G1 proteins per dextramer molecule. Dextramer-HLA-G complex was mixed with HEK293T cells exogenously expressing ILT-2 or cells exogenously expressing ILT-4 and incubated for 30 min. at 4 °C. Anti-HLA-G antibody was added at each concentration and incubated with dextramer-HLA-G complex for 30 min at °C. Cells were added (25,000 cells) and incubated for 30 min

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at 4 °C. After incubation, the mixture of cells and dextramer HLA-G complex were washed by centrifugation resuspended in 30 µL of running buffer (Thermo BD cat. #554657). The resuspended mixture was analyzed for fluorescence signal by flow cytometry using an Intellicyt® iQue Screener Plus. Gating was done first on singlet cells, then live cells using Sytox™ Blue Dead Cell stain (ThermoFisher), then on GFP for cells expressing ILT-2/4, then on APC for bound dextramer-HLA-G complex. All antibodies except MHGB737 could inhibit HLA-G interaction with ILT4, and all antibodies except MHGB737 and MHGB687 could inhibit interaction with ILT2 (Table 23). This suggested that antibodies discovered in this campaign could both target tumors and relieve immune inhibition by the tumor cells.

10 **Table 23. Ligand blocking properties of antibodies**

Antibody	ILT2 EC50 (nM)	ILT4 EC50 (nM)
MHGB665	1.62	1.74
MHGB669	1.70	1.59
MHGB672	2.12	1.61
MHGB687	NA	1.86
MHGB688	1.72	1.42
MHGB694	0.64	0.20
MHGB732	0.33	0.44
MHGB737	NA	NA
MHGB738	0.73	0.8

Example 6. Epitope mapping

We then asked whether this inhibition of ligand binding was due to direct competition with ILT2/4 for the same binding site on HLA-G. To address this hypothesis, we used hydrogen-deuterium exchange-based LC-MS (described in Example 9) to identify the epitopes on HLA-G for either ILT-2, ILT-4, MHGB732, or MHGB738 (Figure 2). Binding of both MHGB732 and MHGB738 Abs strongly protected the same peptide in the α3 domain (amino acid residues 191-198 of the mature protein, sequence HHPVFDYE (SEQ ID NO: 485)), resulting in average change in deuteration levels > 30%. This peptide was also protected in the presence of ILT2 and to a lesser extent in the presence of ILT4. Both MHGB732 and MHGB738 antibodies also significantly protected (average change in deuteration levels 10% – 30%) a second epitope comprised of residues 249-251 of the mature protein, sequence VPS.

The epitopes were mapped onto the crystal structure of HLA-G (PDB ID 1YDP) ⁶, which showed that the epitope for the MHGB732 and MHGB738 Abs and for ILT2/4 resided in the membrane-proximal region of the $\alpha 3$ domain.

5 Example 7. Effect on NK cell-based cytotoxicity

We then asked whether inhibition of the interaction with HLA-G with ILT-2/4 could mediate anti-tumor activity via NK cell-based cytotoxicity. To address this, we cloned each variable region onto either an IgG1 or a silent IgG4-PAA constant region which lacks effector function. We then tested the ability of each antibody to mediate cytotoxicity of K562-HLA-G cells mediated by NK cells which either
10 express Fc receptors (NK-92) or which lack Fc receptors (NKL). Briefly, K562 cells overexpressing HLA-G cells were labeled with Carboxyfluorescein succinimidyl ester (CFSE) which served as a cell proliferation dye. Antibodies were diluted into a 96-well plate according to the dilutions in **Figure 3A-8B**. K562-HLA-G cells were added to each well of antibody and incubated for 1hr at 4 °C. NKL cells were added at approximately 100,000 cells / well, and the mixture was incubated in the presence of IL2
15 and NKp46 (to activate NKL cells) overnight (NKL cells) or 4 hr (NK-92 cells) at 4 °C. Cells were washed by centrifugation and resuspended in buffer with live/dead stain. The mixture was resuspended in 130 μ L of staining buffer and analyzed by flow cytometry using a FACS Fortessa cytometer. Antibodies which could mediate cytotoxicity in the absence of NK receptors were thought to mediate this interaction via blocking the immune checkpoint interaction between HLA-G and ILT-2/4 (**Figure 3A-8B**). We
20 found that all antibodies which could block ILT2 (all Abs except MHGB687) could enhance NKL cell-mediated cytotoxicity against K562-HLA-G cells in a 24 hr assay (Figures 3A, 4A, 5A, 6A, 7A, 8A) whereas only IgG1-based antibodies could enhance Fc-receptor mediated cytotoxicity. This suggested that ligand blocking could serve as an important anti-tumor mechanism, even in the absence of Fc receptor mediated effector function.

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Example 8. Effector Functions of mAbs

We tested the ability of antibodies to further mediate tumor cell killing via antibody-dependent cellular cytotoxicity (ADCC) against the choriocarcinoma cell line JEG-3 (ATCC HTB-36) which
30 endogenously expresses HLA-G (**Figure 9**). Antibodies were added to JEG-3 cells labeled with BATDA dye (Perkin Elmer cat. # C136-100) which can unidirectionally penetrate into the cells. Upon cell lysis, the dye is released into the solution containing Europium which reacts with the dye to form a fluorescent chelate, whose fluorescence signal can be measured. PBMCs cultured overnight were added at an E:T ratio of 50:1 to JEG-3 cells at 5,000 cells / well and the mixture was incubated for 4 hr at 37 C. The cell

mixture was added at 1:10 into Europium solution, incubated for 15 min at room temperature and fluorescence at 610 nm was monitored to determine signal. The fluorescence signal for 100 % killing was determined using a well containing BADTA-labeled target cells mixed with Triton-X 100 detergent.

Since the anti-HLA-G Abs could display ADCC in vitro, we asked whether this activity could be enhanced. Several studies showed that antibodies having less than 10 % terminal fucosylated Fc display enhanced effector function due to higher affinity binding to Fc receptors ⁷. Thus, we generated MHGB732 and MHGB738 in a low fucose CHO host to produce an antibody with < 10 % terminal fucose (MHGB738.CLF) (Table 24, Figure 10A-D). As a negative control, we generated a version of MHGB738 with an Fc region that could not bind Fc receptors, and this protein was called MHGB745.

The normal fucose and low fucose antibodies were tested for their abilities to induce NK cell-based ADCC against either JEG-3 cells (**Figure 10A**) or against RERF-LC-Ad-1 cells (human lung adenocarcinoma cell line, JCRB1020) (Figure 10B). Low fucose antibodies were generated by expression of the constructs encoding the heavy chain and light chain in CHO cells which natively express the fucosyltransferase enzyme at low levels, leading to production of antibodies have less than 10% core fucose. The ratio of effector cells to target cells is shown in the graph. The assay was performed in the same way as the ADCC assay described above. Both MHGB745 and the isotype control did not induce ADCC in the assay. The two IgG1 Abs, MHGB732 and MHGB738 could induce ADCC while the same antibodies having low fucose Fc regions displayed ~ 10-fold enhanced ADCC activity. This showed that ADCC enhancement could be obtained by use of a low fucose antibody.

We next tested the abilities of the antibodies to mediate complement-dependent cytotoxicity (CDC) (**Figure 10C and 10D**). Briefly, assays were run in 10 % FBS containing DMEM (JEG-3) or RPMI (RERF-LC-Ad-1). Antibodies were added to target cells and incubated for 30 minutes at 37 °C. After incubation, 15-20 % (stock concentration) of rabbit complement (Cedarlane cat. # CL3441-S) and heat inactivated complement was added to the wells respectively in a volume of 25 µl/well. The mixture was incubated for 4-12 hours at 37 °C. Target cell lysis was detected by addition of 100 µl of CellTitre-Glo (Promega cat. # G9242) reagent followed by incubation for 10 minutes at room temperature. Luminescence was monitored using a Tecan Microplate reader SPARK®. The two IgG1 antibodies, MHGB732 and MHGB738 did not mediate CDC. Since the IgG1 Abs could not mediate CDC, we cloned the v-regions into an IgG1 Fc harboring the K248E, T437R (RE) mutations which were shown to specifically enhance CDC activity ⁸. These Abs, having the identical v-regions as their IgG1 counterparts, could mediate CDC activity. We asked whether the RE Fc variant would impact ADCC activity enhancement in the low fucose Abs and whether the low fucose Fc would impact CDC activity of the RE Fc variants. The RE Abs produced in a low fucose host (having < 10 % fucosylated Fc),

MHGB752 and MHGB758 had identical ADCC activity to the low fucose IgG1 Abs MHGB732 and MHGB738 (Figure 10A and 10B). Analogously, the RE Abs produced in a low fucose host had identical CDC activity to the RE Abs produced in a normal fucose host (Figure 10C and 10D).

5 **Table 24. Description of variants of MHGB738 having modified constant regions.**

Protein Name	Description
MHGB732	IgG1
MHGB738	IgG1
MHGB745	L234A, L235A, D265S
MHGB752	IgG1, K248E, T437R (RE)
MHGB758	IgG1, K248E, T437R (RE)
MHGB732.CLF	IgG1, low fucose
MHGB738.CLF	IgG1, low fucose
MHGB758.CLF	IgG1, K248E, T437R (RE), low fucose
MHGB758.CLF	IgG1, K248E, T437R (RE), low fucose

Example 9: Generation of CD3 antibodies

Immunization

10 The generation of anti-CD3 antibody CD3B376 and CD3B450 have been describe in US20200048349. The humanized anti-CD3 v-region featured in CD3B219 was derived from the commercially available antibody SP34-2 (BD Biosciences 551916).

Additional anti-CD3 antibodies were generated using Ablexis transgenic mouse platform, as described below. Ablexis mice were immunized with TRCW5 (SEQ ID NO: 336), including 13 Kappa
 15 mice and 12 Lambda mice. TRCW5 is comprised of the extracellular region of CD3 δ fused by a 26 amino acid linker to the extracellular region of CD3 ϵ as reported in Kim et al, JMB (2000) 302(4): 899-916. This polypeptide had at its C-terminus a human IgG1 Fc domain with a C-terminal Avi-tag used for site-specific biotinylation (Fairhead & Howarth, Methods Mol Biol (2015); 1266: 171–184).

TRCW5 (SEQ ID NO: 336):

20 FKIPIEELEDRVFNCSITWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDKE
 STVQVHYRMGSADDAKKDAKKDDAKKDDAKKDGSDGNEEMGGITQTPYKVSISGTTVILTCP

QYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYL
 RARVSPPSPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
 AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
 LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
 5 RWQQGNVFCSSVMHEALHNHYTQKSLSLSPGKGGGLNDIFEAQKIEWHE

Mice were immunized twice weekly for the duration of 7 weeks. On day 42, mice were boosted for hybridoma fusion by administration of 50 µg TRCW5 and 50 µg CD40 mAb spread over 8 sites, including 6 subcutaneous and 2 intradermal injections. For a final boost, mice received 20 µL injections of Jurkat cells, a T cell line which endogenously expresses the T cell receptor complex, including CD3ε
 10 (Schneider et al (1977) Int. J. Cancer, 19 (5): 621-6), at 4.74x10⁷ cells/mL.

Lymph nodes and spleens were extracted from mice and fusions performed by cohorts. Lymph node cells were counted and combined in a 1:1 ratio with FO myeloma cells (ATCC (CRL-1646)) and incubated for 10 d at 37 °C prior to antibody screening. Supernatants from hybridoma fusion cells were then assayed by ELISA for binding to TRCW5 using TRCW5 either non-specifically immobilized on the
 15 plate (ELISA, Thermo cat. # 34022) or by streptavidin conjugation to biotinylated-TRCW5 (SPARCL ELISA, Lumigen), according to manufacturers' instructions. ELISA assays were performed by coating plates with 0.5 µg/mL TRCW5 and 0.5 µg/mL HVEM-Fc (R&D cat. # 365-HV) overnight @ 4 °C. Plates were blocked by addition of 0.4 % (w/v) bovine serum albumin (BSA) in phosphate-buffered saline (PBS) overnight @ 4 °C. Plates were washed with 1 X PBS supplemented with 0.02 % (v/v) Tween 20.
 20 To each well, 50 µL of hybridoma supernatant was applied and incubated for 1 hr at room temperature. Bound antibody was detected by addition of goat anti-mouse IgG Fc conjugated to horseradish peroxidase (Jackson cat. # 115-036-071) diluted 1:10,000 in blocking buffer followed by incubation for 30 min at room temperature. 3,3',5,5'-tetramethylbenzidine (TMB) substrate buffer (Thermo cat. # 34022) was added at 25 µL / well and incubated for 10 min in the dark. Reactions were stopped by addition of 25 µL /
 25 well of 4 M H₂SO₄. Luminescence was read at 450 nm using BioTek® Epoch2 Microplate Reader. Hits were selected having signal at least 3-fold higher than background.

The two assay formats resulted in 426 hits (264 hits from ELISA, 194 from SPARCL ELISA, 70 hits were identified in both assays). Of these 426 initial hits, 49 ELISA and 32 SPARCL ELISA hits were confirmed. The hybridoma fusions corresponding to the positive binders were refed and tested for
 30 their abilities to bind Jurkat cells, using flow cytometry. The results suggested that three antibodies, including clone 003_F12, clone 036_E10 and clone 065_D03, showed significant binding to Jurkat cells, endogenously expressing CD3, based on mean fluorescence index (MFI, see Table 25). While clones 003_F12 and 036_E10 (from human kappa mice) were confirmed positive for human kappa light chain by

ELISA, clone 065_D03 (from human lambda mouse) was negative for human lambda. The variable genes of these three clones were then sequenced.

Table 25. Mean fluorescence index (MFI) for binding of selected clones to Jurkat cells

Clone ID	MFI (arbitrary units)
003_F12	176147
036_E10	43133
065_D03	136269
No Ab	2075.61
10 nM UCHT1	89214.29

5 Next, these three clones were screened for their abilities to bind primary human and cyno T cells. Briefly, primary human and cyno pan T cells were resuspended at 1×10^6 cells/mL in flow staining buffer and cells were plated at 50,000 cells/well. To each well, 50 μ L of hybridoma supernatant were added and the mixture was incubated on ice for 30 min. After incubation, 200 μ L of staining buffer was added and cells were pelleted by centrifugation at 300 X G for 5 min. Anti-mouse IgG conjugated to
 10 Alexa-647 was added at 2 μ g/mL in staining buffer in 50 μ L total volume and incubated for 30 min on ice. 150 μ L of staining buffer was added and cells were pelleted by centrifugation at 300 X G for 5 min. Cells were resuspended in 30 μ L of running buffer containing 1:1,000-diluted Sytox green dead cell stain and run on iQue Screener. Cells were gated on FCS vs SCS to eliminate debris. Singlets were gated on SCS-A vs SCS-H, and from singlet population, live cells were chosen using BL1 channel for low-
 15 negative with Sytox green. CD3 binding was assessed by comparing test articles to negative control by RL1 (Alexa-647) geomeans. In this assay, clone 065_D03 showed the highest cell binding signal (**FIG. 11A-11B**).

20 The variable region of the Clone 065_D03 was then cloned into an IgG1 backbone, resulting in the antibody termed CD3B815 (sequences are shown in **Table 26**). CD3B815 was screened again for binding to Jurkat cells and showed positive binding to Jurkat cells.

Table 26. CD3B815 amino acid sequences.

Protein	SEQ ID NO:	Amino acid sequences

CD3B815 Heavy Chain	337	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGL EWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDT AIYYCTRGWGPFQDYWGQGLVTSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTV DKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
CD3B815 Light Chain	338	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWWYQQRNGSPRLLI KYASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQQNSWPY TFGGGTGLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKSTYSLSTLTLSKADYEK HKVYACEVTHQGLSPVTKSFNRGEC

Humanization and scFv formatting of CD3 binding domains

The light chain (LC) of the v-region of CD3B815 was humanized in scFv format. Briefly, the LC from CD3B815 was grafted onto the human IGHV3-21*04 germline and two positions (Y49K and L78V, according to Kabat) were identified for human to mouse back mutations. This resulted in variants, having either Y49K, L78V, or both Y49K and L78V. The LC from CD3B815 also contained an NS motif which presents a risk for deamidation at positions 92-93. Therefore, several variants generated also contained N92G. These variants and associated mutations are described in Table 27, and the VH and the VL amino acid and nucleic acid sequences are shown in Tables 28 and 29. CDR sequences are shown in Tables 30-32.

Table 27. Mutations in humanized csFv variants.

scFv identification	Description	VL mutations
CD3W234	CD3B815-HL-scFV, Contains mouse VL	none
CD3W238	CDR of CD3B815 grafted into IGKV1D-39*01	none
CD3W241	CDR of CD3B815 grafted into IGKV1D-39*01	L78V

CD3W242	CDR of CD3B815 grafted into IGKV1D-39*01	Y49K
CD3W243	CDR of CD3B815 grafted into IGKV1D-39*01	Y49K, L78V
CD3W244	CDR of CD3B815 grafted into IGKV1D-39*01	L78V, N92G
CD3W245	CDR of CD3B815 grafted into IGKV1D-39*01	Y49K, N92G
CD3W246	CDR of CD3B815 grafted into IGKV1D-39*01	Y49K, L78V, N92G
CD3W247	CDR of CD3B815 grafted into IGKV1D-39*01	N92G
CD3W248	CD3B815-HL-scFV, Contains mouse VL	N92G

Table 28 shows the VH and the VL amino acid sequences of selected anti-CD3 antibodies. **Table 29** shows the VH and the VL DNA sequences of selected anti-CD3 antibodies. **Table 30** shows the Kabat HCDR1, HCDR2 and the HCDR3 amino acid sequences of selected anti-CD3 antibodies. **Table 31** shows the Kabat LCDR1, LCDR2 and the LCDR3 amino acid sequences of selected anti-CD3 antibodies. **Table 32** shows CDRs and variable domains of the anti-CD3 antibodies. **Figure 13** shows the alignment of the VL region of of CD3B815, CD3W244, CD3W245, CD3W246, and CD3W247.

Table 28. VH and VL amino acid sequences of selected anti-CD3 antibodies.

mAb	VH name	VH sequence	VH SEQ ID NO:	name	VL sequence	VL SEQ ID NO:
CD3B815	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN WVRQAPGKGLE WVSSISTSSNYIY YADSVKGRFTFS RDNAKNSLDLQ MSGLRAEDTAIY YCTRGWGPFDY WGQGTLLTVSS	339	CD3L372	DILLTQSPGILSVSP GERVSFSCRARQSI GTAIHWYQQRN GSPRLLIKYASESIS GIPSRFSGSGSGTD FTLTINSVEEDIA DYVCQQSNSWPY TFGGGTKLEIK	340
CD3W244	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN	339	CD3L394	DIQMTQSPSSLSAS VGDRVITITCRARQ SIGTAIHWYQQKP	341

		WVRQAPGKGLE WVSSISTSSNYIY YADSVKGRFTFS RDNAKNSLDLQ MSGLEAEDTAIY YCTRGWGPFDDY WGQGTLLTVSS			GKAPKLLIYYASE SISGVPSRFSGSGS GTDFTLTISSVQPE DFATYYCQSGS WPYTFGQGTKEI K	
CD3W245	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN WVRQAPGKGLE WVSSISTSSNYIY YADSVKGRFTFS RDNAKNSLDLQ MSGLEAEDTAIY YCTRGWGPFDDY WGQGTLLTVSS	339	CD3L395	DIQMTQSPSSLSAS VGDRVITTCRARQ SIGTAIHWYQQKP GKAPKLLIKYASE SISGVPSRFSGSGS GTDFTLTISSLQPE DFATYYCQSGS WPYTFGQGTKEI K	342
CD3W246	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN WVRQAPGKGLE WVSSISTSSNYIY YADSVKGRFTFS RDNAKNSLDLQ MSGLEAEDTAIY YCTRGWGPFDDY WGQGTLLTVSS	339	CD3L396	DIQMTQSPSSLSAS VGDRVITTCRARQ SIGTAIHWYQQKP GKAPKLLIKYASE SISGVPSRFSGSGS GTDFTLTISSVQPE DFATYYCQSGS WPYTFGQGTKEI K	343
CD3W247	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN WVRQAPGKGLE WVSSISTSSNYIY YADSVKGRFTFS RDNAKNSLDLQ	339	CD3L397	DIQMTQSPSSLSAS VGDRVITTCRARQ SIGTAIHWYQQKP GKAPKLLIYYASE SISGVPSRFSGSGS GTDFTLTISSLQPE DFATYYCQSGS	344

		MSG LRAEDTAIY YCTR GWGPF DY WGQGT LVT VSS			WPYTFGQGTKLEI K	
CD3W248	CD3H488	EVQLVESGGGL VKPGGSLRLSCA ASGFTFSRYNMN WVRQAPGKGLE WVSSISTSSNIY YADSVKGRFTFS RDNAKNSLDLQ MSG LRAEDTAIY YCTR GWGPF DY WGQGT LVT VSS	339	CD3L398	DILLTQSPGILSVSP GERVSFSCRARQSI GTAIHWYQQR TN GSPRL LIKYASESIS GIPSRFSGSGSGTD FTLTINSVEEDIA DY YCQQSGSWPY TFGGGTKLEIK	345
CD3B376	CD3H219	QVQLQQSGPRL VRPSQTLSLTCAI SGDSVFNNNA WSWIRQSPSRGL EWLGRTYYRSK WLYDYAVSVKS RITVNPDTSRNQ FTLQLNSVTPED TALYYCARGYSS SFDYWGQGT LV TVSS	346	CD3L150	QSALTQPASVSGS PGQSITISCTGTSSN IGTYKFVSWYQQH PDKAPKVLLYEVS KRPSGVSSRFSGS KSGNTASLTISGLQ AEDQADYHCVSY AGSGTLLFGGGTK LTVL	347
CD3B450	CD3H231	QVQLQQSGPGL VKPSQTLSLTCAI SGDSVFNNNA WSWIRQSPSRGL EWLGRTYYRSK WLYDYAVSVKS RITINPDTSKNQF SLQLNSVTPEDT AVYYCARGYSS	348	CD3L197	QSALTQPASVSGS PGQSITISCTGTSSN IGTYKFVSWYQQH PGKAPKVMIEVS KRPSGVSNRFSGS KSGNTASLTISGLQ AEDEADYYCVSY AGSGTLLFGGGTK LTVL	349

		SFDYWGGQTLV TVSS				
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Table 29. VH and VL nucleic acid sequences of the humanized csFv variants.

Binding domain name	VH nucleic acid Sequence	VH SEQ ID NO:	VL nucleic acid sequence	VL SEQ ID NO:
CD3B815	GAGGTGCAACTGGTGG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAAGTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCCT GGTCACCGTCTCCTCA	350	GATATACTTCTTACCCAGA GTCCCGGCATCCTCTCCGT TAGCCCTGGGGAGAGAGT CTCATTCTCATGCCGAGCC AGACAGTCAATTGGTACC GCAATACACTGGTATCAA CAGCGGACCAATGGTTCT CCCCGACTTCTGATAAAGT ACGCATCAGAATCAATTA GTGGAATACCATCAAGAT TTAGTGGCTCAGGGAGTG GAACCGATTTTACTCTGAC CATCAACTCAGTGGAACT GAGGACATTGCCGACTAC TACTGTCAACAAAGCAAT AGTTGGCCATATACCTTCG GAGGCGGAATAAATTGG AGATAAAA	351
CD3W244	GAGGTGCAACTGGTGG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG	350	GACATCCAGATGACACAG TCACCTTCTAGTTTGTCTG CTTCTGTAGGCGACCGTGT AACTATCACCTGTCGAGCC	352

	TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAACTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCTT GGTCACCGTCTCCTCA		CGTCAAAGTATTGGTACTG CCATTCACTGGTACCAACA AAAACCTGGCAAAGCTCC AAAACCTCTTGATCTACTAT GCCTCCGAAAGCATATCA GGGGTCCCAAGCAGATTC TCAGGCAGTGGCAGTGGC ACTGACTTCACTCTCACCA TTTCTAGCGTGCAACCAGA GGACTTCGCCACTTATTAC TGCCAACAGTCAGGGAGC TGGCCCTACACCTTCGGCC AAGGTACAAAACCTGGAGA TCAAA	
CD3W245	GAGGTGCAACTGGTG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAACTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT	350	GACATACAAATGACACAA TCACCTCTTCTCTTTCTG CAAGCGTTGGCGACCGTG TCACTATCACTTGTCGAGC CCGCCAGTCCATAGGTACT GCCATTCACTGGTATCAAC AGAAGCCTGGCAAGGCTC CCAAACTCCTGATTAAGTA TGCCAGCGAGAGCATTTT CGGCGTACCTTCAAGATT TCCGGCTCCGGTAGTGGG ACAGATTTCACTCTCACTA TATCTAGCCTCCAACCAGA AGATTTCGCCACTTACTAC TGTCACAATCAGGTTTCAT GGCCTTACACTTTCGGCCA	353

	TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCCCT GGTCACCGTCTCCTCA		GGGGACAAAATTGGAGAT CAAG	
CD3W246	GAGGTGCAACTGGTGG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAACTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCCCT GGTCACCGTCTCCTCA	350	GACATCCAAATGACTCAA TCACCTAGCAGCCTCTCCG CCTCCGTTGGAGATAGAG TGACAATAACTTGCCGAG CCCGGCAAAGTATCGGAA CTGCTATTCACTGGTATCA ACAAAAACCTGGAAAGGC ACCTAAGCTCTTGATTAAA TACGCTTCTGAGTCCATCT CCGGCGTGCCTTCACGATT CAGCGGCAGCGGTAGTGG TACTGACTTTACCCCTCACT ATTAGTTCTGTTTCAGCCAG AGGACTTCGCAACTTATTA CTGCCAACAGAGTGGTTC CTGGCCATACACTTTTGCC CAGGGGACTAAATTGGAA ATCAAA	354
CD3W247	GAGGTGCAACTGGTGG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAACTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC	350	GACATCCAAATGACTCAA AGCCCCCTCTAGTTTGAGTG CATCTGTAGGTGACCGGG TAACAATCACCTGCCGTGC CCGGCAAAGTATAGGTAC TGCAATCCACTGGTACCA GCAAAAACCCGGCAAAGC ACCAAAGCTGCTCATATA CTATGCTAGTGAGAGCATT	355

	CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCCT GGTCACCGTCTCCTCA		TCTGGCGTTCCTAGTCGAT TTTCTGGATCAGGGAGTG GAACTGATTTTACACTGAC AATCAGCAGCCTCCAACC CGAAGACTTCGCCACCTA CTATTGTCAGCAGTCTGGG TCCTGGCCTTACACATTCTG GTCAAGGAACTAAATTGG AGATCAAA	
CD3W248	GAGGTGCAACTGGTGG AGTCTGGGGGAGGCCT GGTCAAGCCTGGGGGG TCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCA CCTTCAGTAGATATAAC ATGAACTGGGTCCGCCA GGCTCCAGGGAAGGGG CTGGAGTGGGTCTCATC CATTAGTACTAGTAGTA ATTACATATACTACGCA GACTCAGTGAAGGGCC GATTACCTTCTCCAGA GACAACGCCAAGAACT CACTGGATCTGCAAATG AGCGGCCTGAGAGCCG AGGACACGGCTATTTAT TACTGTACGAGAGGCTG GGGGCCTTTTGACTACT GGGGCCAGGGAACCCT GGTCACCGTCTCCTCA	350	GACATTTTGCTGACACAG AGCCCTGGTATCCTCTCAG TCAGTCCAGGGGAACGCG TTTCATTTAGCTGCCGTGC TCGACAGAGCATTGGGAC CGCAATCCACTGGTACCA ACAAAGAACTAACGGTTC ACCACGGCTTTTGATTAAAG TATGCCTCCGAATCCATCA GTGGCATTCCCTAGTCGTTT TTCTGGATCAGGATCAGG CACCGACTTTACTCTCACA ATTAATAGTGTCGAAAGT GAGGACATTGCAGACTAT TATTGTCAGCAATCCGGTT CCTGGCCCTATACTTTTGG TGGTGGTACTAAGTTGGA AATTAAA	356

CD3B376	CAGGTGCAGCTGCAGC AGTCTGGCCCTAGACTC GTGCGGCCCTTCCCAGAC CCTGTCTCTGACCTGTG CCATCTCCGGCGACTCC GTGTTCAACAACAACGC CGCCTGGTCCTGGATCC GGCAGAGCCCTTCTAGA GGCCTGGAATGGCTGG GCCGGACCTACTACCGG TCCAAGTGGCTGTACGA CTACGCCGTGTCCGTGA AGTCCCGGATCACCGTG AACCCTGACACCTCCCG GAACCAGTTCACCCTGC AGCTGAACTCCGTGACC CCTGAGGACACCGCCCT GTACTACTGCGCCAGAG GCTACTCCTCCTCCTTC GACTATTGGGGCCAGG GCACCCTCGTGACCGTG TCCTCT	357	AGTCTGCTCTGACCCAGCC TGCCTCCGTGTCTGGCTCT CCCGGCCAGTCCATCACC ATCAGCTGTACCGGCACCT CCTCCAACATCGGCACCTA CAAGTTCGTGTCCTGGTAT CAGCAGCACCCCGACAAG GCCCCCAAAGTGCTGCTGT ACGAGGTGTCCAAGCGGC CCTCTGGCGTGTCTCCAG ATTCTCCGGCTCCAAGTCT GGCAACACCGCCTCCCTG ACCATCAGCGGACTGCAG GCTGAGGACCAGGCCGAC TACCACTGTGTGTCCTACG CTGGCTCTGGCACCCCTGCT GTTTGGCGGAGGCACCAA GCTGACCGTGCTG	358
CD3B450	CAAGTGCAACTCCAACA AAGCGGCCCAGGGCTG GTAAAGCCTTACAGAC CCTCTCACTTACTTGCG CAATATCTGGGGACTCC GTGTTTAATAACAATGC TGCATGGAGCTGGATTC GCCAGAGCCCAAGTCG CGGGCTCGAGTGGCTTG GTCGAACCTATTACCGC TCCAAGTGGCTCTATGA CTACGCAGTAAGCGTCA	359	CAGTCTGCTCTGACCCAGC CTGCCTCCGTGTCTGGCTC TCCCGGCCAGTCCATCACC ATCAGCTGTACCGGCACCT CCTCCAACATCGGCACCTA CAAGTTCGTGTCCTGGTAT CAGCAGCACCCCGCAAG GCCCCCAAAGTGATGATC TACGAGGTGTCCAAGCGG CCCTCCGGCGTGTCCAACA GATTCTCCGGCTCCAAGTC CGGCAACACCGCCTCCCT	360

	AATCACGGATAACAATC AACCCTGACACATCCAA GAATCAGTTTAGTCTGC AACTCAACTCAGTCACC CCTGAGGATACCGCAGT GTATTATTGTGCCAGAG GGTACAGCTCTTCCTTT GATTACTGGGGCCAAG GTACACTGGTAACAGTA TCAAGC		GACAATCAGCGGACTGCA GGCCGAGGACGAGGCCGA CTACTACTGTGTGTCCTAC GCCGGCTCTGGCACCTGC TGTTTGGCGGCGGAACAA AGCTGACCGTGCTG	
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Table 30. Kabat HCDR1, HCDR2 and HCDR3 amino acid sequences of selected anti-CD3 antibodies.

mAb	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CD3B815	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3W244	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3W245	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3W246	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3W247	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3W248	RYNMN	361	SISTSSNYIYYADSVKG	362	GWGPFDY	363
CD3B376	NNNAAWS	364	RTYYRSKWLYDYAVS VKS	365	GYSSSFYD	366
CD3B450	NNNAAWS	364	RTYYRSKWLYDYAVS VKS	365	GYSSSFYD	366

Table 31. Kabat LCDR1, LCDR2 and LCDR3 amino acid sequences of selected anti-CD3 antibodies.

mAb	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CD3B815	RARQSIGTAIH	367	YASESIS	368	QQSNSWPYT	369
CD3W244	RARQSIGTAIH	367	YASESIS	368	QQSGSWPYT	370
CD3W245	RARQSIGTAIH	367	YASESIS	368	QQSGSWPYT	370
CD3W246	RARQSIGTAIH	367	YASESIS	368	QQSGSWPYT	370
CD3W247	RARQSIGTAIH	367	YASESIS	368	QQSGSWPYT	370
CD3W248	RARQSIGTAIH	367	YASESIS	368	QQSGSWPYT	370
CD3B376	TGTSSNIGTYKFVS	371	EVSKRPS	372	VSYAGSGTLL	373
CD3B450	TGTSSNIGTYKFVS	371	EVSKRPS	372	VSYAGSGTLL	373

Table 32. HCDR1, HCDR2, HCD3, LCD1, LCD2, LCD3, VH and VL of anti-CD3 antibodies

Antibody	Region	Amino Acid sequence	SEQ ID NO:
CD3B815	HCDR1	RYNMN	361
	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFY	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSNSWPYT	369
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	339
	VL (CD3L372)	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWYQQR TNGSPRLLIKYASESISGIPSRFSGSGSGTDFTLTINSVES EDIADYYCQQNSWPYTFGGGTKLEIK	340
CD3W244	HCDR1	RYNMN	361

	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFYD	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSGSWPYT	370
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	339
	VL (CD3L394)	DIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWYQQ KPGKAPKLLIYYASESISGVPSRFSGSGSGTDFTLTISV QPEDFATYYCQQSGSWPYTFGQGTKLEIK	341
CD3BW245	HCDR1	RYNMN	361
	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFYD	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSGSWPYT	370
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	339
CD3BW246	VL (CD3L395)	DIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWYQQ KPGKAPKLLIKYASESISGVPSRFSGSGSGTDFTLTISL QPEDFATYYCQQSGSWPYTFGQGTKLEIK	342
	HCDR1	RYNMN	361
	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFYD	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSGSWPYT	370
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN	339

		AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	
	VL (CD3L396)	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQ KPGKAPKLLIKYASESISGVPSRFSGSGSGTDFLTITSSV QPEDFATYYCQQSGSWPYTFGQGTKLEIK	343
CD3BW247	HCDR1	RYNMN	361
	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFY	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSGSWPYT	370
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	339
	VL (CD3L397)	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQ KPGKAPKLLIYYASESISGVPSRFSGSGSGTDFLTITSSL QPEDFATYYCQQSGSWPYTFGQGTKLEIK	344
CD3BW248	HCDR1	RYNMN	361
	HCDR2	SISTSSNYIYYADSVKG	362
	HCDR3	GWGPFY	363
	LCDR1	RARQSIGTAIH	367
	LCDR2	YASESIS	368
	LCDR3	QQSGSWPYT	370
	VH (CD3H488)	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNW VRQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDN AKNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LVTVSS	339
	VL (CD3L398)	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWYQQR TNGSPRLIKYASESISGIPSRFSGSGSGTDFLTINSVES EDIADYYCQQSGSWPYTFGGGTKLEIK	345
CD3B376	HCDR1	NNNAAWS	364
	HCDR2	RTYYRSKWLYDYAVSVKS	365

	HCDR3	GYSSSFY	366
	LCDR1	TGTSSNIGTYKFVS	371
	LCDR2	EVSKRPS	372
	LCDR3	VSYAGSGTLL	373
	VH (CD3H219)	QVQLQQSGPRLVRPSQTLSTCAISGDSVFNNNAAWS WIRQSPSRGLEWLGRTYYRSKWLYDYAVSVKSRITVN PDTSRNQFTLQLNSVTPEDTALYYCARGYSSSFYWG QGTLVTVSS	346
	VL (CD3L150)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQ QHPDKAPKVLLYEVSKRPSGVSSRFSGSKSGNTASLTI SGLQAEDQADYHCVSYAGSGTLLFGGGTKLTVL	347
CD3B450	HCDR1	NNNAAWS	364
	HCDR2	RTYYRSKWLYDYAVSVKS	365
	HCDR3	GYSSSFY	366
	LCDR1	TGTSSNIGTYKFVS	371
	LCDR2	EVSKRPS	372
	LCDR3	VSYAGSGTLL	373
	VH (CD3H231)	QVQLQQSGPGLVKPSQTLSTCAISGDSVFNNNAAWS WIRQSPSRGLEWLGRTYYRSKWLYDYAVSVKSRITIN PDTSKNQFSLQLNSVTPEDTAVYYCARGYSSSFYWG QGTLVTVSS	348
	VL (CD3L197)	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQ QHPGKAPKVMIEVSKRPSGVSNRFSGSKSGNTASLTI SGLQAEDQADYHCVSYAGSGTLLFGGGTKLTVL	349

Consensus sequence

FIG. 13 shows the alignment of the VL regions of CD3B815, CD3W244, CD3W245, CD3W246, and CD3W247. A consensus amino acid sequence of **SEQ ID NO: 374** was determined for the VL region,

5 HCDR and LCDR residues are underlined.

SEQ ID NO: 374

DIQX₁TQSPX₂X₃LSX₄SX₅GX₆RVX₇X₈X₉CRARQSIGTAIHWWYQQKX₁₀X₁₁X₁₂X₁₃PX₁₄LLIX₁₅YASESI
SGX₁₆PSRFSGSGSGTDFTLTIX₁₇SX₁₈QX₁₉EDX₂₀AX₂₁YYCQXS₂₂SWPYTFGX₂₃GTKLEIK

wherein, X₁ is L or M; X₂ is G or S; X₃ is I or S; X₄ is V or A; X₅ is P or V; X₆ is E or D; X₇ is S or T; X₈ is F or I; X₉ is S or T; X₁₀ is T or P; X₁₁ is N or G; X₁₂ is G or K; X₁₃ is S or A; X₁₄ is R or K; X₁₅ is K or Y; X₁₆ is I or V; X₁₇ is N or S; X₁₈ is V or L; X₁₉ is S or P; X₂₀ is I or F; X₂₁ is D or T; X₂₂ is N or G; or X₂₃ is G or Q.

5 Epitope Identification

The epitope on CD3 was determined by hydrogen-deuterium exchange mass spectrometry (HDX-MS). The antibody clone OKT3 was used as a control for the HDX experiment, since its epitope on CD3ε was known from crystal structure (PDB ID 1SY6) (Kjer-Nielsen, L. *et al.*; *Proc Natl Acad Sci U S A* **101**, 7675-7680).

- 10 *On-Exchange Experiment for HDX-MS.* On-exchange reaction was initiated by mixing 10 μL of 10 μM CD3W220 (SEQ ID NO: 375), which was comprised of CD3εγ fused with a 26-aa linker region fused onto a serum albumin domain, with or without 1.2 molar-excess of ligand and 30 μL of H₂O or a deuterated buffer (20 mM MES, pH 6.4, 150 mM NaCl in 95% D₂O or 20 mM Tris, pH 8.4, 150 mM NaCl in 95% D₂O). The reaction mixture was incubated for 15, 50, 150, 500, or 1,500 s at 1.2 °C. The
15 on-exchanged solution was quenched by the addition of chilled 40 μL of 8 M urea, 1 M TCEP, pH 3.0 and immediately analyzed.

CD3W220 (CD3εγ-HSA-6xHis) (SEQ ID NO: 375):

- QDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDH
LSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVGSADDAKKDAKKDDAKKDDAKKDG
20 SQSIKGNHLVKVYDYQEDGSVLLTCDAAEAKNITWFKDGMIGFLTEDKKKWNLGSNAKDPGR
MYQCKGSQNKSKPLQVYYRMGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDH
VKLVNEVTEFAKTCVADESAENCDSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECF
LQHKDDNPNLRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFT
ECCQAADKAACLLPKLDEL RDEGKASSAKQRLKASLQKFGERAFAKAWAVARLSQRFPAEFA
25 EVSKLVTDLTKVHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVE
NDEMPADLP SLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLRLAKTYETTL
EKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCLEQLGEYKFQNALLVRYTKKVPQVSTP
TLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNR
RPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMD
30 DFAAFVEKCKKADDKETCFAEEGKKLVAASQAALGLGGGSHHHHHHHH

General Procedure for HDX-MS Data Acquisition. HDX-MS sample preparation was performed with automated HDx system (LEAP Technologies, Morrisville, NC). The columns and pump were;

protease, protease type XIII (protease from *Aspergillus saitoi*, type XIII) /pepsin column (w/w, 1:1; 2.1 x 30 mm) (NovaBioAssays Inc., Woburn, MA); trap, ACQUITY UPLC BEH C18 VanGuard Pre-column (2.1 x 5 mm) (Waters, Milford, MA), analytical, Accucore C18 (2.1 x 100 mm) (Thermo Fisher Scientific, Waltham, MA); and LC pump, VH-P10-A (Thermo Fisher Scientific). The loading pump
 5 (from the protease column to the trap column) was set at 600 $\mu\text{L}/\text{min}$ with 99% water, 1% acetonitrile, 0.1% formic acid. The gradient pump (from the trap column to the analytical column) was set from 8% to 28% acetonitrile in 0.1% aqueous formic acid in 20 min at 100 $\mu\text{L}/\text{min}$.

MS Data Acquisition. Mass spectrometric analyses were carried out using an LTQTM Orbitrap Fusion Lumos mass spectrometer (Thermo Fisher Scientific) with the capillary temperature at 275 $^{\circ}\text{C}$,
 10 resolution 150,000, and mass range (m/z) 300 – 1,800.

HDX-MS Data Extraction. BioPharma Finder 3.0 (Thermo Fisher Scientific) was used for the peptide identification of non-deuterated samples prior to the HDX experiments. HDExaminer version 2.5 (Sierra Analytics, Modesto, CA) was used to extract centroid values from the MS raw data files for the HDX experiments.

15 *HDX-MS Data Analysis.* The extracted HDX-MS data were further analyzed in Excel. All exchange time points (at pH 6.4 or pH 8.4 at 1.2 $^{\circ}\text{C}$) were converted to the equivalent time points at pH 7.4 and 23 $^{\circ}\text{C}$ (e.g., 15 s at pH 6.4 at 1.2 $^{\circ}\text{C}$ is equivalent of 0.15 s at pH 7.4 at 23 $^{\circ}\text{C}$; **Table 33**).

Table 33. HDX reaction conditions and exchange times versus exchange times corrected to pH 7.4 and 23 $^{\circ}\text{C}$.

Time adjusted to pH 7.4, 23 $^{\circ}\text{C}$ (s)	pH 6.4 1.2 $^{\circ}\text{C}$ (s)	pH 8.4 1.2 $^{\circ}\text{C}$ (s)
0.015	-----	-----
0.05	-----	-----
0.15	15	-----
0.5	50	-----
1.5	150	-----
5	500	-----
15	1,500	15
50	-----	50
150	-----	150
500	-----	500
1,500	-----	1,500

Results. Incubation of the KLCB91, the bispecific antibodies containing CD3W245 as an anti-CD3 arm, with recombinant CD3 ϵ resulted in different patterns of overall protection and degrees of protection at specific segments of the antigen. KLCB91 and OKT3 both protected non-continuous segments (**FIG. 14**) indicating conformational non-identical epitopes. The protected segments were mapped onto the crystal structure of CD3 ϵ (PDB 1SY6) to visualize the binding epitopes in three dimensions.

Consistent with the crystal structure of OKT3 bound to CD3 ϵ (Uniprot ID P07766), the epitope of OKT3 was found to consist of peptides covering spanning residues 29-37, 79-84, and 87-89 of CD3 ϵ (**SEQ ID NO: 375** and Figure 14). CD3W245 bound to an epitope partially overlapping with that of OKT3, and included amino acid residues 29-37, 55-63, and 79-84 of CD3 ϵ (**SEQ ID NO: 375** and Figure 14).

Binding of humanized anti-CD3 scFv variants to CD3 after heat shock.

The variable regions of the anti-CD3 molecules were formatted as scFv in VH-VL orientation using linker GTEGKSSGSGSESKST (**SEQ ID NO: 376**) (**Table 34**) for expression in *E. coli*, and then screened for binding to recombinant CD3 (homodimeric CD3 $\epsilon\gamma$ -Fc, CD3W147, **SEQ ID NO: 377**), binding to T cells, and thermostability.

CD3W147 (SEQ ID NO: 377):

QDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDH
LSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVGSADDAKKDAKKDDAKKDDAKKDG
SQQIKGNHLVKVYDYQEDGSVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSNAKDPRG
MYQCKGSQNKSKPLQVYYRMGSGSLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ
FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS
KAKGQPREPQVYTFPPSQEEMTKNQVSLRCLVKGFYPSDIAVEWESNGQPENNYKTTKPVLDSD
GSFRLESRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGGGHHHHHH

Table 34. csFv-HL-E.c. amino acid sequences.

scFv	SEQ ID NO:	Amino acid sequence
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CD3W234-HL-E.c.	378	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWQGTL VTVSSGTEGKSSSGSGSESKSTDILLTQSPGILSVSPGERV SFSCRARQSIGTAIHWYQQRNGSPRLLIKYASESISGIP SRFSGSGSGTDFTLTINSVESEDIADYYCQQSNSWPYTF GGGTKLEIKGPGGQHHHHHHGAYPYDVPDYAS
CD3W238-HL-E.c.	379	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWQGTL VTVSSGTEGKSSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIYYASESISG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSNSWPY TFGQGTKLEIKGPGGQHHHHHHGAYPYDVPDYAS
CD3W242-HL-E.c.	380	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWQGTL VTVSSGTEGKSSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIYYASESISG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSNSWPY TFGQGTKLEIKGPGGQHHHHHHGAYPYDVPDYAS
CD3W243-HL-E.c.	381	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWQGTL VTVSSGTEGKSSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIYYASESISG VPSRFSGSGSGTDFTLTISVQPEDFATYYCQQSNSWPY TFGQGTKLEIKGPGGQHHHHHHGAYPYDVPDYAS
CD3W244-HL-E.c.	382	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWQGTL VTVSSGTEGKSSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIYYASESISG

		VPSRFSGSGSGTDFTLTISVQPEDFATYYCQQSGSWPY TFGQGTKLEIKGPGGQH HHHHHGAYPYDVPDYAS
CD3W245-HL-E.c.	383	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LTVVSSGTEGKSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIKYASESISG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSGSWPY TFGQGTKLEIKGPGGQH HHHHHGAYPYDVPDYAS
CD3W246-HL-E.c.	384	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LTVVSSGTEGKSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIKYASESISG VPSRFSGSGSGTDFTLTISVQPEDFATYYCQQSGSWPY TFGQGTKLEIKGPGGQH HHHHHGAYPYDVPDYAS
CD3W247-HL-E.c.	385	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LTVVSSGTEGKSSGSGSESKSTDIQMTQSPSSLSASVGDR VTITCRARQSIGTAIHWYQQKPGKAPKLLIYYASESISG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSGSWPY TFGQGTKLEIKGPGGQH HHHHHGAYPYDVPDYAS
CD3W248-HL-E.c.	386	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWV RQAPGKGLEWVSSISTSSNYIYYADSVKGRFTFSRDNA KNSLDLQMSGLRAEDTAIYYCTRGWGPFDYWGQGT LTVVSSGTEGKSSGSGSESKSTDILLTQSPGILSVSPGERV SFSCRARQSIGTAIHWYQRTNGSPRLIKYASESISGIP SRFSGSGSGTDFTLTINSVESEDIADYYCQQSGSWPYTF GGGTKLEIKGPGGQH HHHHHGAYPYDVPDYAS

Briefly, scFv-coding sequences were cloned into a pADLTM-22c vector having a PelB leader sequence for secretion. *E. coli* cells were transformed with plasmid and grown overnight at 37 °C in 2xYT microbial growth medium supplemented with 100 µg/mL Carbenicillin. Protein expression was

induced by addition of 1 mM IPTG and cultures were grown overnight. After expression, cells were pelleted by centrifugation at 2,200 X g for 5 min and supernatants were collected and tested directly for binding to biotinylated CD3W147 by ELISA.

For ELISA analysis, botinylated CD3W147 (**SEQ ID NO: 377**) was immobilized on the plate in concentrations ranging from 0.039 ug/mL to 2.5 ug/mL in 2-fold dilutions followed by incubation at room temperature for 45 min. Bound scFv was detected using chicken anti-HA-horseradish peroxidase and then detected with chemiluminescence substrate. All tested scFv molecules derived from CD3B815 bound CD3e (**FIG. 12**).

The scFv molecules were then tested for their abilities to bind T cells, using flow cytometry. Briefly, human T cells were thawed and resuspended into flow staining buffer at 1×10^6 cells/mL and plated at 50,000 cells/well. A positive control, CD3W36 was comprised of an anti-CD3 antibody SP34 formatted as LH-scFv, and a negative control, B23, an scFv targeted against the F-glycoprotein from respiratory syncytial virus, were used for comparison of binding. E. coli supernatants were added at 150 μ L/well and incubated at 4 °C for 1 hr. After incubation, plates were washed with staining buffer and detected with anti-His antibody conjugated to Alexa-647 in staining buffer. After incubation, 200 μ L of IntelliCyt running buffer was added to the mixture, and cells were resuspended in 30 μ L running buffer containing 1:1,000 Sytox Green dead cell stain and analyzed on iQue Screener. Gating and analysis were performed as above. All scFv molecules derived from CD3B815 displayed mean fluorescence indices consistent with T cell binding (**Table 35**).

Table 35. T cell-based binding of humanized scFv molecules.

Protein	MFI (n=2)
CD3W245-HL-E.c.	178140.0
CD3W244-HL-E.c.	165631.0
CD3W246-HL-E.c.	153895.8
CD3W238-HL-E.c.	137380.4
CD3W242-HL-E.c.	126105.9
CD3W243-HL-E.c.	111347.6
CD3W241-HL-E.c.	120793.8
CD3W247-HL-E.c.	110932.3
CD3W248-HL-E.c.	60437.1
CD3W234-HL-E.c.	66790.3
B23	51.8

CD3W36	99451.6
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Example 10: Generation of bispecific HLA-G x CD3 antibodies

The VH/VL regions of the anti-HLA-G antibodies generated in Example 1-3 and the VH/VL regions of the anti-CD3 antibody of Example 4 were engineered into bispecific format and expressed as IgG1.

Engineering of CD3 scFvs for HLA-G x CD3 bispecific generation

CD3 VH/VL regions were engineered as scFvs in either VH-Linker-VL or VL-linker-VH orientations using the linker of SEQ ID NO: 8 (Table 36). The VH-Linker-VL or VL-linker-VH scFv molecules binding CD3 were further engineered into a scFv-hinge-CH2-CH3 format comprising Fc silencing mutation (L234A/L235A/D265S) and the T350V/L351Y/F405A/Y407V mutations designed to promote selective heterodimerization (Table 37). The polypeptides of SEQ ID NOs: 387 or 492 were used as the constant domain hinge-CH2-CH3. DNA sequences of anti-CD3 molecules in scFv format and scFv-hinge-CH2-CH3 format are shown in Table 38.

SEQ ID NO: 387 (huIgG1_G1m(17)-hinge-Fc_C220S_AAS_ZWA)

EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVVSVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYVYPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFA
LVSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQKSLSLSPG

SEQ ID NO: 492

EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVVSVSHEDPEVKF
NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSD
DGSFALVSKLTVDKSRWQQGNVFSFSVMHEALHNHYTQKSLSLSPGK

Table 36 shows the scFv sequences of selected anti-CD3 antibodies

Acronym	Amino acid Sequence of scFv	SEQ ID NO:
CD3W244_HL	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRTITCRARQSIGTAIHVYQKQP	388

	GKAPKLLIYYASESISGVPSRFSGSGSGTDFTLTISVVQPEDFATYY CQQSGSWPYTFGQGTKLEIK	
CD3W244_LH	DIQMTQSPSSLSASVGDRVTTTCRARQSIGTAIHWYQQKPGKAPK LLIYYASESISGVPSRFSGSGSGTDFTLTISVVQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLLTVSS	389
CD3W245_HL	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVTTTCRARQSIGTAIHWYQQK GKAPKLLIKYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYY CQQSGSWPYTFGQGTKLEIK	390
CD3W245_LH	DIQMTQSPSSLSASVGDRVTTTCRARQSIGTAIHWYQQKPGKAPK LLIKYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLLTVSS	391
CD3W246_HL	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVTTTCRARQSIGTAIHWYQQK GKAPKLLIKYASESISGVPSRFSGSGSGTDFTLTISVVQPEDFATYY CQQSGSWPYTFGQGTKLEIK	392
CD3W246_LH	DIQMTQSPSSLSASVGDRVTTTCRARQSIGTAIHWYQQKPGKAPK LLIKYASESISGVPSRFSGSGSGTDFTLTISVVQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLLTVSS	393

CD3W247_HL	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLVTVSSGGSEGKSSGSGSESK STGGSIDIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWWYQKPK GKAPKLLIYYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYY CQQSGSWPYTFGQGTKLEIK	394
CD3W247_LH	DIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWWYQKPKGKAPK LLIYYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWRQAPGKGLEWVSSIST SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLVTVSS	395
CD3W248_HL	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLVTVSSGGSEGKSSGSGSESK STGGSIDILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWWYQRTN GSPRLIKYASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQ QSGSWPYTFGGGTKLEIK	396
CD3W248_LH	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWWYQRTNGSPRL LIKYASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQQSGS WPYTFGGGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWRQAPGKGLEWVSSIST SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLVTVSS	397
CD3B450-LH	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPGKAPKVM YEVSKRPSGVSNRFSGSGSGNTASLTISGLQAEDEADYYCVSYAGSGTL LFGGGTKLTVLGGSEGKSSGSGSESKSTGGSQVQLQSGPGLVKPSQTL SLTCAISGDSVFNNNAAWSWIRQSPSRGLEWLGRYYRSKWLYDYAVS VKSRTINPDTSKNQFSLQLNSVTPEDTAVYYCARGYSSSFYWGQGTL VTVSS	398
CD3B219-LH	QTVVTQEPLTVSPGGTVTLTCRSSTGAVTTSNYANWVQKPGQAPRG LIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSN LWVFGGGTKLTVLGGSEGKSSGSGSESKSTGGSEVQLVESGGGLVQPG GSLRLSCAASGFTFNTYAMNWRQAPGKGLEWVARIRSKYNNYATYY	399

	AASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCVRHGNFGNSYVS WFAYWGQGLTVTVSS	
null-scFv	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGCAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGQG TKVEIKGGSGSGGCPGCGSGGEVQLLESGGGLVQPGGSLRLSCAAS GFTFSSYAMSWVRQAPGKLEWVSAISGSGGSTYYADSVKGRFTISR NSKNTLYLQMNSLRAEDTAVYYCAKYDGIYGELDFWGCGLTVTVSS	400

Table 37 Amino acid sequences of selected anti-CD3 scFv-Fc arms.

Acronym	HC protein SEQ ID NO:	SEQ ID NO:
CD3W244-HL-Fc	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGLTVTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQKP GKAPKLLIYYASESISGVPSRFSGSGSGTDFTLTISVQPEDFATYY CQQSGSWPYTFGQGTKLEIKEPKSSDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	401
CD3W244-LH-Fc	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQKPGKAPK LLIYYASESISGVPSRFSGSGSGTDFTLTISVQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGLTVTVSSSEPKSSDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	402

CD3W245-HL-Fc	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFQDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQKP GKAPKLLIKYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYY CQQSGSWPYTFGQGTKLEIKEPKSSDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	403
CD3W245-LH-Fc	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQKPGKAPK LLIKYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSIST SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFQDYWGQGTLLTVSSEPKSSDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	404
CD3W246-HL-Fc	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFQDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWYQQKP GKAPKLLIKYASESISGVPSRFSGSGSGTDFTLTISVQPEDFATYY CQQSGSWPYTFGQGTKLEIKEPKSSDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPG	405

CD3W246-LH-Fc	DIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWYQQKPGKAPK LLIKYASESISGVPSRFSGSGSGTDFTLTISVQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLLTVSSEPKSSDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	406
CD3W247-HL-Fc	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGSDIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWYQQK GKAPKLLIYYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYY CQQSGSWPYTFGQGTKLEIKEPKSSDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	407
CD3W247-LH-Fc	DIQMTQSPSSLSASVGDRVITTCRARQSIGTAIHWYQQKPGKAPK LLIYYASESISGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSG SWPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGG LVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTS SNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTR GWGPFDYWGQGTLLTVSSEPKSSDKTHTCPPCPAPEAAGGPSVF LFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYVPPSREEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	408

CD3W248-HL-Fc	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGK GLEWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLR AEDTAIYYCTRGWGPFDYWGQGTLLTVSSGGSEGKSSGSGSESK STGGS DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWYQRTN GSPRL LIKYASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQ QSGSWPYTFGGGKLEIKEPKSSDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSRWQ QGNVFSCSVMEALHNHYTQKSLSLSPGK	409
CD3W248-LH-Fc	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWYQRTNGSPRL LIKYASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQSGS WPYTFGGGKLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGGL VKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGLEWVSSISTSS NYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDTAIYYCTRG WGPFDYWGQGTLLTVSSEPKSSDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSRWQ QGNVFSCSVMEALHNHYTQKSLSLSPGK	410
CD3B450-LH-Fc	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPGKAP KVMIEVSKRPSGVSNRFGSGKSGNTASLTISGLQAEDEADYYC VSYAGSGTLLFGGGTKLTVLGGSEGKSSGSGSESKSTGGSQVQL QQSGPGLVKPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRGLE WLGRYYRSKWLYDYAVSVKSRITINPDTSKNQFSLQLNSVTPE DTAVYYCARGYSSSFYWGQGTLLTVSSEPKSSDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQ VSLTCLVKGFYP SDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSRWQ QGNVFSCSVMEALHNHYTQKSLSLSPG	411

CD3B219-LH-Fc	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGSEGKSSGSGSESKSTGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGL EWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSL KTEDTAVYYCVRHGNFGNSYVSWFAYWGQGLTVTVSSEPSSD KTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPEVTCVVS SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV LSDSGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPG	412
null-scFv-Fc	DIQMTQSPSSLSASVGDRVITTCRASQSISSYLNWYQQKPGCAPKLLIYA ASSLQSGVPSRFSFGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGQG TKVEIKGGGSGSGGCGPPCGSGGGEVQLLES GGGLVQPGGSLRLSCAAS GFTFSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISR NSKNTLYLQMNSLRAEDTAVYYCAKYDGIYGELDFWCGGLTVTVSSEP KSSDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPEVTCVVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	413

Table 38. DNA SEQ ID NOs for anti-CD3 scFv and scFv-hinge-CH2-CH3 (scFv-Fc)

	scFv DNA SEQ ID NO	scFv-Fc DNA SEQ ID NO
CD3W244_HL	414	426
CD3W244_LH	415	427
CD3W245_HL	416	428
CD3W245_LH	417	429

CD3W246_HL	418	430
CD3W246_LH	419	431
CD3W247_HL	420	432
CD3W247_LH	421	433
CD3W248_HL	422	434
CD3W248_LH	423	435
CD3B450_LH	424	436
CD3B219_LH	425	437

SEQ ID NO: 414 (CD3W244_HL)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
 GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
 5 GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
 ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
 GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
 TCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAGTC
 CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGGAAGCGACATCCAGATGACCCAGAGC
 10 CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCTGCGCCGCGAGA
 GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
 CTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
 ACCGACTTCACCCTGACCATCAGCAGCGTGACGCCAGAGGACTTCGCCACCTACTACTGCCA
 GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

15 SEQ ID NO: 415 (CD3W244_LH)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
 TCACCTGTCTGCGCCGCGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
 AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
 TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCGTGACGCCAGAGGA
 20 CTTGCGCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
 AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC

CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA
5 GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGC

SEQ ID NO: 416 (CD3W245_HL)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
10 GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
TCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
15 CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
CAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

20 SEQ ID NO: 417 (CD3W245_LH)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCAGAGGA
25 CTTGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
30 ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA
GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGC

SEQ ID NO: 418 (CD3W246_HL)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
5 ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
TCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
10 GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
CAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCTGACCATCAGCAGCGTGACAGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

SEQ ID NO: 419 (CD3W246_LH)

15 GACATCCAGATGACCCAGAGCCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCTGACCATCAGCAGCGTGACAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
20 AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA
25 GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGC

SEQ ID NO: 420 (CD3W247_HL)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
30 GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT

TCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
5 CTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCCCTGACCATCAGCAGCCTGCAGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

SEQ ID NO: 421 (CD3W247_LH)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
10 TCACCTGTCGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCCTGACCATCAGCAGCCTGCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
15 CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA
GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
20 GGTGGGGGCCATTCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGC

SEQ ID NO: 422 (CD3W248_HL)

GAGGTGCAACTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCT
CCTGTGCAGCCTCTGGATTACCTTCAGTAGATATAACATGAACTGGGTCCGCCAGGCTCCA
GGGAAGGGGGCTGGAGTGGGTCTCATCCATTAGTACTAGTAGTAATTACATATACTACGCAGA
25 CTCAGTGAAGGGCCGATTACCTTCTCCAGAGACAACGCCAAGAAGTCACTGGATCTGCAAA
TGAGCGGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTACGAGAGGCTGGGGGCCTTTT
GACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGCGGATCTGAGGGAAAGTCCA
GCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCTTGCTGACTCAGTCTCC
AGGCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTTCTCCTGCAGGGCCAGACAGAGC
30 ATTGGCACAGCCATACACTGGTATCAGCAAAGAACAATGGTTCTCCAAGGCTTCTCATAAA
GTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTTAGCGGCAGTGGATCAGGGACAG
ATTTTACTCTTACCATCAACAGTGTGGAGTCTGAAGATATTGCAGATTATTACTGTCAACAA
AGTGGGAGCTGGCCGTACACGTTCCGAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO: 423 (CD3W248_LH)

GACATCTTGCTGACTCAGTCTCCAGGCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTT
CTCCTGCAGGGCCAGACAGAGCATTGGCACAGCCATACACTGGTATCAGCAAAGAACAAAT
GGTTCTCCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTT
5 AGCGGCAGTGGATCAGGGACAGATTTTACTCTTACCATCAACAGTGTGGAGTCTGAAGATAT
TGCAGATTATTACTGTCAACAAAGTGGGAGCTGGCCGTACACGTTCCGAGGGGGGACCAAG
CTGGAATAAAAAGGCGGATCTGAGGGAAAAGTCCAGCGGCTCCGGCAGCGAAAAGCAAGTCCA
CCGGCGGAAGCGAGGTGCAACTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCT
CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGATATAACATGAACTGGGTCC
10 GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCCATTAGTACTAGTAGTAATTACATA
TACTACGCAGACTCAGTGAAGGGCCGATTACCTTCTCCAGAGACAACGCCAAGAAGTCACT
GGATCTGCAAATGAGCGGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTACGAGAGGC
TGGGGGCCCTTTTACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

SEQ ID NO: 426 (CD3W244_HL-scFv-Fc)

15 GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAAGCAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCCAT
20 TCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
CTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
25 ACCGACTTCACCTTGACCATCAGCAGCGTGCAGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGGAGCCC
AAATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGAC
CGTCAGTCTTCCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAG
GTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACG
30 TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCA
AAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCCATCCCGGGAGGAGATGACCAA

GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
CGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAAC
GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
5 CCTGTCTCCGGGTAAA

SEQ ID NO: 427 (CD3W244_LH-scFv-Fc)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
10 TCAGCGGCAGCGGCAGCGGCACCGACTTCACCTGACCATCAGCAGCGTGCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTACCTTCAGCCGCTACAACATGAACTGGGT
15 GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA
GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGAGCCCA
AATCTAGCGACAAAACCTCACACATGTCCACCGTGCCCAGCACCTGAAGCAGCAGGGGGACC
20 GTCAGTCTTCCTCTTCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGG
TCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGT
GGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAC
GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAA
25 AGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAG
AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC
30 CTGTCTCCGGGTAAA

SEQ ID NO: 428 (CD3W245_HL-scFv-Fc)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA

GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
TCGACTACTGGGGCCAGGGCACCTTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAATC
5 CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
CAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCTGACCATCAGCAGCCTGCAGCCAGAGGACTTCGCCACCTACTACTGCCA
10 GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGGAGCCC
AAATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGAC
CGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAG
GTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
15 CGTACCGTGTGGTCAGCGTCCTCACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCA
AAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAA
GAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGAGACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
20 CGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAAC
GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAA

SEQ ID NO: 429 (CD3W245_LH-scFv-Fc)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
25 TCACCTGTGCTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCTGACCATCAGCAGCCTGCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
30 CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACA

GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGCGAGCCCA
AATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACC
GTCAGTCTTCCTCTTCCCCC AAAACCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGG
5 TCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGT
GGACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCAC
GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
AGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCCATCCCGGGAGGAGATGACCAAG
10 AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCTCCCGTGTGGACTCCGAC
GGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACG
TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC
CTGTCTCCGGGTAAA

15 **SEQ ID NO: 430 (CD3W246_HL-scFv-Fc)**

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
20 GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
TCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCA CTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
25 CAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCCCTGACCATCAGCAGCGTGACGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGGAGCCC
AAATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGAC
CGTCAGTCTTCCTCTTCCCCC AAAACCAAGGACACCCCTCATGATCTCCCGGACCCCTGAG
30 GTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACG
TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCA

AAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAA
GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
CGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAAC
5 GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAA

SEQ ID NO: 431 (CD3W246_LH-scFv-Fc)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
10 AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCTTGACCATCAGCAGCGTGCCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
15 AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTACCTTCAGCCGCTACAACATGAACTGGGT
GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTACCTTCAGCCGCGACAACGCCAAGAACA
GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGAGCCCA
20 AATCTAGCGACAAAACACTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACC
GTCAGTCTTCCTCTTCCCCCAAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGG
TCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGT
GGACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGGAGGAGCAGTACAACAGCAC
GTACCGTGTTGTCAGCGTCTCACCCTGCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
25 AGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAAG
AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC
GGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACG
30 TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC
CTGTCTCCGGGTAAA

SEQ ID NO: 432 (CD3W247_HL-scFv-Fc)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
5 GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT
TCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGCGGCGGATCTGAGGGAAAAGTC
CAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCCAGATGACCCAGAGC
CCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCATCACCTGTCGTGCCCCGCCAGA
GCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGCAAGGCCCCAAAGCTGCTGAT
10 CTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCTTCAGCGGCAGCGGCAGCGGC
ACCGACTTCACCCCTGACCATCAGCAGCCTGCAGCCAGAGGACTTCGCCACCTACTACTGCCA
GCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGGAGCCC
AAATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGAC
CGTCAGTCTTCTCTTCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAG
15 GTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACG
TGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCA
AAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCCATCCCGGGAGGAGATGACCAA
20 GAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGA
CGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAAC
GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
CCTGTCTCCGGGTAAA

25 **SEQ ID NO: 433 (CD3W247_LH-scFv-Fc)**

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCCTGACCATCAGCAGCCTGCAGCCAGAGGA
30 CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTC
CACCGGCGGAAGCGAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGC
AGCCTGCGCCTGAGCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGT

GCGCCAAGCCCCAGGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCCAGCAGCAACTAC
ATCTACTACGCCGACAGCGTGAAGGGCCGCTTACCTTCAGCCGCGACAACGCCAAGAACA
GCCTGGACCTGCAGATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGC
GGTTGGGGCCCATTCGACTACTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGAGCCCA
5 AATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACC
GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGG
TCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGT
GGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAC
GTACCGTGTTGTCAGCGTCTCACCCTGCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA
10 AGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAGCCAA
AGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCCATCCCGGGAGGAGATGACCAAG
AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTG
GGAGAGCAATGGGCAGCCGGAGAACAATAAGACACGCTCCCGTGCTGGACTCCGAC
GGCTCCTTCGCCCTCGTGAGCAAGCTCACCCTGGACAAGTCTAGATGGCAGCAGGGGAACG
15 TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCC
CTGTCTCCGGGTAAA

SEQ ID NO: 434 (CD3W248_HL-scFv-Fc)

GAGGTGCAACTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCT
CCTGTGCAGCCTCTGGATTACCTTCAGTAGATATAACATGAACTGGGTCCGCCAGGCTCCA
20 GGGAAGGGGCTGGAGTGGGTCTCATCCATTAGTACTAGTAGTAATTACATATACTACGCAGA
CTCAGTGAAGGGCCGATTACCTTCTCCAGAGACAACGCCAAGAACTCACTGGATCTGCAAA
TGAGCGGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTACGAGAGGCTGGGGGCCTTTT
GACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGCGGATCTGAGGGAAAGTCCA
GCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCGACATCTTGCTGACTCAGTCTCC
25 AGGCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTTCTCCTGCAGGGCCAGACAGAGC
ATTGGCACAGCCATACACTGGTATCAGCAAAGAACAATGGTTCTCCAAGGCTTCTCATAAA
GTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTTAGCGGCAGTGGATCAGGGACAG
ATTTTACTCTTACCATCAACAGTGTGGAGTCTGAAGATATTGCAGATTATTACTGTCAACAA
AGTGGGAGCTGGCCGTACACGTTTCGGAGGGGGGACCAAGCTGGAAATAAAAGAGCCCAAAT
30 CTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTC
AGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA
CATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGA
CGGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTA

CCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGT
GCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGG
GCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAGAAC
CAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGA
5 GAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGC
TCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTT
CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGT
CTCCGGGTAAA

SEQ ID NO: 435 (CD3W248_LH-scFv-Fc)

10 GACATCTTGCTGACTCAGTCTCCAGGCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTT
CTCCTGCAGGGCCAGACAGAGCATTGGCACAGCCATACACTGGTATCAGCAAAGAACAAAT
GGTTCTCCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTT
AGCGGCAGTGGATCAGGGACAGATTTTACTCTTACCATCAACAGTGTGGAGTCTGAAGATAT
TGCAGATTATTACTGTCAACAAAGTGGGAGCTGGCCGTACACGTTCCGAGGGGGGACCAAG
15 CTGGAATAAAAAGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAAGCAAGTCCA
CCGGCGGAAGCGAGGTGCAACTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCT
CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGATATAACATGAACTGGGTCC
GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCCATTAGTACTAGTAGTAATTACATA
TACTACGCAGACTCAGTGAAGGGCCGATTACCTTCTCCAGAGACAACGCCAAGAACTCACT
20 GGATCTGCAAATGAGCGGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTACGAGAGGC
TGGGGGCCCTTTTACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGAGCCCCAAATC
TAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCA
GTCTTCTCTTCCCCC AAAACCAAGGACACCTCATGATCTCCCGACCCCTGAGGTCAC
ATGCGTGGTGGTGAGCGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGAC
25 GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC
CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
CAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGG
CAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAGAACC
AGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
30 AGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCT
CCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTC
TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTC
TCCGGGTAAA

SEQ ID NO: 424 (CD3W450_LH-scFv)

CAGTCTGCTCTGACCCAGCCTGCCTCCGTGTCTGGCTCTCCCGGCCAGTCCATCACCATCAGC
TGTACCGGCACCTCCTCCAACATCGGCACCTACAAGTTCGTGTCCTGGTATCAGCAGCACCC
CGGCAAGGCCCCCAAAGTGATGATCTACGAGGTGTCCAAGCGGCCCTCCGGCGTGTCCAAC
5 AGATTCTCCGGCTCCAAGTCCGGCAACACCGCCTCCCTGACAATCAGCGGACTGCAGGCCGA
GGACGAGGCCGACTACTACTGTGTGTCCTACGCCGGCTCTGGCACCCCTGCTGTTTGGCGGCG
GAACAAAGCTGACCGTGCTGGGCGGCTCCGAGGGCAAGAGCAGCGGCAGCGGCAGCGAGA
GCAAGAGCACCGGCGGCAGCCAAGTGCAACTCCAACAAAGCGGCCAGGGCTGGTAAAGCC
TTCACAGACCCTCTCACTTACTTGCGCAATATCTGGGGACTCCGTGTTTAATAACAATGCTGC
10 ATGGAGCTGGATTTCGCCAGAGCCCAAGTCGCGGGCTCGAGTGGCTTGGTGAACCTATTACC
GCTCCAAGTGGCTCTATGACTACGCAGTAAGCGTCAAATCACGGATAACAATCAACCCTGAC
ACATCCAAGAATCAGTTTAGTCTGCAACTCAACTCAGTCACCCCTGAGGATACCGCAGTGTA
TTATTGTGCCAGAGGTACAGCTCTTCCTTTGATTACTGGGGCCAAGGTACACTGGTAACAG
TATCAAGC

15 SEQ ID NO: 436 (CD3W450_LH-scFv-Fc)

CAGTCTGCTCTGACCCAGCCTGCCTCCGTGTCTGGCTCTCCCGGCCAGTCCATCACCATCAGC
TGTACCGGCACCTCCTCCAACATCGGCACCTACAAGTTCGTGTCCTGGTATCAGCAGCACCC
CGGCAAGGCCCCCAAAGTGATGATCTACGAGGTGTCCAAGCGGCCCTCCGGCGTGTCCAAC
AGATTCTCCGGCTCCAAGTCCGGCAACACCGCCTCCCTGACAATCAGCGGACTGCAGGCCGA
20 GGACGAGGCCGACTACTACTGTGTGTCCTACGCCGGCTCTGGCACCCCTGCTGTTTGGCGGCG
GAACAAAGCTGACCGTGCTGGGCGGCTCCGAGGGCAAGAGCAGCGGCAGCGGCAGCGAGA
GCAAGAGCACCGGCGGCAGCCAAGTGCAACTCCAACAAAGCGGCCAGGGCTGGTAAAGCC
TTCACAGACCCTCTCACTTACTTGCGCAATATCTGGGGACTCCGTGTTTAATAACAATGCTGC
ATGGAGCTGGATTTCGCCAGAGCCCAAGTCGCGGGCTCGAGTGGCTTGGTGAACCTATTACC
25 GCTCCAAGTGGCTCTATGACTACGCAGTAAGCGTCAAATCACGGATAACAATCAACCCTGAC
ACATCCAAGAATCAGTTTAGTCTGCAACTCAACTCAGTCACCCCTGAGGATACCGCAGTGTA
TTATTGTGCCAGAGGTACAGCTCTTCCTTTGATTACTGGGGCCAAGGTACACTGGTAACAG
TATCAAGCGAGCCCCAAATCTAGCGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGA
AGCAGCAGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCAAGGACACCCCTCATGATCT
30 CCCGGACCCCTGAGGTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAA
GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAA
TGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACC

ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGG
AGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGA
CATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACGCCTCCC
GTGCTGGACTCCGACGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATG
5 GCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGC
AGAAGAGCCTCTCCCTGTCTCCGGGT

SEQ ID NO: 425 (CD3B219_LH-scFv)

CAGACAGTGGTGACCCAGGAACCTAGCCTCACCGTGAGCCCCGGAGGAACCGTGACCCCTGA
CCTGCAGAAGCAGCACCGGCGCCGTGACCACCAGCAACTACGCCAACTGGGTGCAGCAGAA
10 ACCTGGCCAGGCCCCCTAGAGGCCTGATTGGCGGCACCAATAAGAGGGCCCCCGGAACCCCT
GCCAGGTTTAGCGGCAGCCTGCTGGGCGGCAAGGCTGCTCTGACCCTGTCCGGAGTGCAGCC
CGAGGATGAGGCCGAGTACTACTGCGCCCTGTGGTACAGCAACCTCTGGGTGTTTCGGCGGCG
GCACAAAGCTGACCGTGCTCGGCGGCTCCGAGGGCAAGAGCAGCGGCAGCGGCAGCGAGA
GCAAGAGCACCGGCGGCAGCGAAGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGC
15 CCGGAGGAAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTTACCTTCAACACCTACGCCATG
AACTGGGTGAGACAGGCCCCCGGAAAGGGCCTGGAATGGGTGCGCAGGATCAGGTCCAAGT
ACAACAACCTACGCCACCTACTACGCTGCCAGCGTGAAGGGCAGGTTACCATCAGCAGGGA
CGACAGCAAGAACAGCCTGTACCTGCAGATGAACTCCCTGAAGACCGAGGACACCGCCGTG
TACTACTGCGTGAGGCACGGAAACTTCGGCAACAGCTACGTGAGCTGGTTCGCCTACTGGGG
20 CCAAGGCACACTGGTCACAGTGTCCAGC

SEQ ID NO: 437 (CD3B219_LH-scFv-Fc)

CAGACAGTGGTGACCCAGGAACCTAGCCTCACCGTGAGCCCCGGAGGAACCGTGACCCCTGA
CCTGCAGAAGCAGCACCGGCGCCGTGACCACCAGCAACTACGCCAACTGGGTGCAGCAGAA
ACCTGGCCAGGCCCCCTAGAGGCCTGATTGGCGGCACCAATAAGAGGGCCCCCGGAACCCCT
25 GCCAGGTTTAGCGGCAGCCTGCTGGGCGGCAAGGCTGCTCTGACCCTGTCCGGAGTGCAGCC
CGAGGATGAGGCCGAGTACTACTGCGCCCTGTGGTACAGCAACCTCTGGGTGTTTCGGCGGCG
GCACAAAGCTGACCGTGCTCGGCGGCTCCGAGGGCAAGAGCAGCGGCAGCGGCAGCGAGA
GCAAGAGCACCGGCGGCAGCGAAGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGC
CCGGAGGAAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTTACCTTCAACACCTACGCCATG
30 AACTGGGTGAGACAGGCCCCCGGAAAGGGCCTGGAATGGGTGCGCAGGATCAGGTCCAAGT
ACAACAACCTACGCCACCTACTACGCTGCCAGCGTGAAGGGCAGGTTACCATCAGCAGGGA
CGACAGCAAGAACAGCCTGTACCTGCAGATGAACTCCCTGAAGACCGAGGACACCGCCGTG
TACTACTGCGTGAGGCACGGAAACTTCGGCAACAGCTACGTGAGCTGGTTCGCCTACTGGGG

CCAAGGCACACTGGTCACAGTGTCCAGCGAGCCCAAATCTAGCGACAAAACCTCACACATGT
 CCACCGTGCCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCTTCCTCTTCCCCCAAAACC
 CAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGTGAGCC
 ACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAA
 5 GACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
 CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCC
 CAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTA
 CGTGTACCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTC
 AAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA
 10 ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCGTGAGCAAGCTC
 ACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGC
 TCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

Engineering of CD3 Fabs for HLA-G x CD3 bispecific generation

15 The CD3 specific VH and VL regions were engineered in VH-CH1-hinge-CH2-CH3 (Table 39)
 and VL-CL (Table 40) formats respectively and expressed as IgG1. The polypeptides of **SEQ ID NOs:**
158 or 493 comprising the Fc silencing mutation L234A/L235A/D265S and the CH3 mutation
 T350V/L351Y/F405A/Y407V designed to promote selective heterodimerization were used to generate
 the CD3 specific VH-CH1 - hinge -CH2-CH3 (Table 39). B2B62 was used as an isotype control.

20 **SEQ ID NO: 158 (huIgG1_G1m(17)_AAS_ZWA)**

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
 SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
 DTLNISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
 DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYPS
 25 DIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
 KSLSLSPGK

SEQ ID NO: 493

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
 SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
 30 DTLNISRTPEVTCVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
 DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCLVKGFYPS

DIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPG

DNA sequences of anti-CD3 molecules in VH-CH1-linker-CH2-CH3 format are shown in Table 41.

Table 39. Amino acid sequence of the anti CD3 antibody VH-CH1-hinge-CH2-CH3, heavy chain sequences of selected anti-CD3 antibodies

HC protein	SEQ ID NO:	HC amino acid sequence
CD3W244 HC, CD3W245 HC, CD3W246 HC, CD3W247 HC, CD3W248 HC	438	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGL EWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDT AIYYCTRGWGPFQDYWGQGLTVVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
CD3W244 HC, CD3W245 HC, CD3W246 HC, CD3W247 HC, CD3W248 HC, no C-terminal Lys	491	EVQLVESGGGLVKPGGSLRLSCAASGFTFSRYNMNWVRQAPGKGL EWVSSISTSSNYIYYADSVKGRFTFSRDNAKNSLDLQMSGLRAEDT AIYYCTRGWGPFQDYWGQGLTVVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNAKALPAIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
CD3B376 HC	439	QVQLQQSGPRLVRPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRG LEWLGRITYYRSKWLVDYAVSVKSRITVNPDTSRNQFTLQLNSVTPE DTALYYCARGYSSSFQDYWGQGLTVVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNAKALPAIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFALVSKLTVDK KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

CD3B376 HC, no C- terminal Lys	489	QVQLQQSGPRLVRPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRG LEWLGRTYYRSKWLYDYAVSVKSRITVNPDTSRNQFTLQLNSVTPE DTALYYCARGYSSSFYWGQGLTVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCL LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
CD3B450 HC	440	QVQLQQSGPGLVKPSQTLSTCAISGDSVFNNNAAWSWIRQSPSRG LEWLGRTYYRSKWLYDYAVSVKSRITINPDTSKNQFSLQLNSVTPE DTAVYYCARGYSSSFYWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE VTCVTVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YVYPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK
CD3B219 HC	441	EVQLVESGGGLVQPGGSLRLSCAASGFTFTNTYAMNWVRQAPGKGL EWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSLKT EDTAVYYCVRHGNFGNSYVSWFAYWGQGLTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS FALVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
B23B62 HC	482	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALE WLAHIYWDDDKRYNP SLKSRLTITKDTSKNQVVLTMNMDPVDTA TYYCARLYGFTYGFAYWGQGLTVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYVYPPSREEMTKNQVSLTCL LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFALVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Table 40. Light chain amino acid sequences of selected anti-CD3 antibodies

LC protein	SEQ ID NO:	LC amino acid sequence
CD3W244 LC	442	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWHYQQKPGKAPKLL IYYASESISGVPSRFSGSGSGTDFTLTISLVQPEDFATYYCQQSGSWP YTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEK HKVYACEVTHQGLSPVTKSFNRGEC
CD3W245 LC	443	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWHYQQKPGKAPKLL IKYASESISGVPSRFSGSGSGTDFTLTISLVQPEDFATYYCQQSGSWP YTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEK HKVYACEVTHQGLSPVTKSFNRGEC
CD3W246 LC	444	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWHYQQKPGKAPKLL IKYASESISGVPSRFSGSGSGTDFTLTISLVQPEDFATYYCQQSGSWP YTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEK HKVYACEVTHQGLSPVTKSFNRGEC
CD3W247 LC	445	DIQMTQSPSSLSASVGDRVTITCRARQSIGTAIHWHYQQKPGKAPKLL IYYASESISGVPSRFSGSGSGTDFTLTISLVQPEDFATYYCQQSGSWP YTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEK HKVYACEVTHQGLSPVTKSFNRGEC
CD3W248 LC	446	DILLTQSPGILSVSPGERVSFSCRARQSIGTAIHWHYQQRTNGSPRLLIK YASESISGIPSRFSGSGSGTDFTLTINSVESEDIADYYCQQSGSWPYTF GGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHK VYACEVTHQGLSPVTKSFNRGEC
CD3B376 LC	447	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPDKAPK VLLYEVSQRPSGVSSRFSGSKSGNTASLTISGLQAEDQADYHCVSYA GSGTLLFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKYAASSYLSLTPE QWKSHRSYSCQVTHEGSTVEKTVAPTECS
CD3B450 LC	448	QSALTQPASVSGSPGQSITISCTGTSSNIGTYKFVSWYQQHPGKAPK VMIYEVSQRPSGVSNRFSGSKSGNTASLTISGLQAEDADYYCVSY AGSGTLLFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLI

		SDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTP EQWKSHRYSQCQVTHEGSTVEKTVAPTECS
CD3B219 LC	449	qtvvtqepsltvspggvtltersstgavttsnyanwvqqkpgqaprglignkrapgtparfsgsllggk aaltlsgvqpdeaeaycalwysnlwvfgggtklvtlgqpkapsvtlfppsseelqankatlvelisdfy pgavtvawkadsspvkagvettptskqsnky aassylsltpewkshrsyscqvtthegstvektvapt ecs
B23B62 LC	483	divmtqspdslavslgeratincrasqsvdyngisymhwyqqkpgqppklliyaasnpsesgvpdrfsg sgsgtdfltlisslqaedvavyycqqiiedpwtfgqgkveikrtvaapsvfifppsdeqlksgtasvcell nnfybreakvqwkvdnalqsgnsqesvteqdskdstyslsstltlskadyekhkvyacevthqglsspv tksfnrgec

Table 41. cDNA SEQ ID NOs of anti-CD3 antibodies HC in VH-CH1-hinge-CH2-C3 format and LC in VL-CL format.

Antibody	HC cDNA SEQ ID NO:	LC cDNA SEQ ID NO:
CD3W244	450	454
CD3W245	450	455
CD3W246	450	456
CD3W247	450	457
CD3W248	450	458
CD3B376	451 or 499	459
CD3B450	452	460
CD3B219	453	461

5

SEQ ID NO: 450 (CD3W244, CDRW245, CD3W246, CD3W247, CD3W248 HC cDNA)

GAGGTGCAGCTGGTGGAGAGCGGTGGCGGTCTGGTGAAGCCAGGTGGCAGCCTGCGCCTGA
GCTGTGCCGCCAGCGGTTTCACCTTCAGCCGCTACAACATGAACTGGGTGCGCCAAGCCCCA
GGCAAGGGCCTGGAGTGGGTGAGCAGCATCAGCACCAGCAGCAACTACATCTACTACGCCG
10 ACAGCGTGAAGGGCCGCTTCACCTTCAGCCGCGACAACGCCAAGAACAGCCTGGACCTGCA
GATGAGCGGTCTGCGCGCCGAGGACACCGCCATCTACTACTGCACCCGCGGTTGGGGCCCAT

TCGACTACTGGGGCCAGGGCACCCCTGGTGACCGTGAGCAGCGCCTCCACCAAGGGCCCATC
GGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCC
TGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGC
GGCGTGACACCTTCCCGGTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
5 GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCA
GCAACACCAAGGTGGACAAGAAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGTCC
ACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCTTCCTCTTCCCCCAAAACCCA
AGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGTGAGCCAC
GAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
10 CAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCT
GCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
GCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACG
TGTACCCCCCATCCCGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAAC
15 TACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCGTGAGCAAGCTCAC
CGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC
TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 454 (CD3W244 LC cDNA)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
20 TCACCTGTCGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCGTGACGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
25 CAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC
CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAG
ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGT
CACAAAGAGCTTCAACAGGGGAGAGTGT

30 SEQ ID NO: 455 (CD3W245 LC cDNA)

GACATCCAGATGACCCAGAGCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC

AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
5 CAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC
CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG
ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGT
CACAAAGAGCTTCAACAGGGGAGAGTGT

10 **SEQ ID NO: 456 (CD3W246 LC cDNA)**

GACATCCAGATGACCCAGAGCCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
AAGGCCCCAAAGCTGCTGATCAAGTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCAGAGGA
15 CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC
CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG
20 ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGT
CACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 457 (CD3W247 LC cDNA)

GACATCCAGATGACCCAGAGCCCCAAGCAGCCTGAGCGCCAGCGTCGGCGACCGCGTGACCA
TCACCTGTCTGTGCCCCGCCAGAGCATCGGCACCGCCATCCACTGGTACCAGCAGAAGCCAGGC
25 AAGGCCCCAAAGCTGCTGATCTACTACGCCAGCGAGAGCATCAGCGGTGTGCCAAGCCGCT
TCAGCGGCAGCGGCAGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCAGAGGA
CTTCGCCACCTACTACTGCCAGCAGAGCGGCAGCTGGCCATACACCTTCGGCCAGGGCACCA
AGCTGGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAG
CAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGC
30 CAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA
GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG

ACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGT
CACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID NO: 458 (CD3W248 LC cDNA)

GACATCTTGCTGACTCAGTCTCCAGGCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTT
5 CTCCTGCAGGGCCAGACAGAGCATTGGCACAGCCATACACTGGTATCAGCAAAGAACAAAT
GGTTCTCCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTT
AGCGGCAGTGGATCAGGGACAGATTTTACTCTTACCATCAACAGTGTGGAGTCTGAAGATAT
TGCAGATTATTACTGTCAACAAAGTGGGAGCTGGCCGTACACGTTTCGGAGGGGGGACCAAG
CTGGAAATAAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA
10 GTTGAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCA
AAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGA
GCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGAG
TACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCA
CAAAGAGCTTCAACAGGGGAGAGTGT

15 SEQ ID NO: 451 (CD3B376 HC cDNA)

CAGGTGCAGCTCCAACAGAGTGGTCCCAGACTCGTGAGACCCTCTCAAACTCAGTTTGAC
TTGTGCCATCTCAGGCGATTTCAGTTTTCAACAACAATGCAGCTTGGAGCTGGATTAGGCAGT
CACCTAGTCGCGGTCTTGAATGGCTTGGGCGTACATACTATCGCTCTAAATGGTTGTATGATT
ACGCTGTGTCCGTGAAGAGCCGAATCACCGTAAACCCTGATACCTCCAGGAATCAGTTCACA
20 TTGCAACTGAATAGTGTGACTCCCGAGGATACTGCACTCTATTATTGTGCCCCGAGGATATAG
CAGTAGCTTCGACTATTGGGGACAAGGGACACTCGTTACCGTTAGTTCAGCCTCCACCAAGG
GCCCATCGGTCTTCCCCCTGGCACCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG
GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGGCGCCCT
GACCAGCGGCGTGACACCTTCCCGGTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCA
25 GCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAATCACA
CATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCTTCTCTTCCCCCA
AAACCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAAGCT
GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAAT
30 GCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCTGCACCAAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGC
CCTCCCAGCCCCATCGAGAAAACCATCTCCAAGGCCAAAGGGCAGCCCCGAGAACCACAG
GTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAGAACAGGTGAGCCTGACCTGCCT
GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
35 AACAACACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCGTGAGCAA
GCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG
AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 499 (CD3B376 HC cDNA)

CAGGTGCAGCTCCAACAGAGTGGTCCCAGACTCGTGAGACCCTCTCAAACACTCAGTTTGAC
TTGTGCCATCTCAGGCGATTTCAGTTTTCAACAACAATGCAGCTTGGAGCTGGATTAGGCAGT
5 CACCTAGTCGCGGTCTTGAATGGCTTGGGCGTACATACTATCGCTCTAAATGGTTGTATGATT
ACGCTGTGTCCGTGAAGAGCCGAATCACCGTAAACCCTGATACCTCCAGGAATCAGTTCACA
TTGCAACTGAATAGTGTGACTCCCCGAGGATACTGCACTCTATTATTGTGCCCCGAGGATATAG
CAGTAGCTTCGACTATTGGGGACAAGGGACACTCGTTACCGTTAGTTCAGCCTCCACCAAGG
GCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTG
10 GGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCCCT
GACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCA
GCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC
AAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACA
CATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCTTCTCTTCCCCCA
15 AAACCCAAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGT
GAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAAT
GCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCA
CCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGC
CCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
20 GTGTACGTGTACCCCCCATCCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCT
GGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG
AACAACACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCGTGAGCAA
GCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG
AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT

25 SEQ ID NO: 459 (CD3B376 LC cDNA)

CAGTCTGCTCTGACCCAGCCTGCCTCCGTGTCTGGCTCTCCCGGCCAGTCCATCACCATCAGC
TGTACCGGCACCTCCTCCAACATCGGCACCTACAAGTTTCGTGTCCTGGTATCAGCAGCACCC
CGACAAGGCCCCCAAAGTGCTGCTGTACGAGGTGTCCAAGCGGCCCTCTGGCGTGTCTCCA
GATTCTCCGGCTCCAAGTCTGGCAACACCGCCTCCCTGACCATCAGCGGACTGCAGGCTGAG
30 GACCAGGCCGACTACCACTGTGTGTCTACGCTGGCTCTGGCACCCCTGCTGTTTGGCGGAGG
CACCAAGCTGACCGTGTCTGGGTGAGCCCAAGGCTGCACCCAGTGTCACTCTGTTCGCCCT
CCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCG
GGAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCA
CCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCC
35 TGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTG
GAGAAGACAGTGGCCCCCTACAGAATGTTCA

SEQ ID NO: 452 (CD3B450 HC cDNA)

CAAGTGCAACTCCAACAAAGCGGCCAGGGCTGGTAAAGCCTTCACAGACCCTCTCACTTAC
40 TTGCGCAATATCTGGGGACTCCGTGTTTAATAACAATGCTGCATGGAGCTGGATTGCGCAGA
GCCCAAGTCGCGGGCTCGAGTGGCTTGGTCGAACCTATTACCGCTCCAAGTGGCTCTATGAC

TACGCAGTAAGCGTCAAATCACGGATAACAATCAACCCTGACACATCCAAGAATCAGTTTA
GTCTGCAACTCAACTCAGTCACCCCTGAGGATACCGCAGTGTATTATTGTGCCAGAGGGTAC
AGCTCTTCCTTTGATTACTGGGGCCAAGGTACACTGGTAACAGTATCAAGC
5 GCCTCCACCAAGGGGCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGG
CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGGA
ACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTACAGTCTCAGGACTC
TACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGT
GACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCT
10 TCCTCTTCCCCCAAACCCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTCACATGC
GTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCG
TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGT
GGTCAGCGTCTCACCCTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAG
GTCTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
15 CCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCA
ATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGTGGACTCCGACGGCTCCTTC
GCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
20 GTAAA

SEQ ID NO: 460 (CD3B450 LC cDNA)

CAGTCTGCTCTGACCCAGCCTGCCTCCGTGTCTGGCTCTCCCGGCCAGTCCATCACCATCAGC
TGTACCGGCACCTCCTCCAACATCGGCACCTACAAGTTCGTGTCTGGTATCAGCAGCACCC
25 CGGCAAGGCCCCCAAGTGATCTACGAGGTGTCCAAGCGGCCCTCCGGCGTGTCCAAC
AGATTCTCCGGCTCCAAGTCCGGCAACACCGCCTCCCTGACAATCAGCGGACTGCAGGCCGA
GGACGAGGCCGACTACTACTGTGTCTACGCCGGCTCTGGCACCCCTGCTGTTTGGCGGCG
GAACAAAGCTGACCGTGTGGGTGAGCCCAAGGCTGCACCCAGTGTCACTCTGTTCCCGCCC
TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCC
30 GGGAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACC
ACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC
CTGAGCAGTGGAAGTCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGT
GGAGAAGACAGTGGCCCCCTACAGAATGTTCA

SEQ ID NO: 453 (CD3B219 HC cDNA)

GAAGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGCCCGGAGGAAGCCTGAGACTG
AGCTGCGCCGCGCAGCGGCTTACCTTCAACACCTACGCCATGAACTGGGTGAGACAGGCCCC
CGGAAAGGGCCTGGAATGGGTGCGCAGGATCAGGTCCAAGTACAACAACACTACGCCACCTAC
TACGCTGCCAGCGTGAAGGGCAGGTTACCATCAGCAGGGACGACAGCAAGAACAGCCTGT
ACCTGCAGATGAACTCCCTGAAGACCGAGGACACCGCCGTGTACTACTGCGTGAGGCACGG
40 AAACCTTCGGCAACAGCTACGTGAGCTGGTTGCGCTACTGGGGCCAAGGCACACTGGTCACA
GTGTCCAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCAC
CTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG

TGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC
 TCAGGACTCTACTCCCTCAGCAGCGTGCGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGAC
 CTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCC
 AAATCTTGTGACAAAACCTCACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGGGGGAC
 5 CGTCAGTCTTCTCTTCCCCCAAAACCCAAAGGACACCCCTCATGATCTCCCGGACCCCTGAG
 GTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACG
 TGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
 CGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
 AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCATCGAGAAAACCATCTCCAAAGCCA
 10 AAGGGCAGCCCCGAGAACCACAGGTGTACGTGTACCCCCATCCCGGGAGGAGATGACCAA
 GAACCAGGTGAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
 GGGAGAGCAATGGGCAGCCGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA
 CGGCTCCTTCGCCCTCGTGAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAAC
 GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTC
 15 CCTGTCTCCGGGT

SEQ ID NO: 461 (CD3B219 LC cDNA)

CAGACCGTCGTGACCCAGGAACCTAGCCTGACCGTGTCTCCTGGCGGCACCGTGACCCTGAC
 CTGCAGATCTTCTACAGGCGCCGTGACCACCAGCAACTACGCCAACTGGGTGCAGCAGAAG
 CCAGGCCAGGCTCCAGAGGACTGATCGGCGGCACCAACAAGAGAGCCCCTGGCACCCCTG
 20 CCAGATTCAGCGGATCTCTGCTGGGAGGAAAGGCCGCCCTGACACTGTCTGGCGTGCAGCCT
 GAAGATGAGGCCGAGTACTACTGCGCCCTGTGGTACAGCAACCTGTGGGTGTTGGCGGAG
 GCACCAAGCTGACAGTGCTGGGTGAGCCCAAGGCTGCACCCAGTGTCACCTGTCTCCCGCCC
 TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCC
 GGGAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACC
 25 ACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGC
 CTGAGCAGTGGAAGTCCACAGAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGT
 GGAGAAGACAGTGGCCCCCTACAGAATGTTCA

Engineering of HLA-G Fab-Fc for HLA-G/CD3 bispecific generation

30 The HLA-G specific VH and VL regions were engineered in VH-CH1-hinge-CH2-CH3 and VL-
 CL formats respectively. The polypeptides of **SEQ ID NOs: 462** or **494** comprising the Fc silencing
 mutations L234A/L235A/D265S and the CH3 mutations T350V/T366L/K392L/T394W designed to
 promote selective heterodimerization was used to generate the HLA-G specific VH-CH1-hinge-CH2-
 CH3.

35 **SEQ ID NO: 462 (huIgG1_G1m(17)_AAS_ZWB)**

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
 GLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL
 FPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL

TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVK
GFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH
NHYTQKSLSLSPGK

SEQ ID NO: 494

5 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL
FPPKPKDTLMISRTPEVTCVIVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVK
GFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH
10 NHYTQKSLSLSPG

The polypeptides of SEQ ID NO: 463 or 464 were used to generate the HLA-G specific VL-CL.

SEQ ID NO: 463 (human kappa light chain)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
15 TYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 464 (human lambda light chain)

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNK
YAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

The amino acid sequences of HLA-G Fab-Fc HC and LC are shown in **Tables 42 and 43**, respectively.

20 The cDNA SEQ ID Nos of HLA-G Fab-Fc HC and LC are listed in **Table 44**.

Table 42 shows the amino acid sequences of anti-HLA-G Fab-Fc heavy chains (HCs).

Fab-Fc Heavy chain	SEQ ID NO:	Amino acid sequence
MHGB732-Fab-Fc HC	465	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWY NDYAVSVKSRITINPDTSKNQISLQNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGP SVFLFPPKPKDTLMISRTPEVTCVIVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTK NQVSLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCFSVMHEALHNHYTQKSLSLSPG

MHGB738- Fab-Fc HC	466	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNRAAWNWIQSPSRGLEWLGRTYYRSKWY NDYAVSVKSRITINPDTSKNQISLQNSVTPEDTAVYYCARVRPGIPFDYWGQGTPTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSPREEMTKNQV SLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSPG
MHGB712- Fab-Fc HC	467	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNRAAWNWIQSPSRGLEWLGRTYYRSKWY NDYAVSVKSRITINPDTSKNQISLQNSVTPEDTAVYYCARVRPGIPFDYWGQGTPTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFL FPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSPREEMTKNQV SLLCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSPG

Table 43 shows the amino acid sequences of anti-HLA-G Fab-Fc light chains (LCs).

Fab-Fc Light chain	SEQ ID NO:	Amino acid sequence
MHGB732- Fab-Fc LC	468	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQKPGQPPKLLIYWASTRE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPPTFGQGTKEIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTL TLISKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
MHGB738- Fab-Fc LC	469	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRE SGVPDRFSGSVSGTDFTLTISSLQAEDVAVYYCQYHSTPWTFGQGTKEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTL TLISKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
MHGB712- Fab-Fc LC	470	DIVMTQSPDSLAVSLGERATINCKSSQSVLFSSNNKNYLAWYQQKPGQPPKLLIYWASTRE SGVPDRFSGSVSGTDFTLTISSLQAEDVAVYYCQYHSTPWTFGQGTKEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTL TLISKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

Table 44 shows the cDNA sequences of anti-HLA-G Fab-Fc light chains (LCs) and heavy chains (HCs).

Fab-Fc	SEQ ID NO:	cDNA sequence
MHGB732- Fab-Fc HC	471	CAAGTACAAC TGCAACAAAGTGGTCTCTGGGCTCGTGAAGCCTTCCCAGACTCTCAGCCT CACATGCGCTATAAGTGGGGATTCTGTTTCCTCAAATTCAGCAGCCTGGAATTGGATAC GACAGTCTCCATCCCCTGGCCTTGAGTGGCTTGGTAGAACTTATTACCGATCCAAGTGG TACAATGATTACGCCGTTTCAGTGAAGTCCCGCATTACTATTAATCCCGACACATCTAAG AATCAAATTCATTGCAACTGAATAGCGTAACACCCGAAGATACAGCAGTTTATTATTG

		TGCAGGTGATCGACGCTACGGCATAGTGGGACTTCCTTTCGCCTATTGGGGCCAAGGG ACACTGGTCACTGTGTATCCGCCTCCACCAAGGGGCCATCGGTCTTCCCCCTGGCACC CTCTCCAAGAGCACCTCTGGGGGACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTCGTGGAACCTAGGCGCCCTGACCAGCGGCGTGCACA CCTTCCCGGTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTG CCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAA CACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGACAAAACACACATGTCCA CCGTGCCAGCACCTGAAGCAGCAGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACC CAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGTG AGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGC GTCCTACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT CCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCC CCGAGAACCACAGGTGTACGTGCTGCCCCATCCCGGGAGGAGATGACCAAGAACCA GGTCAGCCTGCTGTGCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGAGAACAACTACCTACCTGGCTCCCGTGTGGACTCCG ACGGCTCCTTCTCTCTACAGCAAGCTACCGTGGACAAGTCTAGATGGCAGCAGGG GAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGA GCCTCTCCCTGTCTCCGGT
MHGB732- Fab-Fc LC	472	GACATCGTAATGACACAGTCACCAGATTCAATGGCAGTTAGTCTGGGTGAAAGGGCAA CAATCAACTGCAAGTCTTCTCAGAGTGTACTGCATAGTTCTAACAAATAAGAACTACCTTA CCTGGTTTCAACAGAAACCAGGTACGCCCCCAAGTTGCTGATTTACTGGGCAAGCACC CGCGAATCCGGCGTTCCCGATCGATTTTCAGGTTCCGGGAGTGGGACCGACTTTACCTT GACCATCTTCTTCTGAGGCCGAAGATGTAGCCGTCTATTACTGCCATCAGTATTACTC TACTCCCCCACATTCGGTCAAGGTACAAAAGTTGAGATAAAACGGACAGTGGCCGCT CCTTCCGTGTTCACTTCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTC GTGTGCTGCTGAACAACTTCTACCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGTCCGGCAACTCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAG CACCTACAGCCTGTCTCCACTGACCTGTCCAAGGCCGACTACGAGAAGCACAAG GTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGTGACCAAGTCTTTCAA CCGGGGCGAGTGT
MHGB738- Fab-Fc HC	473	CAGGTGCAGCTTCAACAGAGCGGACCTGGTCTGGTTAAGCCTTCCCAAACC CTGAGCCTGACTTGTGCTATTTCCGGGGATAGTGTAGCTCCAATAGGGCAG CATGGAACCTGGATCAGACAGTCCCCAAGCCGTGGACTTGAGTGGCTTGAC GTACTTATTACAGGAGTAAATGGTACAATGATTATGCCGTTTCTGTGAAGAGC CGTATTACTATAAACCCAGATACTTCTAAAAATCAAATTTCCCTTCAGCTCAA CTCAGTTACACCAGAGGATACTGCAGTCTATTATTGCGCAAGAGTTTCGACCT GGCATTCCCTTCGATTATTGGGGGACAGGGGACACCCGTTACTGTGTCTCA GCCTCCACCAAGGGCCCATCGGTCTTCCCTGGCACCCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCAGGTGACGGTGTCTGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGC ACACCTTCCCGGTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGT GGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGT GAATCACAAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAATC TTGTGACAAAACCTACACATGTCCACCGTGCCAGCACCTGAAGCAGCAGG GGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCCTCATGATC TCCCGGACCCCTGAGGTACATGCGTGGTGGTGAGCGTGAGCCACGAAGA CCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGC CAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCA GCGTCTCACCGTCTGCAACCAGGACTGGCTGAATGGCAAGGAGTACAAGT

		GCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCA AAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACGTGCTGCCCCCATCC CGGGAGGAGATGACCAAGAACCAGGTCAGCCTGCTGTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGG AGAACAACCTACCTACCTGGCCTCCCGTGTGACTCCGACGGCTCCTTCT TCCTCTACAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACG TCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAA GAGCCTCTCCCTGTCTCCGGGT
MHGB738- Fab-Fc LC	474	GATATTGTTATGACACAGTCCCCAGATTCATTGGCAGTAAGCCTCGGTGAACGGGCTAC TATTAAGTGAAGTCTTCCCAGAGTGTATTGTTCTTTCAAATAACAAAACTACCTGGC ATGGTATCAGCAAAAGCCTGGTCAACCCCTAAACTTCTCATATACTGGGCATCCACTC GGGAGAGCGGTGTGCCAGACCGTTTCTCAGGGAGTGTGTCAGGTACAGATTTTACACT CACAATTTCCAGCCTCCAAGCCGAAGACGTTGCAGTATATTATTGCCAACATATCACTC TACACCTTGGACATTTGGTCAAGGTACTAAAGTCGAAATCAAACGGACAGTGGCCGCT CCTTCCGTGTTTCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTCT GTGTGCCTGCTGAACAATTCTACCCTCGGGAAGCCAAGGTGCAGTGAAGGTGGACA ATGCCCTGCAGTCCGGCAACTCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAG CACCTACAGCCTGTCTCCACTGACCTGTCCAAGGCCGACTACGAGAAGCACAAG GTGTACGCCTCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGTGACCAAGTCTTTCAA CCGGGGCGAGTGT
MHGB712- Fab-Fc HC	475	CAGGTGCAGCTTCAACAGAGCGGACCTGGTCTGGTTAAGCCTTCCCAAACCTGAGCCT GACTTGTGCTATTTCCGGGGATAGTGTAGCTCCAATAGGGCAGCATGGAAGTGGATC AGACAGTCCCCAAGCCGTGGACTTGAGTGGCTTGGACGTAATTATTACAGGAGTAAAT GGTACAATGATTATGCCGTTTCTGTGAAGAGCCGTATTACTATAAACCCAGATACTTCT AAAAATCAAATTTCCCTTCAGCTCAACTCAGTTACACCAGAGGATACTGCAGTCTATTAT TGCGCAAGAGTTGCACCTGGCATTCCCTTCGATTATTGGGGGAGGGGACACCCGTTA CTGTGCTCCTCAGCCTCCACCAAGGGGCCATCGGTCTTCCCTTGGCACCTCCTCCAAGA GCACCTCTGGGGGACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACC GGTGACGGTGTCTGGAAGTCAAGGCGCCTGACCAGCGGCTGCACACCTTCCCGCT GTCCTACAGTCTCAGGACTTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAG CTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGTCCACCGTGCCAG CACCTGAAGCAGCAGGGGGACCGTCAGTCTTCTTCTTCCCCCAAAACCAAGGACACC CTCATGATCTCCCGACCCCTGAGGTACATGCGTGGTGGTGAAGCGTGAGCCAGGAAG ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGAC AAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAAGCTCCTACCGTCT CTGCACCAAGTGGTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC TCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACCACA GGTGTACGTGCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGCTG TGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACCTACCTACCTGGCCTCCCGTGTGACTCCGACGGCTCCTTCTTCT CTCTACAGCAAGCTCACCGTGGACAAGTCTAGATGGCAGCAGGGGAACGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT CCGGGT
MHGB712- Fab-Fc LC	476	GATATTGTTATGACACAGTCCCCAGATTCATTGGCAGTAAGCCTCGGTGAACGGGCTAC TATTAAGTGAAGTCTTCCCAGAGTGTATTGTTCTTTCAAATAACAAAACTACCTGGC ATGGTATCAGCAAAAGCCTGGTCAACCCCTAAACTTCTCATATACTGGGCATCCACTC GGGAGAGCGGTGTGCCAGACCGTTTCTCAGGGAGTGTGTCAGGTACAGATTTTACACT CACAATTTCCAGCCTCCAAGCCGAAGACGTTGCAGTATATTATTGCCAACATATCACTC

		TACACCTTGGACATTTGGTCAAGGTACTAAAGTCGAAATCAAACGGACAGTGGCCGCT CCTTCCGTGTTTCATCTTCCACCTTCCGACGAGCAGCTGAAGTCCGGCACAGCTTCTGTC GTGTGCCTGCTGAACAATTCTACCCCTCGGGAAGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGTCCGGCAACTCCAAGAGTCTGTGACCGAGCAGGACTCCAAGGACAG CACCTACAGCCTGTCTCCACACTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAAG GTGTACGCCTGCGAAGTGACCCATCAGGGCCTGTCTAGCCCTGTGACCAAGTCTTTCAA CCGGGGCGAGTGT
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Engineering of HLA-G scFv-Fc for HLA-G/CD3 bispecific generation

- 5 HLA-G VH/VL regions engineered as scFvs in either VH-Linker-VL or VL-linker-VH orientations using the linker of SEQ ID NO: 8 (**Table 1**) as described in Example 2 were further engineered into a scFv-hinge-CH2-CH3 format comprising the Fc silencing mutation (L234A/L235A/D265S) and the T350V/T366L/K392L/T394W mutations designed to promote selective heterodimerization and expressed as IgG1. The polypeptides of **SEQ ID NOs: 477 or 495** were used as the constant domain hinge-CH2-CH3.

10 **SEQ ID NO: 477 (huIgG1_G1m(17)-hinge-Fc_C220S_AAS_ZWB)**

EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYVLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

15 **SEQ ID NO: 495**

EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVTVSVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYVLPSSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYLTWPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

- 20 Amino acid sequences of anti- HLA-G molecules in scFv-hinge-CH2-CH3 format (scFv-Fc) are shown in **Table 45**. cDNA sequences of anti- HLA-G molecules in scFv-hinge-CH2-CH3 format (scFv-Fc) are listed in **Table 46**.

Table 45. amino acid sequences of anti-HLA-G scFv-Fc bi-specific arms.

scFv-Fc	SEQ ID NO:	Amino acid sequence
MHGB732-LH-scFv-Fc, no C-terminal Lys	478	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPPTFGQGKTVEIKGGSEKSSGSGSEKSTGGSQVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTLLTVTSSEPKSSDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
MHGB732-LH-scFv-Fc	490	DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWFQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYSTPPTFGQGKTVEIKGGSEKSSGSGSEKSTGGSQVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQISLQLNSVTPEDTAVYYCAGDRRYGIVGLPFAYWGQGTLLTVTSSEPKSSDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
MHGB737-LH-scFv-Fc	479	DIQMTQSPSTLSASVGRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESQVPSRFSGSGSGTEFTLTISLQPDFAFYCYQYNSYSLTFGGGTQVDIKGGSEKSSGSGSEKSTGGSEVQLLESGLLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKLEWVSGISGSGFSTYYVDSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKDNLVAGTVFDYWGQGTLLTVTSSEPKSSDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYVLPSSREEMTKNQVSLCLVKGFPYSDIAVEWESNGQPENNYLTWPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG

Table 46. cDNA sequences of anti-HLA-G scFv-Fc bi-specific arms.

scFv-Fc	SEQ ID NO:	cDNA sequence
MHGB732-scFv-LH-Fc	480	GACATCGTGATGACCCAGTCTCCAGACAGCCTGGCTGTGTCTCTGGGCGAGAGAGCTACCATCAACTGCAAGTCCAGCCAGTCCGTGCTGCACTCCTCCAACAACAAGAACTACCTGACCTGGTTCCAGCAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACTGGGCCTCCACCCGCGAGTCTGGTGTGCCGATAGATTCTCCGGCTCTGGCTCTGGCACCAGCTTACCTTGACAATCAGCTCCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCACCAGTACTACAGCACCCCTCTACCTTTGGCCAGGGCACCAAGGTGGAAATCAAGGGCGGATCTGAGGGAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCCAGGTTACGCTGCAGCAGTCTGGCCCTGGACTGGTCAAGCCCTCTCAGACCTGTCTCTGACCTGTGCCATCTCCGGCGACTCCGTGCTCTAATTCTGCCGCTGGAAGTGGATCCGGCAGTCTCC TAGTAGAGGCCTGGAATGGCTGGGCAGAACCTACTACCGGTCCAAGTGGTACAACGAC

		TACGCCGTGTCCGTGAAGTCCCGGATCACCATCAATCCCGACACCTCCAAGAACCAGAT CTCCCTGCAGCTCAACAGCGTGACCCCTGAGGATACCGCCGTGTACTACTGTGCCGGCG ATCGGAGATATGGCATCGTGGGCTGCCTTTTGCTTACTGGGGACAGGGCACACTGGT CACCGTTTCTTCTGAGCCCAAATCTAGCGACAAAACCTCACACTTGTCCACCGTGCCAGC ACCTGAAGCAGCAGGGGGACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCC TCATGATCTCCCGACCCCTGAGGTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGA CCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGAGAGTGCATAATGCCAAGACA AAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCACCCTCC TGACCCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAAGCCC TCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACCACA GGTGACGTGCTCCCCCATCCCGGAGGAGATGACCAAGAACCAGGTGAGCCTGCTG TGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACCTCACCTGCCTCCCGTGTGGACTCCGACGGCTCTTCTTC CTCTACAGCAAGCTCACCGTGGACAAGTCCAGATGGCAGCAGGGGAACGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCAACAACCTACACGCAGAAGTCTCTCTCCCTGTCT CCGGGA
MHGB737- LH-scFv-Fc	481	gatattcagatgacccaatccccagttacccttagtgtagtggtggagaccgagtgaccattacctgcagagcat cccaatccataagctcctggctcgcttggtatcagcaaaagccaggcaaggcacctaagctgttattacaagc atcctcattggagtcggcgctaccctcacgtttctctggctcaggctcgggacagagtttaccattgaccatcttag ccttcagccagatgactttgtacatactattgtcaacaatataacagctactcttgaccttcgggggtgggacca aagtggatattaaaggcggctccgaggggcaagagcagcggcagcggcagcagagcaagagcaccggcgga gcaagtccaacttctgagagtggttggtgcctcgtccagccaggaggttctcgggctctcatgtgtgcaagt ggcttactttcagctcttacgccatgcactgggtgcgacaggctccgggaagggtcttgagtggtgtctgtata agtgggtcaggctttcaacctactatgtcgattccgtcaaggcggtttacaattcaagggaacatttaagaat aactgtatctccaaatgaatagctcagagccgaagataccggtttactactgcgccaagataatctgtggc tgggactgtcttcgactattgggtcagggtacattggtaaccgtaagtagtgagccaaatctagcgcaaaaact cacacatgtccacgtgccagcacctgaagcagcagggggaccgtcagttctcttcccccaaaaacccaagg acacctcatgatctccggaccctgaggtcacatgcgtggtggtgagcgtgagccacgaagacctgaggtca agttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgggaggagcagtaacaacagc acgtaccgtgtggtcagcgtctcaccgtcctgcaccaggactggctgaatggcgaaggtacaagtgcaaggtc ccaacaaagccctccagcccccatcgagaaaacctctcaaaagcgaaggcagccccgagaaccacaggtg tacgtgtgcccccatccgggaggagatgaccaagaaccaggtcagcctgtgtgctggtcaaaggcttctatc ccagcgacatcgccgtggagtgaggagcaatgggcagccggagaacaactacctcacctggcctccgtgctgg actccgacggctccttctctctacagcaagctcaccgtggacaagtctagatggcagcaggggaacgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggt
MHGB732- scFv-LH-Fc	498	GACATCGTGATGACCCAGTCTCCAGACAGCCTGGCTGTGTCTCTGGGCGAGAGAGCTA CCATCAACTGCAAGTCCAGCCAGTCCGTGTGCACTCCTCCAACAACAAGAACTACCTG ACCTGGTTCAGCAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTACTGGGCCTCCAC CCGCGAGTCTGGTGTGCCGATAGATTCTCCGGCTCTGGCTCTGGCACCGACTTTACCC TGACAATCAGCTCCCTGCAGGCCGAGGATGTGGCCGTGTACTACTGCCACCACTACTAC AGCACCCCTCCTACCTTTGGCCAGGGCACCAAGGTGGAATCAAGGGCGGATCTGAGG GAAAGTCCAGCGGCTCCGGCAGCGAAAGCAAGTCCACCGGCGGAAGCCAGGTTTCAGC TGCAGCAGTCTGGCCCTGGACTGGTCAAGCCCTCTCAGACCTGTCTCTGACCTGTGCC ATCTCCGGCGACTCCGTGTCTCTAATTCTGCCGCTGGAAGTGGATCCGGCAGTCTCC TAGTAGAGGCCTGGAATGGCTGGGCAGAACCTACTACCGGTCCAAGTGGTACAACGAC TACGCCGTGTCCGTGAAGTCCCGGATCACCATCAATCCCGACACCTCCAAGAACCAGAT CTCCTGCAGCTCAACAGCGTGACCCCTGAGGATACCGCCGTGTACTACTGTGCCGGCG ATCGGAGATATGGCATCGTGGGCTGCCTTTTGCTTACTGGGGACAGGGCACACTGGT

		CACCGTTTCTTCTGAGCCCAAATCTAGCGACAAAACCTCACACTTGTCCACCGTGCCAGC ACCTGAAGCAGCAGGGGGACCGTCAGTCTTCCTCTTCCCCCAAACCAAGGACACCC TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGA CCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCTCACCGTCC TGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAAGCCC TCCCAGCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCCCGAGAACCACA GGTGTACGTGCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGAGCCTGCTG TGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACCTACCTACCTGGCCTCCCGTGTGGACTCCGACGGCTCCTTCTC CTCTACAGCAAGCTACCGTGGACAAGTCCAGATGGCAGCAGGGGAACGTCTTCTCAT GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGTCTCTCCCTGTCT CCGGGAAAA
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HLA-G x CD3 bispecifics

The VH/VL regions of the anti-CD3 antibodies CD3B376, CD3B450, CD3B219, and CD3W246, engineered as Fab-Fcs and the VH/VL regions of the anti- HLA-G antibodies MHGB738, MHGB732 and MHGB737 engineered as scFv-Fcs in both HL and LH orientations as described above, were expressed to generate bispecific antibodies, yielding HLA-G/CD3 bispecific antibodies with a HLA-G binding arm in a format scFv-hinge-CH2-CH3 and a CD3 binding arm in a format of : heavy chain: VH-CH1-linker-CH2-CH3 and light chain: VL-CL (**Table 47**). B23B62-Fab-Fc arm was used as an isotype control for the CD3-specific arm.

Alternatively, the VH/VL regions of the anti-CD3 antibodies CD3W246, CD3B450, and CD3B219 engineered as scFv-Fcs in HL and/or LH orientations (see **Table 47**) and the VH/VL regions of the anti-HLA-G antibodies MHGB738, MHGB732 and MHGB737 engineered as Fabs as described above, were expressed to generate bispecific antibodies, yielding HLA-G/CD3 bispecific antibodies with a HLA-G binding arm in the format of a heavy chain VH-CH1-linker-CH2-CH3 and light chain VL-CL and a CD3 binding arm in a format scFv-hinge-CH2-CH3. The linker used to generate the anti-scFv is the linker of **SEQ ID NO: 8 (Table 47)**.

T350V_L351Y_F405A_Y407V CH3 mutations were engineered into one heavy chain and T350V_T366L_K392L_T394W CH3 mutations were engineered into the other heavy chain as described above. In addition, both HK2 and CD3 binding arms were engineered to contain Fc effector silencing mutations L234A_L235A_D265S as described above.

The engineered chains were expressed, and the resulting bispecific constructs purified using standard methods. The bispecifics were characterized for their binding to HLA-G and CD3, their *in vitro* cytotoxicity, immune checkpoint response, and *in vivo* efficacy as described in Examples 11-13.

Table 47. HLA-G x CD3 bispecifics.

<u>Bispecific Name</u>	<u>CD3 arm</u>	<u>CD3 arm</u> <u>SEQ ID NO:</u>	<u>HLA-G arm</u>	<u>HLA-G arm</u> <u>SEQ ID NO:</u>
HC3B239	null-scFv-Fc	413	MHGB738-Fab-Fc	HC: 466 LC: 469
HC3B238	CD3W246-HL-scFv-Fc	405	MHGB738-Fab-Fc	HC: 466 LC: 469
HC3B237	CD3W246-LH-scFv-Fc	406	MHGB738-Fab-Fc	HC: 466 LC: 469
HC3B236	CD3B450-LH-scFv-Fc	411	MHGB738-Fab-Fc	HC: 466 LC: 469
HC3B235	CD3B219-LH-scFv-Fc	412	MHGB738-Fab-Fc	HC: 466 LC: 469
HC3B234	null-scFv-Fc	413	MHGB732-Fab-Fc	HC: 465 LC: 468
HC3B233	CD3W246-HL-scFv-Fc	405	MHGB732-Fab-Fc	HC: 465 LC: 468
HC3B232	CD3W246-LH-scFv-Fc	406	MHGB732-Fab-Fc	HC: 465 LC: 468
HC3B231	CD3B450-LH-scFv-Fc	411	MHGB732-Fab-Fc	HC: 465 LC: 468
HC3B230	CD3B219-LH-scFv-Fc	412	MHGB732-Fab-Fc	HC: 465 LC: 468
HC3B128	B23B62-Fab-Fc	HC: 482 LC: 483	MHGB732-LH- scFv	478
HC3B125	CD3B376-Fab-Fc	HC: 489 LC: 447	MHGB732-LH- scFv-Fc	478
HC3B258	CD3B376-Fab-Fc	HC: 439 LC: 447	MHGB732-LH- scFv-Fc	490
HC3B124	CD3B219-Fab-Fc	HC: 441 LC: 449	MHGB732-scFv- Fc	478
HC3B123	CD3W246-Fab-Fc	HC: 438 LC: 444	MHGB732-LH- scFv-Fc	478
HC3B225	B23B62-Fab	HC: 482 LC: 483	MHGB737-scFv- Fc	479

HC3B216	CD3B376-Fab-Fc	HC: 439 LC: 447	MHGB737-scFv-Fc	479
HC3B214	CD3W246-Fab-Fc	HC: 438 LC: 444	MHGB737-scFv-Fc	479

Example 11. BsAb formatting and in vitro testing

T cell redirection against tumor cells has shown significant promise in the clinic, and we asked whether a bispecific antibody (BsAb) which targets HLA-G and the CD3 subunit of the T cell receptor complex would show cytotoxicity against HLA-G expressing tumor cells. Lead v-regions were formatted as BsAbs with a series of CD3-binding redirection arms (**Table 48**). Briefly, target cells (NCI-H2009-b2m) at 50,000 cells per well were incubated with antibody at concentrations starting from 10 nM and serially by half-log per well. Purified primary T cells were added at a ratio of 3:1 and the mixture was incubated for 72 hr at 37°C. Staining solution was prepared adding LIVE/DEAD Near-IR stain (Dead Cell Stain, L34976, Invitrogen) at 1uL per 10⁶ cells and Brilliant violet anti CD25 (Biolegend cat. # 302630) at 5uL per 10⁶ cells in BD FACS staining buffer. Cell mixtures were dissociated with Accutase prior to addition analysis by flow cytometry. Cells were gated on FSC-A vs SSC-A and CFSE (BL-1) vs SSC-A and non-viable tumor cells were identified by total tumor target cell population for CFSE (BL-1) vs Near IR Live/Dead (RL2-H) gating. Data was analyzed using ForeCyt (Sartorius) advanced metrics to calculate tumor cytotoxicity. All BsAbs displayed the ability to enhance T cell-mediated cytotoxicity when the HLA-G binding v-region was paired with a CD3 binding arm with EC50 values that were correlated to the binding affinities of both the HLA-G targeting arm and the CD3 targeting arm (**Table 48**).

20 **Table 48. BsAb designs and cytotoxicity**

<u>BsAb Name</u>	<u>CD3 arm</u>	<u>HLA-G arm</u>	<u>Cytotoxicity, EC50 (M)</u>
HC3B239	null-scFv-Fc	MHGB738-Fab-Fc	NA
HC3B238	CD3W246-HL-scFv-Fc	MHGB738-Fab-Fc	1.72542E-11
HC3B237	CD3W246-LH-scFv-Fc	MHGB738-Fab-Fc	1.32773E-10
HC3B236	CD3B450-LH-scFv-Fc	MHGB738-Fab-Fc	4.53748E-09
HC3B235	CD3B219-LH-scFv-Fc	MHGB738-Fab-Fc	8.37E-11

HC3B234	null-scFv-Fc	MHGB732-Fab-Fc	N/A
HC3B233	CD3W246-HL-scFv-Fc	MHGB732-Fab-Fc	N/A
HC3B232	CD3W246-LH-scFv-Fc	MHGB732-Fab-Fc	6.77438E-12
HC3B231	CD3B450-LH-scFv-Fc	MHGB732-Fab-Fc	1.26465E-10
HC3B230	CD3B219-LH-scFv-Fc	MHGB732-Fab-Fc	9.91577E-12
HC3B128	B23B62-Fab	MHGB732-LH-scFv	No data
HC3B125	CD3B376-Fab-Fc, no C-terminal Lys	MHGB732-LH-scFv-Fc, no C-terminal Lys	5.65197E-11
HC3B258	CD3B376-Fab-Fc	MHGB732-LH-scFv-Fc	Binding same as HC3B125
HC3B124	CD3B219-Fab-Fc	MHGB732-scFv-Fc	3.849E-12
HC3B123	CD3W246-Fab-Fc	MHGB732-LH-scFv-Fc	3.24183E-12
HC3B225	B23B62-Fab	MHGB737-scFv-Fc	No data
HC3B216	CD3B376-Fab-Fc	MHGB737-scFv-Fc	1.8984E-09
HC3B214	CD3W246-Fab-Fc	MHGB737-scFv-Fc	1.37611E-10

The BsAbs were further tested for their abilities to mediate T-cell activation and T cell-based cytotoxicity against additional cell lines: Hup-T3 and RERF-LC-Ad-1 (**Figures 15A-15D**). **Figures 15A-15D** show cytotoxicity mediated by HC3B125 against HLA-G expressing tumor cells.

Two BsAbs, HC3B125 and HC3B258, differed only in the presence (HC3B258) or absence (HC3B125) of a codon to express the C-terminal lysine, K447 in the heavy chain. Since the C-terminal lysine of the heavy chain of antibodies is normally proteolytically processed, the two Abs displayed identical mass spectra (**Table 49**). Additionally, they displayed identical biophysical properties, such as thermal stability and binding affinity for both T cells and for K562-HLA-G cells. Additionally,

HC3B258 displayed similar cytotoxicity properties as HC3B125 (Figure 16).

Table 49. Comparison of the biophysical properties of HC3B125 and HC3B258.

Molecule	Exp. Mass (Da)	Kd (pM)	Tonset	Tm1	Tm2	Tagg	T cell binding (EC50, M)	K562-HLA-G cell binding (EC50, M)
HC3B258	128,772.4	13 ± 1.2	55.0°C	63.0°C	81.1°C	63.9 °C	6.0E-08	1.1E-08
HC3B125	128,772.5	11 ± 0.5	55.3°C	63.6°C	81.3°C	65.3 °C	6.0E-08	1.2E-08

5 Example 12. Observation of immune checkpoint response

We observed that anti-HLA-G mAbs whose mechanism of cytotoxicity features effector function (e.g. ADCC) and CD3 x HLA-G BsAbs could induce killing of all cell types which expressing HLA-G. Tumors often escape immune surveillance via up-regulation of certain immune checkpoint modulators which can inhibit immune cells, such as PD-L1 or CTLA-4⁹. We thus asked whether targeting cancer cells for T cell mediated cytotoxicity via CD3 x HLA-G BsAbs could overcome expression of immune checkpoint modulators on tumor cells. We measured whether HLA-G-expressing tumor cells expressed immune checkpoint ligands (Table 50). Briefly, cells were cultured as in Example 11, and were then stained with commercial antibodies targeting the receptors indicated in Table 50. Fluorescence was measured using flow cytometry to determine relative expression levels of each receptor. Interestingly, we observed that RERF-LC-Ad1 cells expressed PD-L1 at levels significantly higher than other target cells and that CD3 x HLA-G BsAbs could still mediate T cell based cytotoxicity against RERF-LC-Ad1 cells (Figures 15A-15D). We observed that our Abs, which target the $\alpha 3$ domain of HLA-G on tumor cells for T cell based cytotoxicity could overcome immune checkpoint ligand expression on tumor cells.

Table 50. Comprehensive analysis of immune checkpoint antigen expression on HLA-G expressing tumor cells

Ligand name/Cell line name	Signal fold over negative control				
	RERF-LCAd1	JEG-3	HUP-T3	BICR6	HCC1806

PD-L1(CD274, B7-H1)	43	7	9		
PD-L2(CD273, B7-DC)	2	1	2		
Nectin-1 (CD111, PVRL1)	2	1	1		
Poliovirus receptor (CD155)	18	1	23		
HVEM (CD270, TNFRSF14)	3	1	1		
B7H3(CD276)	21	9	1		
Galectin-9	1	2	3		
B7-1 (CD80, CD28L)	1	1	1		
MICA/B	6		2		11
ULBP1	1		1		1
ULBP2/5/6	2		2		10
ULBP3	3		2		6
ULBP4	2		1		1
NKG2D-Fc	1		1		1
NKp46-Fc	1		1		1
NKp44-Fc	1		1		1
NKp30-Fc	1		1		1
CD46	1	5	9	12	
CD55	141	73	21	15	
CD59	78	15	291	120	
<i>In vitro</i> T cell-based cytotoxicity	yes	no	yes	yes	
<i>in vitro</i> ADCC background	ok	ok	ok	ok	ok
<i>in vitro</i> CDC	no	partial	not tested	not tested	not tested

Example 13. *In vivo* efficacy

While the correlation between HLA-G expression in patients and a poor prognosis has been established in most types of cancer, the direct role of HLA-G in tumor escape *in vivo* has thus far not been demonstrated. There are no murine homologues of HLA-G, but also ILT-2, therefore studying of the role of HLA-G requires xenograft models and humanized mice.

Abs and BsAbs were tested for their abilities to mediate anti-tumor efficacy *in vivo* in a series of mouse studies. The study shown in (Figure 17A-17B, Table 51) consisted of efficacy experiment with the pancreatic tumor model PAXF 1657 (Charles River Discovery Research Services Germany GmbH) implanted subcutaneously in humanized female hNSG-SGM3 mice (NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl} Tg(CMV-IL3, CSF2, KITLG) from the Jackson Laboratory. Mice engrafted with human umbilical cord blood-derived CD34⁺ hematopoietic stem cells (HSCs) from three different donors (#2595, #2597 and #5867) had been checked by the animal distributor for the sufficient degree of engraftment of HSCs (>25% human CD45⁺ cells) 10 to 11 weeks after engraftment. PAXF 1657 tumors were implanted 18 days after arrival and the degree of engraftment was re-checked 2 days prior to randomization. The

experiment comprised eight groups of 10 or 11 mice each bearing one PAXF 1657 tumor. The absolute tumor volumes (ATVs) were determined by two-dimensional measurement with a digital caliper (S_Cal EVO Bluetooth, Switzerland) on the day of randomization and then twice weekly. Tumor volumes were calculated according to the formula: Tumor volume = $(l \times w^2) \times 0.5$, where l = largest diameter and w = width (perpendicular diameter) of the tumor (in mm). At tumor volumes of 46.7 mm³ to 117.7 mm³, mice were distributed among the eight groups, aiming at comparable group mean and median tumor volumes while simultaneously ensuring an even distribution, as much as possible, among the groups of mice humanized with HSCs from the three donors. Each antibody was evaluated at two or three dose levels and was administered on days 0, 3, 7, 10, 14, 17, 21, 24 (intravenously, 2x/week). Antitumor efficacy of all groups was assessed using the vehicle control group as a reference. Tumor growth inhibition (TGI) was determined at the end of the treatment period by the comparison of changes in tumor volumes of the test groups relative to changes in the control group and is expressed as the delta TGI value (denoted TGI in text) in percent. The TGI was calculated using the absolute tumor volumes according to the following formula: $\Delta TGI_x [\%] = (1 - \text{Mean}(T_x - T_0) / \text{Mean}(C_x - C_0)) \times 100$, where T_0 and C_0 are the absolute tumor volumes in the test and the control group at the start of treatment (i.e. day of randomization) and T_x and C_x are the corresponding absolute tumor volumes at the end of the treatment period. This was day 25 in this study. The experiment was terminated on day 27. HC3B125 significantly inhibited growth of the tumor model PAXF 1657 in hNSG-SGM3 mice. Tumor growth inhibition compared to the vehicle control group was statistically significant for all three dose levels evaluated (Kruskal-Wallis test combined with Dunn's post test, Table 50). Tumors regressed completely in 6/11 animals in the 0.002 mg, 8/11 animals in the 0.006 mg and 9/11 in the 0.02 mg HC3B125 groups. At the end of the experiment, there were 6/7/6 tumor-free survivors in the 0.002 mg/0.006 mg/0.02 mg HC3B125 groups respectively.

Tumor growth was not inhibited by HC3B128 at either dose level tested. While a small reduction in group mean tumor volume was observed at the higher doses of HC3B128 compared to the control group, the differences were not statistically significant (Table 50).

Table 51. Pancreatic PDX model efficacy statistics

Group I D	Treatment ¹	Dose Level [mg/day]	Schedule [Day]	Rout e	Delta TGI [%] (Day) ₂	Regressions ₃			Td [Days]	Tq [Days]
						PR	CR	TF S		
Tumor Model PAXF 1657 – Exp. S317h										
1	Control Vehicle	0.1 ml/dose	0,3,7,10,14,17,21,2 4	i.v.	n/a	0	0	0	7.2	12.6

2	HC3B128.00 4	0.02	0,3,7,10,14,17,21,2 4	i.v.	8.4 (25)	0	0	0	8.9	13.5
3	HC3B128.00 4	0.2	0,3,7,10,14,17,21,2 4	i.v.	16.2 (25)	0	0	0	9.7	15.3
4	HC3B125	0.002	0,3,7,10,14,17,21,2 4	i.v.	98.5 (25)	2	6	6	n.r.	n.r.
5	HC3B125	0.006	0,3,7,10,14,17,21,2 4	i.v.	104.4 (25)	3	8	7	n.r.	n.r.
6	HC3B125	0.02	0,3,7,10,14,17,21,2 4	i.v.	97.9 (25)	1	9	6	n.r.	n.r.

n/a = not applicable; n.r. = not reached (i.e. group median RTVs always < 200%/400%)

Vehicle for antibodies: PBS

² Delta TGI values in each group were calculated on the first measurement day after the final 2QW treatment was administered (day 25) according to the formula given in the section **Error! Reference source not found.**; for additional TGI, T/C and tumor regression values, see Appendix 1.

³ Partial (PR) and complete regressions (CR) were determined according to the section **Error! Reference source not found.** TFS: tumor-free survivor; Td, tumor doubling time; tq, tumor quadrupling time.

Treatment with HC3B125 could also result in tumor growth inhibition in a HuP-T3 cell line derived xenograft (CDX) model (**Figure 18, Table 52**). The study consisted of efficacy experiment with the pancreatic tumor model HuP-T3 (Sigma-Aldrich) implanted subcutaneously (10e6 cells/mouse in 50% Cultrex (R&D Systems)) in T cell humanized NSG (Jackson Laboratories) mice. The experiment comprised six groups of 10 mice each bearing one HuP-T3 tumor. On day 7, at tumor volumes of 75 mm³ to 150 mm³, mice were randomized into six groups, aiming to have comparable group mean and median tumor volumes. Mice were engrafted intraperitoneally with T cells (20e6 cells/mouse, 0.2 mL/animal; ALLCELLS 6093 T Cell Donor) after randomization on the same day as randomization. HC3B125 antibody was evaluated at five dose levels. Antitumor efficacy of all groups was assessed using the NullxCD3 treated group as a reference. Treatment started 1 day post T cell engraftment and was performed on days 8, 11, 14, 17, 21, 24, 28, 31, 35, 38, 42, 48 (intraperitoneally, 2x/week). Tumor growth inhibition was determined at the end of the treatment period by the comparison of changes in group mean tumor volumes of the test groups relative to changes in that of the NullxCD3 treated control group and was expressed as the delta TGI value (denoted TGI in text) in percent. Day 42 post tumor implantation was used as the last day for TGI calculations. The experiment was terminated on day 46. HC3B125 significantly inhibited growth of the tumor model HuPT3 in hNSG mice. Tumor growth inhibition compared to the NullxCD3 treated control group was statistically significant for all five dose levels evaluated (**Table 52**).

Table 52. HuP-T3 model efficacy statistics

Group	Construct	Dose/animal	%ΔTGI (Day 42)	No of CRs (Day 42)
1	CD3xNull	-		
2	HC3B125	0.05 mg/kg	112% ***p<0.0001	
3	HC3B125	0.1 mg/kg	118% ***p<0.0001	1/9 CRs
4	HC3B125	0.3 mg/kg	130% ***p<0.0001	1/10 CRs
5	HC3B125	1 mg/kg	129% ***p<0.0001	
6	HC3B125	5 mg/kg	118% ***p<0.0001	3/10 CRs

Example 14. Efficacy of HC3B258 in Established Patient-Derived Xenograft Tumor Models in T-Cell Humanized NSG Mice

5 To explore the correlation between HLA-G expression and *in vivo* antitumor efficacy the HC3B258 antibody was evaluated in a panel of ten human patient-derived xenograft (PDX) solid tumor models (Charles River Discovery Research Services Germany GmbH) in female NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG) mice humanized intraperitoneally (*ip*) with human pan-T cells (Table 53). PDX models selected for panel inclusion represented tumor models across various solid tumor indications and demonstrated varying levels (including no expression) of HLA-G target expression as determined by Western blot (WB) evaluation.

PDX models were derived from patient surgical specimens. Tumors harvested from xenografts in serial passage were excised and cut into 3-4 mm length fragments, then implanted subcutaneously (SC) in the flank of NSG mice. Tumor bearing mice were randomized when tumors reached 100-200mm³ into 3 groups of 5 animals based on tumor volume, such that all groups had similar mean values. On the day of randomization, animals were humanized with *in vitro* activated and expanded human pan T cells (ALLCELLS, donor 6093) at a concentration of 1×10⁸ cells/mL, for an *ip* injection

of 2×10^7 cells in 0.2 mL per mouse. On the day after T-cell humanization, mice were dosed intravenously (*iv*) twice a week with HC3B258 at either 0.03 or 0.3 mg/kg, or vehicle, for a total of 6 doses (days 1, 5, 8, 12, 15 and 19 post T-cell humanization). T-cell-humanized mice were given Fc block (Clone 2.4G2; BioXCell,) at 0.2 mg/mouse *ip* and intravenous immunoglobulin (IVIG) (Gammagard, NDC#00944-2700-05) at 10 mg/mouse *ip* at least 30 minutes prior to HC3B258 dosing to correct for the low Ig environment in the NSG mouse.

Tumor volume was calculated using the formula:

$$\text{tumor volume (mm}^3\text{)} = (D \times d^2 / 2)$$

where 'D' represents the larger diameter, and 'd' the smaller diameter of the tumor as determined by caliper measurements. Antitumor efficacy, including biological and statistical significance, was compared between HC3B258-treated groups and the vehicle-treated control group at the end of the treatment when at least 4 mice remained in each group (ranged 34-42 days). Antitumor efficacy was expressed as a percent tumor growth inhibition (% Δ TGI) and defined as the difference between mean tumor burden of the treatment and control groups, calculated as

$$\% \Delta \text{TGI} = [(TV_c - TV_{c0}) - (TV_t - TV_{t0})] / (TV_c - TV_{c0}) \times 100$$

where 'TV_c' is the mean tumor burden of a given control group, 'TV_{c0}' is the mean initial tumor burden of a given control group, 'TV_t' is the mean tumor burden of the treatment group, and 'TV_{t0}' is the mean initial tumor burden of the treatment group. A complete response (CR) was defined as no palpable tumor on the final day of analysis. Statistical significance of tumor volume measurements was calculated using the Δ TGI analysis (InVivoLDA Shiny App Version 4.0, Johnson&Johnson). Differences between groups were considered significant when $p \leq 0.05$.

Western blot (WB) analysis was performed on PDX total protein lysates using anti-HLA-G antibody 4H84 (Abcam). PDX total protein lysates (each at 5 mg/mL) were received from Charles River, Germany. Each sample (10 μ L) was loaded on a NuPAGE® 4-12% Bis-Tris Mini gel. The MagicMark™ XP Western Protein Standard and the Full Range Rainbow Molecular Weight Marker were used as protein markers. The NuPAGE® MOPS SDS Running Buffer was used. The gel ran 15 minutes at 70 V, followed by 50 minutes at 200 V. After electrophoresis, the gel was transferred to a polyvinylidene fluoride (PVDF) membrane using the XCell II Blot Module (ThermoFisher Scientific), following the manufacturer's protocol. After 2 hours of blotting at 30 V, the membrane was transferred in Odyssey blocking buffer for 1 hour at RT. The membrane was incubated overnight at 4°C with the primary antibody 4H84 (1:200) and anti-vinculin diluted (1:5,000) in Odyssey blocking buffer. After 3 to 4 washing steps with Tris-buffered saline / 0.1% Tween 20 (TBST), the membrane was incubated with the appropriate secondary antibody (diluted 1:1,000 in Odyssey blocking buffer containing 0.1% Tween 20) for 1 hour at RT. After 3 to 5 washing steps with TBST, the membrane was scanned on the Odyssey IR

imaging system (LI-COR Biosciences) at 700 nm. The data was analyzed as follows. The 2 IR fluorescent detection channels of the Odyssey System enable simultaneous 2-color target analysis, for HLA-G and vinculin, used as a loading control. The fluorescence intensity (FI) of each sample in both channels was determined (Image Studio) and normalized by dividing the FI value of HLA-G by the FI of vinculin.

- 5 Robust antitumor efficacy and complete responses (CRs) were observed following HC3B258 treatment at 0.03 and 0.3 mg/kg in several PDX models with WB>1 (PRXF MRI-H1579, LXFA 2204, and RXF 488) and WB 0.1-1.0 (RXF 2706 and PAXF 2175) levels of HLA-G protein expression. Treatment with HC3B258 in the other PDX models (RXF 616, BXF 439, and MEXF 1792) expressing comparable levels of HLA-G resulted in dose-dependent antitumor efficacy, with an intermediate
- 10 response to treatment at 0.03 mg/kg, demonstrating a possible inherent resistance mechanism in these models (Table 53). Treatment with HC3B258 at either dose level did not result in biologically significant antitumor efficacy in the PDX models with negative HLA-G protein expression. Taken together, these results indicate potent specific antitumor efficacy at varying levels of HLA-G target expression, while no effect is present in the absence of HLA-G expression.
- 15 **Table 53. Effect of HC3B258 Treatment on Established Patient-Derived Xenograft Tumor Models in T-Cell Humanized NSG Mice.**

PDX Model	Tumor Type	%ΔTGI 0.03 mg/kg	%ΔTGI 0.3 mg/kg	CRs 0.03 mg/kg	CRs 0.3 mg/kg	WB
PRXF MRI-H1579	Prostate	110%	112%	5/5	5/5	2.5
LXFA 2204	Lung	118%	118%	5/5	5/5	4.8
RXF 488	Renal	166%	164%	5/5	5/5	1.33
RXF 2706	Renal	123%	123%	4/4	3/3	0.62
PAXF 2175	Pancreatic	132%	132%	5/5	5/5	0.26
RXF 616	Renal	60%	101%	0/5	1/5	0.36
BXF 439	Bladder	58%	113%	0/5	0/5	0.53
MEXF 1792	Melanoma	39%	99%	0/5	0/5	1.1
GXF 281	Gastric	-14%	-2%	0/5	0/5	0.02
PAXF 546	Pancreatic	8%	-12%	0/5	0/5	0.07

p≤0.05 versus control except where noted as not significant (ns); CR – complete response.

References

- 1 Lee, N. *et al.* The membrane-bound and soluble forms of HLA-G bind identical sets of
endogenous peptides but differ with respect to TAP association. *Immunity* **3**, 591-600,
doi:10.1016/1074-7613(95)90130-2 (1995).
- 2 Juch, H. *et al.* A novel sandwich ELISA for alpha1 domain based detection of soluble HLA-G
5 heavy chains. *J Immunol Methods* **307**, 96-106, doi:10.1016/j.jim.2005.09.016 (2005).
- 3 Morales, P. J., Pace, J. L., Platt, J. S., Langat, D. K. & Hunt, J. S. Synthesis of beta(2)-
microglobulin-free, disulphide-linked HLA-G5 homodimers in human placental villous
cytotrophoblast cells. *Immunology* **122**, 179-188, doi:10.1111/j.1365-2567.2007.02623.x (2007).
- 4 Carosella, E. D., Favier, B., Rouas-Freiss, N., Moreau, P. & Lemaoult, J. Beyond the increasing
10 complexity of the immunomodulatory HLA-G molecule. *Blood* **111**, 4862-4870,
doi:10.1182/blood-2007-12-127662 (2008).
- 5 Carosella, E. D., Rouas-Freiss, N., Tronik-Le Roux, D., Moreau, P. & LeMaoult, J. HLA-G: An
Immune Checkpoint Molecule. *Adv Immunol* **127**, 33-144, doi:10.1016/bs.ai.2015.04.001 (2015).
- 6 Clements, C. S. *et al.* Crystal structure of HLA-G: a nonclassical MHC class I molecule
15 expressed at the fetal-maternal interface. *Proc Natl Acad Sci U S A* **102**, 3360-3365,
doi:10.1073/pnas.0409676102 (2005).
- 7 Shields, R. L. *et al.* Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to
human Fcgamma RIII and antibody-dependent cellular toxicity. *J Biol Chem* **277**, 26733-26740,
doi:10.1074/jbc.M202069200 (2002).
- 20 8 Zhang, D. *et al.* Functional optimization of agonistic antibodies to OX40 receptor with novel Fc
mutations to promote antibody multimerization. *MAbs* **9**, 1129-1142,
doi:10.1080/19420862.2017.1358838 (2017).
- 9 Wilky, B. A. Immune checkpoint inhibitors: The linchpins of modern immunotherapy. *Immunol
Rev* **290**, 6-23, doi:10.1111/imr.12766 (2019).

We claim:

- 1) An isolated protein comprising an antigen binding domain that binds human leukocyte antigen G (HLA-G), wherein the antigen binding domain that binds HLA-G comprises
 - a) a heavy chain complementarity determining region (HCDR) 1, a HCDR2 and a HCDR3 of a heavy chain variable region (VH) of SEQ ID NO: 50 and a light chain complementarity determining region (LCDR) 1, a LCDR2 and a LCDR3 of a light chain variable region (VL) of SEQ ID NO: 51; or
 - b) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 52 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 53; or
 - 10 c) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 54 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 55; or
 - d) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 56 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 57; or
 - e) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 58 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 59; or
 - 15 f) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 60 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 61; or
 - g) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 62 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 63; or
 - 20 h) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 64 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 65; or
 - i) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 66 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 67; or
 - j) the HCDR1, the HCDR2 and the HCDR3 of the VH of SEQ ID NO: 68 and the LCDR1, the LCDR2 and the LCDR3 of the VL of SEQ ID NO: 69.
- 25 2) The isolated protein of claim 1, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
 - a) SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
 - b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
 - 30 c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
 - d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
 - e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
 - f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
 - g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;

- h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
- i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.
- 3) The isolated protein of claim 1 or 2, wherein the antigen binding domain that binds HLA-G is a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.
- 5 4) The isolated protein of claim 3, wherein the antigen binding domain that binds HLA-G is the Fab.
- 5) The isolated protein of claim 3, wherein the antigen binding domain that binds HLA-G is the scFv.
- 6) The isolated protein of claim 5, wherein the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).
- 7) The isolated protein of claim 6, wherein the L1 comprises
 - 10 a) about 5-50 amino acids;
 - b) about 5-40 amino acids;
 - c) about 10-30 amino acids; or
 - d) about 10-20 amino acids.
- 8) The isolated protein of claim 6, wherein the L1 comprises an amino acid sequence of SEQ ID NOs: 8,
 - 15 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 9) The isolated protein of claim 8 wherein the L1 comprises the amino acid sequence of SEQ ID NO: 8.
- 10) The isolated protein of any one of claims 1-9, wherein the antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68 and the VL of SEQ ID
 - 20 NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.
- 11) The isolated protein of claim 10, wherein the antigen binding domain that binds HLA-G comprises:
 - a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
 - b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
 - c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
 - 25 d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
 - e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
 - f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
 - g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
 - h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
 - 30 i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
 - j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69;
- 12) The isolated protein of any one of claims 1-11, wherein the antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 265, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 266, 267, 268, or 269.

- 13) The isolated protein of any one of claims 1-12, wherein the protein is conjugated to a half-life extending moiety.
- 5 14) The isolated protein of claim 13, wherein the half-life extending moiety is an immunoglobulin (Ig), a fragment of the Ig, an Ig constant region, a fragment of the Ig constant region, a Fc region, transferrin, albumin, an albumin binding domain or polyethylene glycol.
- 15) The isolated protein of any one of claims 1-14, wherein the isolated protein is a monospecific protein.
- 10 16) The isolated protein of any one of claims 1-14, wherein the isolated protein is a multispecific protein.
- 17) The isolated protein of claim 16, wherein the multispecific protein is a bispecific protein.
- 18) The isolated protein of claim 16, wherein the multispecific protein is a trispecific protein.
- 19) The isolated protein of any one of claims 1-18, further comprising an immunoglobulin (Ig) constant region or a fragment of the Ig constant region thereof.
- 15 20) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises a Fc region.
- 21) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises a CH2 domain.
- 22) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises a CH3 domain.
- 20 23) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises the CH2 domain and the CH3 domain.
- 24) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises at least portion of a hinge, the CH2 domain and the CH3 domain.
- 25 25) The isolated protein of claim 19, wherein the fragment of the Ig constant region comprises a hinge, the CH2 domain and the CH3 domain.
- 26) The isolated protein of any one of claims 19-25, wherein the antigen binding domain that binds HLA-G is conjugated to the N-terminus of the Ig constant region or the fragment of the Ig constant region.
- 27) The isolated protein of any one of claims 19-25, wherein the antigen binding domain that binds HLA-G is conjugated to the C-terminus of the Ig constant region or the fragment of the Ig constant region.
- 30 28) The isolated protein of any one of claims 19-27, wherein the antigen binding domain that binds HLA-G is conjugated to the Ig constant region or the fragment of the Ig constant region via a second linker (L2).

- 29) The isolated protein of claim 41, wherein the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 30) The isolated protein of any one of claims 16-29, wherein the multispecific protein comprises an
5 antigen binding domain that binds an antigen on a lymphocyte.
- 31) The isolated protein of claim 30, wherein the lymphocyte is a T cell.
- 32) The isolated protein of claim 30, wherein the T cell is a CD8⁺ T cell
- 33) The isolated protein of claim 30, wherein the lymphocyte is a natural killer (NK) cell.
- 34) The isolated protein of any one of claims 16-33, wherein the multispecific protein comprises an
10 antigen binding domain that binds CD3, CD3 epsilon (CD3ε), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-1, CD195, or NKG2C.
- 35) The isolated protein of claim 34, wherein the multispecific protein comprises an antigen binding domain that binds CD3ε.
- 36) The isolated protein of claim 34, wherein the antigen binding domain that binds CD3ε comprises:
15 a) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
- b) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347;
- c) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349;
- 20 d) a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 361, a HCDR2 of SEQ ID NO: 362, a HCDR3 of SEQ ID NO: 363, a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 367, a LCDR2 of SEQ ID NO: 368 and a LCDR3 of SEQ ID NO: 369;
- e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;
- 25 f) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;
- g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
- h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
- 30 i) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
- j) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344; or
- k) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345.
- 37) The isolated protein of any one of claims 19-36, wherein the Ig constant region or the fragment of the Ig constant region is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

- 38) The isolated protein of any one of claims 19-37, wherein the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in reduced binding of the protein to a Fcγ receptor (FcγR).
- 39) The isolated protein of claim 38, wherein the at least one mutation that results in reduced binding of the protein to the FcγR is selected from the group consisting of L234A/L235A/D265S, F234A/L235A, L234A/L235A, V234A/G237A/ P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A, V234A/G237A, K214T/E233P/ L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index.
- 40) The isolated protein of any one of claims 19-37, wherein the Ig constant region or the fragment of the Ig constant region comprises at least one mutation that results in enhanced binding of the protein to the FcγR.
- 41) The isolated protein of claim 40, wherein the at least one mutation that results in enhanced binding of the protein to the FcγR is selected from the group consisting of S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L, F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is according to the EU index.
- 42) The isolated protein of any one of claims 38-41, wherein the FcγR is FcγRI, FcγRIIA, FcγRIIB or FcγRIII, or any combination thereof.
- 43) The isolated protein of any one of claims 19-42, wherein the Ig constant region of the fragment of the Ig constant region comprises at least one mutation that modulates a half-life of the protein.
- 44) The isolated protein of claim 43, wherein the at least one mutation that modulates the half-life of the protein is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.
- 45) The isolated protein of any one of the claims 19-44, wherein the protein comprises at least one mutation in a CH3 domain of the Ig constant region.
- 46) The isolated protein of claim 45, wherein the at least one mutation in the CH3 domain of the Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.

- 47) An isolated multispecific protein comprising a first antigen binding domain that binds HLA-G and a second antigen binding domain that binds a lymphocyte antigen.
- 5 48) The isolated multispecific protein of claim 47, wherein the lymphocyte antigen is a T cell antigen.
- 49) The isolated multispecific protein of claim 47, wherein the T cell antigen is a CD8⁺ T cell antigen.
- 50) The isolated multispecific protein of claim 47, wherein the lymphocyte antigen is a NK cell antigen.
- 51) The isolated multispecific protein of any one of claims 47-50, wherein the lymphocyte antigen is
CD3, CD3 epsilon (CD3ε), CD8, KI2L4, NKG2E, NKG2D, NKG2F, BTNL3, CD186, BTNL8, PD-
10 1, CD195, or NKG2C.
- 52) The isolated multispecific protein of claim 51, wherein the lymphocyte antigen is CD3ε.
- 53) The isolated multispecific protein of any one of claims 47-52, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise a scFv, a (scFv)₂, a Fv, a Fab, a F(ab')₂, a Fd, a dAb or a VHH.
- 15 54) The isolated multispecific protein of claim 53, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the Fab.
- 55) The isolated multispecific protein of claim 53, wherein the first antigen binding domain that binds HLA-G and/or the second antigen binding domain that binds the lymphocyte antigen comprise the
20 scFv.
- 56) The isolated multispecific protein of claim 55, wherein the scFv comprises, from the N- to C-terminus, a VH, a first linker (L1) and a VL (VH-L1-VL) or the VL, the L1 and the VH (VL-L1-VH).
- 57) The isolated multispecific protein of claim 56, wherein the L1 comprises
- a) about 5-50 amino acids;
- 25 b) about 5-40 amino acids;
- c) about 10-30 amino acids; or
- d) about 10-20 amino acids.
- 58) The isolated multispecific protein of claim 57, wherein the L1 comprises the amino acid sequence of
SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31,
30 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 59) The isolated multispecific protein of claim 58, wherein the L1 comprises the amino acid sequence of
SEQ ID NO: 8.
- 60) The isolated multispecific protein of any one of claims 47-59, wherein the first antigen binding domain that binds HLA-G comprises the HCDR1 of SEQ ID NOs: 70, 73, 75, 78, 81, or 85, the

- HCDR2 of SEQ ID NOs: 71, 76, 79, 82, or 86, the HCDR3 of SEQ ID NOs: 72, 74, 77, 80, 83, 84, or 87, the LCDR1 of SEQ ID NOs: 88, 91, 93, 95, 97, 99, 101, or 102, the LCDR2 of SEQ ID NOs: 89 or 103, and the LCDR3 of SEQ ID NOs: 90, 92, 94, 96, 98, 100, or 104.
- 61) The isolated multispecific protein of any one of claims 47-60, wherein the first antigen binding domain that binds HLA-G comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 of
- 5 a) SEQ ID NOs: 70, 71, 72, 88, 89, and 90, respectively;
b) SEQ ID NOs: 73, 71, 74, 91, 89, and 92, respectively;
c) SEQ ID NOs: 75, 76, 77, 93, 89, and 94, respectively;
10 d) SEQ ID NOs: 78, 79, 80, 95, 89, and 96, respectively;
e) SEQ ID NOs: 81, 82, 83, 97, 89, and 98, respectively;
f) SEQ ID NOs: 78, 71, 84, 99, 89, and 100, respectively;
g) SEQ ID NOs: 78, 71, 84, 101, 89, and 100, respectively;
h) SEQ ID NOs: 85, 86, 87, 102, 103, and 104, respectively; or
15 i) SEQ ID NOs: 78, 71, 84, 95, 89, and 96, respectively.
- 62) The isolated multispecific protein of any one of claims 47-61, wherein the first antigen binding domain that binds HLA-G comprises
- a) the VH of SEQ ID NO: 50 and the VL of SEQ ID NO: 51;
b) the VH of SEQ ID NO: 52 and the VL of SEQ ID NO: 53;
20 c) the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55;
d) the VH of SEQ ID NO: 56 and the VL of SEQ ID NO: 57;
e) the VH of SEQ ID NO: 58 and the VL of SEQ ID NO: 59;
f) the VH of SEQ ID NO: 60 and the VL of SEQ ID NO: 61;
g) the VH of SEQ ID NO: 62 and the VL of SEQ ID NO: 63;
25 h) the VH of SEQ ID NO: 64 and the VL of SEQ ID NO: 65;
i) the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67; or
j) the VH of SEQ ID NO: 68 and the VL of SEQ ID NO: 69.
- 63) The isolated multispecific protein of any one of claims 47-61, wherein the first antigen binding domain that binds HLA-G comprises the VH of SEQ ID NOs: 50, 52, 54, 56, 58, 60, 62, 64, 66, or
30 68, and the VL of SEQ ID NOs: 51, 53, 55, 57, 59, 61, 63, 65, 67, or 69.
- 64) The isolated multispecific protein of any one of claims 47-63, wherein the first antigen binding domain that binds HLA-G comprises the amino acid sequence of SEQ ID NOs: 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, or 269.

- 65) The isolated multispecific protein of any one of claims 47-56, wherein the second antigen binding domain that binds the lymphocyte antigen comprises
- a) the HCDR1 of SEQ ID NO: 364, the HCDR2 of SEQ ID NO: 365, the HCDR3 of SEQ ID NO: 366, the LCDR1 of SEQ ID NO: 371, the LCDR2 of SEQ ID NO: 372 and the LCDR3 of SEQ ID NO: 373;
 - b) the VH of SEQ ID NO: 346 and the VL of SEQ ID NO: 347;
 - c) the VH of SEQ ID NO: 348 and the VL of SEQ ID NO: 349;
 - d) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 369;
 - e) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 340;
 - f) the HCDR1 of SEQ ID NO: 361, the HCDR2 of SEQ ID NO: 362, the HCDR3 of SEQ ID NO: 363, the LCDR1 of SEQ ID NO: 367, the LCDR2 of SEQ ID NO: 368 and the LCDR3 of SEQ ID NO: 370;
 - g) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 341;
 - h) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 342;
 - i) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 343;
 - j) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 344; or
 - k) the VH of SEQ ID NO: 339 and the VL of SEQ ID NO: 345.
- 66) The isolated multispecific protein of any one of claims 47-65, wherein the first antigen binding domain that binds HLA-G is conjugated to a first immunoglobulin (Ig) constant region or a fragment of the first Ig constant region and/or the second antigen binding domain that binds the lymphocyte antigen is conjugated to a second immunoglobulin (Ig) constant region or a fragment of the second Ig constant region.
- 67) The isolated multispecific protein of claim 66, further comprising a second linker (L2) between the first antigen binding domain that binds HLA-G and the first Ig constant region or the fragment of the first Ig constant region and the second antigen binding domain that binds the lymphocyte antigen and the second Ig constant region or the fragment of the second Ig constant region.
- 68) The isolated multispecific protein of claim 67, wherein the L2 comprises the amino acid sequence of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40.
- 69) The isolated multispecific protein of any one of claims 66-68, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region is an IgG1, an IgG2, and IgG3 or an IgG4 isotype.

- 70) The isolated multispecific protein of claim 66-69, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprises at least one mutation that results in reduced binding of the multispecific protein to a Fc γ R.
- 5 71) The isolated multispecific protein of claim 70, wherein the at least one mutation that results in reduced binding of the multispecific protein to the Fc γ R is selected from the group consisting of L234A/L235A/D265S, F234A/L235A, L234A/L235A, V234A/G237A/
P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A,
V234A/G237A, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M,
10 H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A,
L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and
S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the
EU index.
- 72) The isolated multispecific protein of any one of claims 66-69, wherein the first Ig constant region or
15 the fragment of the first Ig constant region and the second Ig constant region or the fragment of the
second Ig constant region comprises at least one mutation that results in enhanced binding of the
multispecific protein to a Fc γ receptor (Fc γ R).
- 73) The isolated multispecific protein of claim 72, wherein the at least one mutation that results in
enhanced binding of the multispecific protein to the Fc γ R is selected from the group consisting of
20 S239D/I332E, S298A/E333A/K334A, F243L/R292P/Y300L, F243L/R292P/Y300L/P396L,
F243L/R292P/Y300L/V305I/P396L and G236A/S239D/I332E, wherein residue numbering is
according to the EU index.
- 74) The isolated multispecific protein of any one of claims 70-73, wherein the Fc γ R is Fc γ RI, Fc γ RIIA,
Fc γ RIIB or Fc γ RIII, or any combination thereof.
- 25 75) The isolated multispecific protein of any one of claims 66-74, wherein the first Ig constant region or
the fragment of the first Ig constant region and the second Ig constant region or the fragment of the
second Ig constant region comprises at least one mutation that modulates a half-life of the
multispecific protein.
- 76) The isolated multispecific protein of claim 75, wherein the at least one mutation that modulates the
30 half-life of the multispecific protein is selected from the group consisting of H435A, P257I/N434H,
D376V/N434H, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue
numbering is according to the EU index.
- 77) The isolated multispecific protein of any one of the claims 66-76, comprising at least one mutation in
a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig

- constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region.
- 78) The isolated multispecific protein of claim 77, wherein the at least one mutation in a CH3 domain of the first Ig constant region or in a CH3 domain of the fragment of the first Ig constant region and/or at least one mutation in a CH3 domain of the second Ig constant region or in a CH3 domain of the fragment of the second Ig constant region is selected from the group consisting of T350V, L351Y, F405A, Y407V, T366Y, T366W, F405W, T394W, T394S, Y407T, Y407A, T366S/L368A/Y407V, L351Y/F405A/Y407V, T366I/K392M/T394W, F405A/Y407V, T366L/K392M/T394W, L351Y/Y407A, T366A/K409F, L351Y/Y407A, T366V/K409F, T366A/K409F, T350V/L351Y/F405A/Y407V and T350V/T366L/K392L/T394W, wherein residue numbering is according to the EU index.
- 79) The isolated multispecific protein of any one of claims 66-78, wherein the first Ig constant region or the fragment of the first Ig constant region and the second Ig constant region or the fragment of the second Ig constant region comprise the following mutations:
- a) L235A_L235A_D265S_T350V_L351Y_F405A_Y407V in the first Ig constant region and L235A_L235A_D265S_T350V_T366L_K392L_T394W in the second Ig constant region; or
- b) L235A_L235A_D265S_T350V_T366L_K392L_T394W in the first Ig constant region and L235A_L235A_D265S_T350V_L351Y_F405A_Y407V in the second Ig constant region.
- 80) An immunoconjugate comprising the isolated protein of any one of claims 1-46 conjugated to a therapeutic agent or an imaging agent.
- 81) A pharmaceutical composition comprising the isolated protein of any one of claims 1-46 and a pharmaceutically acceptable carrier.
- 82) A polynucleotide encoding the isolated protein of any one of claims 1-46.
- 83) A vector comprising the polynucleotide of claim 82.
- 84) A host cell comprising the vector of claim 83.
- 85) A method of producing the isolated protein of any one of claims 1-46, comprising culturing the host cell of claim 84 in conditions that the protein is expressed, and recovering the protein produced by the host cell.
- 86) An immunoconjugate comprising the isolated multispecific protein of any one of claims 47-79 conjugated to a therapeutic agent or an imaging agent.
- 87) A pharmaceutical composition comprising the isolated multispecific protein of any one of claims 47-79 and a pharmaceutically acceptable carrier.
- 88) A polynucleotide encoding the isolated multispecific protein of any one of claims 47-79.

- 89) A vector comprising the polynucleotide of claim 88.
- 90) A host cell comprising the vector of claim 89.
- 91) A method of producing the isolated multispecific protein of any one of claims 47-79, comprising culturing the host cell of claim 90 in conditions that the multispecific protein is expressed, and recovering the multispecific protein produced by the host cell.
- 5
- 92) A method of treating a HLA-G expressing cancer in a subject, comprising administering a therapeutically effective amount of the isolated protein of any one of claims 1-46, the isolated multispecific protein of any one of claims 47-79, the immunoconjugate of claim 80 or 86, or the pharmaceutical composition of claim 81 or 87 to the subject for a time sufficient to treat the HLA-G expressing cancer.
- 10
- 93) A method of reducing the amount of HLA-G expressing tumor cells in a subject, comprising administering the isolated protein of any one of claims 1-46, the isolated multispecific protein of any one of claims 47-79, the immunoconjugate of claim 80 or 86, or the pharmaceutical composition of claim 81 or 87 to the subject for a time sufficient to reduce the amount of HLA-G expressing tumor cells.
- 15
- 94) The method of any one of claims 92-93, wherein the HLA-G expressing cancer is a lung cancer, a pancreatic cancer, a renal cancer, a head and neck cancer, an ovarian cancer, an esophageal cancer, a colorectal cancer, a uterine cancer, or a breast cancer.
- 20
- 95) The method of any one of claims 92-94, wherein the isolated protein or the isolated multispecific protein is administered in combination with a second therapeutic agent.
- 96) The method of claim 95, wherein the second therapeutic agent is surgery, chemotherapy, or radiation, or any combination thereof.
- 97) A method of detecting the presence of cancer in a subject, comprising administering the immunoconjugate of claim 80 or 86 to a subject suspected to have cancer and visualizing the biological structures to which the immunoconjugate is bound, thereby detecting the presence of cancer.
- 25
- 98) A kit comprising the isolated protein of any one of claims 1-46, the isolated multispecific protein of any one of claims 47-79, the immunoconjugate of claim 80 or 86, or the pharmaceutical composition of claim 81 or 87.
- 30
- 99) An anti-idiotypic antibody binding to the isolated protein of any one of claims 1-46.

- 100) An isolated protein comprising an antigen binding domain that binds to an epitope on HLA-G, wherein the epitope is a discontinuous epitope comprising the amino acid sequences of HHPVFDYE (SEQ ID NO: 485) and VPS.
- 101) An isolated protein comprising an amino acid sequence of SEQ ID NO: 478.
- 5 102) The isolated protein of claim 101 comprising an amino acid sequence of SEQ ID NO: 490.
- 103) The isolated protein of claims 101 or 102 further comprising amino acid sequences of SEQ ID NOs: 489 and 447.
- 104) The isolated protein of claim 103 further comprising an amino acid sequence of SEQ ID NO: 439.
- 10 105) An isolated protein comprising amino acid sequences of SEQ ID NOs: 465 and 468.
- 106) An isolated protein comprising amino acid sequences of SEQ ID NOs: 466 and 469.
- 107) An isolated protein comprising amino acid sequences of SEQ ID NOs: 467 and 470.