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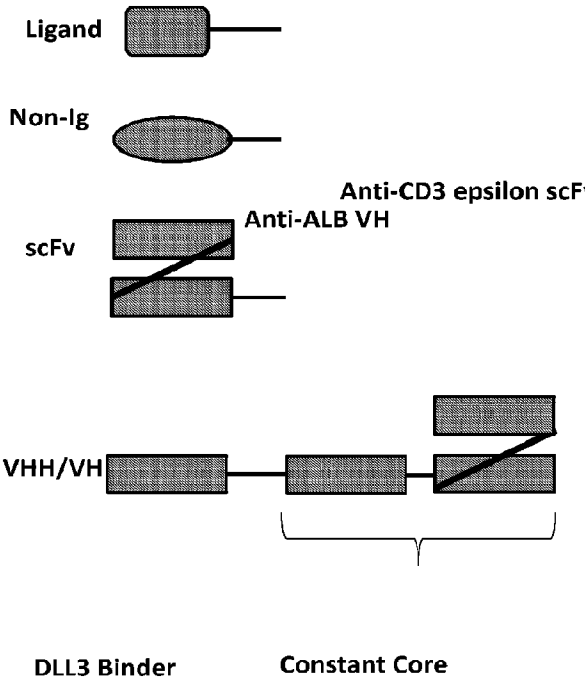
(71) **Demandeur/Applicant:**
HARPOON THERAPEUTICS, INC., US

(72) **Inventeurs/Inventors:**
WESCHE, HOLGER, US;
SUN, LIPING, US

(74) **Agent:** GOWLING WLG (CANADA) LLP

(54) **Titre : PROTEINES TRISPECIFIQUES CIBLANT DLL3 ET METHODES D'UTILISATION**
(54) **Title: DLL3 TARGETING TRISPECIFIC PROTEINS AND METHODS OF USE**



(57) **Abrégé/Abstract:**
Provided herein are DLL3 binding proteins and DLL3 targeting multispecific proteins (e.g., DLL3 targeting trispecific protein) comprising a domain binding to CD3, a half-life extension domain, and a domain binding to DLL3 (such as a DLL3 binding protein as provided herein). Also provided are pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such DLL3 binding proteins, DLL3 targeting trispecific proteins. Also disclosed are methods of using the disclosed DLL3 binding proteins, DLL3 targeting trispecific proteins in the prevention, and/or treatment diseases, conditions and disorders.

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Abstract:

Provided herein are DLL3 binding proteins and DLL3 targeting multispecific proteins (e.g., DLL3 targeting trispecific protein) comprising a domain binding to CD3, a half-life extension domain, and a domain binding to DLL3 (such as a DLL3 binding protein as provided herein). Also provided are pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such DLL3 binding proteins, DLL3 targeting trispecific proteins. Also disclosed are methods of using the disclosed DLL3 binding proteins, DLL3 targeting trispecific proteins in the prevention, and/or treatment diseases, conditions and disorders.

DLL3 TARGETING TRISPECIFIC PROTEINS AND METHODS OF USE

CROSS-REFERENCE

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 63/196,619 filed June 3, 2021; U.S. Provisional Patent Application No. 63/288,939 filed December 13, 2021; and U.S. Provisional Patent Application No. 63/345,150 filed May 24, 2022; each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] The selective destruction of an individual cell or a specific cell type is often desirable in a variety of clinical settings. For example, it is a primary goal of cancer therapy to specifically destroy tumor cells, while leaving healthy cells and tissues intact and undamaged. One such method is by inducing an immune response against the tumor, to make immune effector cells such as natural killer (NK) cells or cytotoxic T lymphocytes (CTLs) attack and destroy tumor cells.

SUMMARY OF THE INVENTION

[0003] Described herein is a method of treating cancer, the method comprising administration of an effective amount of a Delta Like Ligand 3 (DLL3) targeting trispecific protein to a subject, wherein said protein comprises (a) a first domain (A) which specifically binds to human CD3; (b) a second domain (B) which is a half-life extension domain; and (c) a third domain (C) which specifically binds to DLL3, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 100 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 14 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 5 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 2 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 1 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 15 μg to about 3600 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 15 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 45 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 135 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 405 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 1215 μg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 3600 μg. In some embodiments, the DLL3 targeting

trispecific protein is administered at a dosage of about 5 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 7 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 10 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 12 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 14 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 20 mg. In some embodiments, the DLL3 targeting trispecific protein is administered at a dosage of about 50 mg. In some embodiments, the DLL3 targeting trispecific protein is administered once a week. In some embodiments, the DLL3 targeting trispecific protein is administered twice per week. In some embodiments, the DLL3 targeting trispecific protein is administered every other week. In some embodiments, the DLL3 targeting trispecific protein is administered every three weeks. In some embodiments, the DLL3 targeting trispecific protein is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally.

[0004] Described herein is a method of treating cancer, the method comprising administration of an effective amount of a DLL3 targeting trispecific protein to a subject, wherein said protein comprises (a) a first domain (A) which specifically binds to human CD3; (b) a second domain (B) which is a half-life extension domain; and (c) a third domain (C) which specifically binds to DLL3, wherein the domains are linked in the order H_2N-(A)-(B)-(C)-COOH, or by linkers L1 and L2, and wherein the DLL3 targeting trispecific protein is administered according to a schedule comprising the following steps: (i) administration of a first dose of the DLL3 targeting trispecific protein, and (ii) administration of a second dose of the DLL3 targeting trispecific protein, wherein the second dose is higher than the first dose. In some embodiments, the first dose is about 1 mg to about 100 mg. In some embodiments, the first dose is about 1 mg to about 50 mg. In some embodiments, the first dose is about 1 mg to about 20 mg. In some embodiments, the first dose is about 1 mg to about 10 mg. In some embodiments, the first dose is about 1 mg to about 5 mg. In some embodiments, the first dose is about 1 mg to about 3 mg. In some embodiments, the first dose is about 2000 μg. In some embodiments, the first dose is about 3600 μg. In some embodiments, the first dose is administered for about 1 week to about 36 weeks. In some embodiments, the first dose is administered for about 1 week to about 27 weeks. In some embodiments, the first dose is administered for about 1 week to about 18 weeks. In some embodiments, the first dose is administered for about 1 week to about 9 weeks. In some embodiments, the first dose is administered once a day. In some embodiments, the first dose is administered twice a day. In some embodiments, the first dose is administered three times a day. In some embodiments, the first dose is administered five times a day. In some embodiments, the

first dose is administered once a week. In some embodiments, the first dose is administered twice per week. In some embodiments, the first dose is administered every other week. In some embodiments, first dose is administered every three weeks. In some embodiments, the first dose is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally. In some embodiments, the second dose is about 1 mg to about 100 mg. In some embodiments, the second dose is about 1 mg to about 50 mg. In some embodiments, the second dose is about 50 mg to about 100 mg. In some embodiments, the second dose is about 7.2 mg. In some embodiments, the second dose is about 12 mg. In some embodiments, the second dose is about 24 mg. In some embodiments, the second dose is about 36mg. In some embodiments, the second dose is administered for about 1 week to about 36 weeks. In some embodiments, the second dose is administered for about 1 week to about 27 weeks. In some embodiments, the second dose is administered for about 1 week to about 18 weeks. In some embodiments, the second dose is administered for about 1 week to about 9 weeks. In some embodiments, the second dose is administered once a day. In some embodiments, the second dose is administered twice a day. In some embodiments, the second dose is administered three times a day. In some embodiments, the second dose is administered five times a day. In some embodiments, the second dose is administered once a week. In some embodiments, the second dose is administered twice per week. In some embodiments, the second dose is administered every other week. In some embodiments, the second dose is administered every three weeks. In some embodiments, the second dose is maintained to the end of the schedule after the administration of the first dose. In some embodiments, the second dose is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally.

[0005] In some embodiments, the DLL3 targeting trispecific protein has an elimination half-time of at least 12 hours, at least 20 hours, at least 25 hours, at least 30 hours, at least 35 hours, at least 40 hours, at least 45 hours, at least 50 hours, or at least 100 hours. In some embodiments, the third domain comprises a VHH domain. In some embodiments, the VHH domain is human, humanized, affinity matured, or a combination thereof. In some embodiments, the third domain comprises one or more sequences selected from the group consisting of SEQ ID NO: 1-442. In some embodiments, the first domain comprises a variable light chain and variable heavy chain each of which is capable of specifically binding to human CD3. In some embodiments, the first domain is humanized or human. In some embodiments, the second domain binds human serum albumin. In some embodiments, the second domain comprises a scFv, a variable heavy domain (VH), a variable light domain (VL), a peptide, a ligand, or a small molecule. In some embodiments, linkers L1 and L2 are each independently selected from $(GS)_n$ (SEQ ID NO: 1809), $(GGS)_n$ (SEQ ID NO: 1810), $(GGGS)_n$ (SEQ ID NO: 1811), $(GGSG)_n$ (SEQ ID NO:

1812), $(GGSGG)_n$ (SEQ ID NO: 1813), $(GGGGS)_n$ (SEQ ID NO: 1814), or GGGGSGGGS (SEQ ID NO: 1808), wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, linkers L1 and L2 are each independently $(GGGGS)_4$ (SEQ ID NO: 1817), $(GGGGS)_3$ (SEQ ID NO: 1818) or GGGGSGGGS (SEQ ID NO: 1808). In some embodiments, the domains are linked in the order H_2N-(C)-L1-(B)-L2-(A)-COOH. In some embodiments, the DLL3 targeting trispecific protein is less than about 80 kDa. In some embodiments, the DLL3 targeting trispecific protein is about 50 to about 75 kDa. In some embodiments, the DLL3 targeting trispecific protein is less than about 60 kDa. In some embodiments, the DLL3 targeting trispecific protein comprises a sequence selected from the group consisting of SEQ ID NO: 1890-1891. In some embodiments, the DLL3 targeting trispecific protein comprises a sequence as set forth in SEQ ID NO: 1890. In some embodiments, the cancer is a tumorous disease, an autoimmune disease or an infection disease associated with DLL3. In some embodiments, the cancer is a neuroendocrine cancer, a prostate cancer, a lung cancer, a stomach cancer, a squamous cell carcinoma, a pancreatic cancer, a cholangiocarcinoma, a triple negative breast cancer or an ovarian cancer. In some embodiments, the cancer is a small cell lung cancer. In some embodiments, the cancer is a neuroendocrine prostate cancer.

INCORPORATION BY REFERENCE

[0006] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0008] **Fig. 1** illustrates the various domains of an exemplary DLL3 targeting trispecific protein of this disclosure.

[0009] **Fig. 2** illustrates results of a T cell dependent cellular cytotoxicity (TDCC) assay on DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domains of this disclosure, DH18, DH11, DH67, and DH56.

[0010] **Fig. 3** illustrates results of a TDCC assay on DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure DH2, DH43, DH10, and DH6.

[0011] Fig. 4 illustrates results of a TDCC assay on DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure DH82, DH23, DH89, and DH17.

[0012] Fig. 5 illustrates results of a TDCC assay on DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure DH83, DH12, DH61, and DH29.

[0013] Fig. 6 illustrates results of a TDCC assay on DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure DH58, and DH70, and a control trispecific protein.

[0014] Fig. 7 illustrates results of a TDCC assay on DMS-153 cells, using exemplary affinity matured DLL3 targeting trispecific proteins containing exemplary DLL3 targeting domains of this disclosure 1A011, 2E05, 1H012, 2E02, and 1C03.

[0015] Fig. 8 illustrates results of a TDCC assay on DMS-153 cells, using exemplary affinity matured DLL3 binding trispecific proteins containing exemplary DLL3 targeting domains of this disclosure 2E010, 2E01, 2H02, 2A04, and 2F11.

[0016] Fig. 9 illustrates results of a TDCC assay on DMS-153 cells, using exemplary affinity matured DLL3 binding trispecific proteins containing exemplary DLL3 targeting domains of this disclosure 2E011, 3C04, 4H04, 4H011, and 4D09.

[0017] Fig. 10 illustrates results of a TDCC assay on DMS-153 cells, using exemplary affinity matured DLL3 binding trispecific proteins containing exemplary DLL3 targeting domains of this disclosure 4B07, 4E02, 4C06, 3H011, and 3D07.

[0018] Fig. 11 illustrates results of a TDCC assay on DMS-153 cells, using exemplary affinity matured DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure 3H06, and 4B011, and parental DLL binder domains DH43, DH6, and a control trispecific protein.

[0019] Fig. 12 illustrates results of a TDCC assay on DMS-153 cells, using exemplary purified affinity matured CHO expressed DLL3 binding trispecific proteins containing exemplary DLL3 targeting domains of this disclosure 2E05-M106Y, 2E05-M106Q, 4D09-M34L, and 4H11-M34L.

[0020] Fig. 13 illustrates results of a TDCC assay on DMS-153 cells, using exemplary purified affinity matured CHO expressed DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure 1A011 (labelled as 1A11 on Fig. 13), 1H012 (labelled as 1H12 on Fig. 13), 2E02, and 2E05.

[0021] Fig. 14 illustrates results of a TDCC assay on DMS-153 cells, using exemplary purified affinity matured CHO expressed DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure 2H02, 3C04, 4D09, and 4H11.

[0022] Fig. 15 illustrates results of a TDCC assay on DMS-153 cells, using exemplary purified DLL3 targeting trispecific proteins containing parental exemplary DLL3 binding domains DH43 and DH6, and a control trispecific protein that targets GFP.

[0023] Fig. 16 illustrates results of a TDCC assay DMS-153 cells, using exemplary DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure from second round of affinity maturation.

[0024] Fig. 17 illustrates an image of a 10-20% TRIS Glycine SDS-PAGE loaded with 2.4 micrograms of non-reduced protein per lane and stained with Coomassie. The lane numbers are indicated by the numbers at the top of the gel image and the migration of molecular weight standards are indicated by the number on the right side of the gel image (in kilodaltons). Gel loading: Lane 1 empty, lane 2 molecular weight standard, lane 3 empty, lane 4 anti-DLL3 trispecific containing DLL3 binding domain 51G2, lane 5 anti-DLL3 trispecific containing DLL3 binding domain 51G10, lane 6 anti-DLL3 trispecific containing DLL3 binding domain 51H5, lane 7 anti-DLL3 trispecific containing DLL3 binding domain 51X5, lane 8 anti-DLL3 trispecific containing DLL3 binding domain 52B1, lane 9 anti-DLL3 trispecific containing DLL3 binding domain 52C4, lane 10 anti-DLL3 trispecific containing DLL3 binding domain 52D4, lane 11 anti-DLL3 trispecific containing DLL3 binding domain 51A2, lane 12 containing DLL3 binding domain anti-DLL3 trispecific 51A5, lane 13 anti-DLL3 trispecific containing DLL3 binding domain 51F3, lane 14 empty, and lane 15 empty.

[0025] Fig. 18 illustrates results of a TDCC assay on DMS-53 cells, using exemplary purified affinity matured CHO expressed DLL3 targeting trispecific proteins containing exemplary DLL3 binding domains of this disclosure 51G2, 51G10, 51H5, 51X5, 52B1, 52C4, 52D4, 51A2, and parental DLL3 binder domain DH6, and a control trispecific protein.

[0026] Fig. 19 illustrates results of a TDCC assay on DMS-153 cells, using exemplary purified affinity matured CHO expressed DLL3 targeting trispecific proteins of this disclosure, containing exemplary DLL3 binding domains of this disclosure 51G2, 51G10, 51H5, 51X5, 52B1, 52C4, 52D4, 51A2, and parental DLL3 binder domain DH6, and a control binding trispecific protein that targets GFP.

[0027] Fig. 20 provides a schematic illustration of a DLL3 targeting trispecific protein containing an exemplary DLL3 binding protein of this disclosure (DLL3 binder), a CD3 binding domain (anti-CD3 epsilon scFv), and an albumin binding (anti-ALB) domain, in an anti-DLL3: anti-ALB: anti-CD3 orientation (TAC orientation).

[0028] Fig. 21 provides a schematic illustration of a DLL3 targeting trispecific protein containing an exemplary DLL3 binding protein of this disclosure (DLL3 binder), a CD3 binding domain (anti-CD3 epsilon scFv), and an albumin binding (anti-ALB) domain, in an anti-CD3: anti-ALB: anti-DLL3 orientation (CAT orientation).

[0029] Fig. 22 illustrates results of a T cell dependent cellular cytotoxicity (TDCC) assay on NCI-H2171cells, using exemplary DLL3 trispecific proteins containing a DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration or in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA) or bovine serum albumin (BSA).

[0030] Fig. 23 illustrates results of a T cell dependent cellular cytotoxicity (TDCC) assay on DMS-79 cells, using exemplary DLL3 targeting trispecific proteins containing a DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration or in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence or absence of human serum albumin (HSA).

[0031] Fig. 24 illustrates results of a T cell dependent cellular cytotoxicity (TDCC) assay on SHP77 cells, using exemplary DLL3 trispecific proteins containing a DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration or in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA) or bovine serum albumin (BSA).

[0032] Fig. 25 illustrates results of a T cell dependent cellular cytotoxicity (TDCC) assay on WM2664 cells, using exemplary DLL3 trispecific proteins containing a DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration or in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA) or bovine serum albumin (BSA).

[0033] Fig. 26 depicts binding of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration to human T cells from four different donors as compared to that of a controls with secondary antibody alone or cells without any antibody or trispecific molecule.

[0034] Fig. 27 depicts binding of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration to human T cells from four different donors as compared to that of a controls with secondary antibody alone or cells without any antibody or trispecific molecule.

[0035] Fig. 28 depicts binding of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration to human DLL3 expressing cell lines NCI-H82 (top left), SHP77 (top right),

DMS53 (bottom left) or NCI-H2171 (bottom right) compared to a trispecific molecules with an GFP binding domain.

[0036] Fig. 29 depicts binding of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration to human DLL3 expressing cell lines NCI-H82 (top left), SHP77 (top right), DMS53 (bottom left) or NCI-H2171 (bottom right) compared to a trispecific molecules with an GFP binding domain.

[0037] Fig. 30 illustrates the results of a TDCC assay on NCI-H82 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0038] Fig. 31 illustrates the results of a TDCC assay on SHP77 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0039] Fig. 32 illustrates the results of a TDCC assay on DMS53 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0040] Fig. 33 illustrates the results of a TDCC assay on NCI-H2171 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0041] Fig. 34 illustrates the results of a TDCC assay on NCI-H82 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0042] Fig. 35 illustrates the results of a TDCC assay on SHP77 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0043] Fig. 36 illustrates the results of a TDCC assay on DMS53 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0044] Fig. 37 illustrates the results of a TDCC assay on NCI-H2171 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0045] Fig. 38 illustrates the results of a flow cytometry measurements of CD69 expression on T cells co-cultured with NCI-H82 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0046] Fig. 39 illustrates the results of a flow cytometry measurements of CD25 expression on T cells co-cultured with NCI-H82 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0047] Fig. 40 illustrates the results of a flow cytometry measurements of CD69 expression on T cells co-cultured with DMS53 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA , using T cells from four different donors.

[0048] Fig. 41 illustrates the results of a flow cytometry measurements of CD25 expression on T cells co-cultured with DMS53 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0049] Fig. 42 illustrates the results of a flow cytometry measurements of CD69 expression on T cells co-cultured with NCI-H82 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0050] Fig. 43 illustrates the results of a flow cytometry measurements of CD25 expression on T cells co-cultured with NCI-H82 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0051] Fig. 44 illustrates the results of a flow cytometry measurements of CD69 expression on T cells co-cultured with DMS53 cells with a titration of an exemplary DLL3 targeting trispecific

proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

[0052] Fig. 45 illustrates the results of a flow cytometry measurements of CD25 expression on T cells co-cultured with DMS53 cells with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0053] Fig. 46 illustrates the results of IFNγ measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0054] Fig. 47 illustrates the results of IFNγ measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0055] Fig. 48 illustrates the results of IL-2 measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0056] Fig. 49 illustrates the results of IL-2 measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0057] Fig. 50 illustrates the results of TNFα measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0058] Fig. 51 illustrates the results of TNFα measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-

DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA).

[0059] Fig. 52 illustrates the results of IFNγ measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0060] Fig. 53 illustrates the results of IFNγ measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0061] Fig. 54 illustrates the results of IL-2 measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0062] Fig. 55 illustrates the results of IL-2 measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0063] Fig. 56 illustrates the results of TNFα measurements in conditioned media from co-cultures of T cells and NCI-H82 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0064] Fig. 57 illustrates the results of TNFα measurements in conditioned media from co-cultures of T cells and SHP77 cells incubated with a titration of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA).

[0065] Fig. 58 depicts that an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration or an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, was able to inhibit

tumor growth in mice injected with a mixture of human T cells and NCI-H82 small cell lung cancer cells at dosages 20 μg/kg,100 μg/kg or 500 μg/kg.

[0066] Fig. 59 depicts that an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, was able to eliminate NCI-H82 xenograft tumors growth in mice injected with human T cells at dosages of 10 μg/kg and 100 μg/kg.

[0067] Fig. 60 depicts that an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, was able to inhibit tumor growth in mice injected with a mixture of human T cells and SHP77 small cell lung cancer cells at dosages 10 μg/kg and 100 μg/kg.

[0068] Fig. 61 depicts pharmacokinetic profile of exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration (ID numbers 1 and 2) or an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration (ID numbers 3 and 4). Serum levels of the DLL3 targeting trispecific proteins at various time points following injection into cynomolgus monkeys, at 0.3 mg/kg, are shown in the plot.

[0069] Fig. 62 depicts pharmacokinetic profile of an exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, at various time points following injection into cynomolgus monkeys, at 1 mg/kg or 10 mg/kg, are shown in the plot.

[0070] Fig. 63 depicts transient cytokine increase after first dosing of an exemplary DLL3 binding TriTAC molecule of this disclosure at 1 mg/kg and 10 mg/kg or a vehicle control. The top panel shows transient increase of IFNγ, the second panel shows transient increase of IL-6, and third panel show transient increase in IL-10.

[0071] Fig. 64 illustrates the results of a TDCC assay on DMS53 cells, using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, using freshly thawed protein, or using protein present in a serum sample from a cynomolgus monkey collected 168 h after dosing with 10 mg/kg DLL3 targeting trispecific protein, measured in the presence of 8.4% cynomolgus monkey serum.

[0072] Fig. 65 illustrates DLL3 trispecific antigen-binding protein Phase 1/2 trial design.

[0073] Fig. 66 demonstrates the patient time on treatment, weekly dose per patient, number of prior therapies, and the patient identification number.

[0074] Fig. 67 shows maximum percent target lesion response from baseline in each cohort.

[0075] Fig. 68 illustrates the target lesion reduction over time for a patient.

[0076] **Fig. 69** illustrates the pharmacokinetic data of the DLL3 trispecific antigen-binding protein for the different dosing cohorts.

[0077] **Fig. 70** demonstrates the result of a flow analysis. **Fig. 70A** demonstrates the T cell margination level after treatment. **Fig. 70B** demonstrates the T cell activation marker induction after treatment.

[0078] **Fig. 71A** demonstrates the target lesion diameter change over time for patient 111. **Fig. 71B** CT scans illustrate the reduction in sum of target lesion diameters for patient 111.

[0079] **Fig. 72A** demonstrates the target lesion diameter change over time for patient 112. **Fig. 72B** CT scans illustrate the reduction in sum of target lesion diameters for patient 112.

[0080] **Fig. 73** demonstrates the target lesion diameter change over time for patient 113.

[0081] **Fig. 74** shows the concentration-time profile (**Fig. 74A**) and Cmax by dose (**Fig. 74B**).

[0082] **Fig. 75** shows T-cell margination (CD8+, **Fig. 75C**) and peripheral IL-6 (**Fig. 75A**) and MCP-1 (**Fig. 75B**) concentrations after first and repeat or target dose.

DETAILED DESCRIPTION OF THE INVENTION

[0083] Described herein, in some embodiments, are proteins that specifically bind delta-like ligand 3 (DLL3) and multispecific (*e.g.*, trispecific) containing the same, pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such proteins thereof. Also provided are methods of using at least one of: the disclosed DLL3 binding proteins, or DLL3 targeting trispecific proteins containing the same, in the prevention, and/or treatment of diseases, conditions and disorders. The DLL3 targeting trispecific proteins are capable of specifically binding to DLL3 as well as CD3 and have a half-life extension domain, such as a domain that is capable of specifically binding to human albumin (ALB). **Fig. 1** depicts one non-limiting example of a trispecific DLL3-binding protein. In some embodiments, the DLL3 targeting trispecific protein comprises an antibody, such as a trispecific antibody.

Certain definitions

[0084] An "antibody" typically refers to a Y-shaped tetrameric protein comprising two heavy (H) and two light (L) polypeptide chains held together by covalent disulfide bonds and non-covalent interactions. Human light chains comprise a variable domain (VL) and a constant domain (CL) wherein the constant domain may be readily classified as kappa or lambda based on amino acid sequence and gene loci. Each heavy chain comprises one variable domain (VH) and a constant region, which in the case of IgG, IgA, and IgD, comprises three domains termed CH1, CH2, and CH3 (IgM and IgE have a fourth domain, CH4). In IgG, IgA, and IgD classes the CH1 and CH2 domains are separated by a flexible hinge region, which is a proline and

cysteine rich segment of variable length (generally from about 10 to about 60 amino acids in IgG). The variable domains in both the light and heavy chains are joined to the constant domains by a "J" region of about 12 or more amino acids and the heavy chain also has a "D" region of about 10 additional amino acids. Each class of antibody further comprises inter-chain and intra-chain disulfide bonds formed by paired cysteine residues. There are two types of native disulfide bridges or bonds in immunoglobulin molecules: interchain and intrachain disulfide bonds. The location and number of interchain disulfide bonds vary according to the immunoglobulin class and species. Interchain disulfide bonds are located on the surface of the immunoglobulin, are accessible to solvent and are usually relatively easily reduced. In the human IgG1 isotype there are four interchain disulfide bonds, one from each heavy chain to the light chain and two between the heavy chains. The interchain disulfide bonds are not required for chain association. As is well known the cysteine rich IgG1 hinge region of the heavy chain has generally been held to consist of three parts: an upper hinge, a core hinge, and a lower hinge. Those skilled in the art will appreciate that that the IgG1 hinge region contain the cysteines in the heavy chain that comprise the interchain disulfide bonds (two heavy/heavy, two heavy/light), which provide structural flexibility that facilitates Fab movements. The interchain disulfide bond between the light and heavy chain of IgG1 are formed between C214 of the kappa or lambda light chain and C220 in the upper hinge region of the heavy chain. The interchain disulfide bonds between the heavy chains are at positions C226 and C229 (all numbered per the EU index according to Kabat, et al., infra.)

[0085] As used herein the term "antibody" includes polyclonal antibodies, multiclonal antibodies, monoclonal antibodies, chimeric antibodies, humanized and primatized antibodies, CDR grafted antibodies, human antibodies, recombinantly produced antibodies, intrabodies, multispecific antibodies, bispecific antibodies, monovalent antibodies, multivalent antibodies, anti-idiotypic antibodies, synthetic antibodies, including muteins and variants thereof, immunospecific antibody fragments such as Fd, Fab, F(ab')2, F(ab') fragments, single-chain fragments (*e.g.*, ScFv and ScFvFc), disulfide-linked Fvs (sdFv), a Fd fragment consisting of the VH and CH1 domains, linear antibodies, single domain antibodies such as sdAb (VH, VL, or VHH domains); and derivatives thereof including Fc fusions and other modifications, and any other immunoreactive molecule so long as it comprises a domain having a binding site for preferential association or binding with a DLL3 protein. Moreover, unless dictated otherwise by contextual constraints the term further comprises all classes of antibodies (*i.e.* IgA, IgD, IgE, IgG, and IgM) and all subclasses (*i.e.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2). Heavy-chain constant domains that correspond to the different classes of antibodies are typically denoted by the corresponding lower case Greek letter alpha , delta, epsilon , gamma , and mu , respectively.

Light chains of the antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (kappa) and lambda (lambda), based on the amino acid sequences of their constant domains.

[0086] In some embodiments, the DLL3 binding domain of the DLL3 targeting trispecific proteins of this disclosure comprise a heavy chain only antibody, such as a VH or a VHH domain. In some cases, the DLL3 binding proteins comprise a heavy chain only antibody that is an engineered human VH domain. In some examples, the engineered human VH domain is produced by panning of phage display libraries. In some embodiments, the DLL3 binding domain of the DLL3 targeting trispecific proteins of this disclosure comprise a VHH. The term "VHH," as used herein, refers to single chain antibody binding domain devoid of light chain. In some cases, a VHH is derived from an antibody of the type that can be found in Camelidae or cartilaginous fish which are naturally devoid of light chains or to a synthetic and non-immunized VHH which can be constructed accordingly. Each heavy chain comprises a variable region encoded by V-, D- and J exons. A VHH, in some cases, is a natural VHH, such as a Camelid-derived VHH, or a recombinant protein comprising a heavy chain variable domain. In some embodiments, the VHH is derived from a species selected from the group consisting of camels, llamas, vicugnas, guanacos, and cartilaginous fish (such as, but not limited to, sharks). In another embodiment, the VHH is derived from an alpaca (such as, but not limited to, a Huacaya Alpaca or a Suri alpaca).

[0087] As used herein, "Variable region" or "variable domain" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain (VL) and the heavy-chain (VH) variable domains. The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, National Institute of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity. ScFv fragments (for single chain fragment variable), which in some cases are obtained

by genetic engineering, associates in a single polypeptide chain, the VH and the VL region of an antibody, separated by a peptide linker.

[0088] In some embodiments of this disclosure, the DLL3 binding domain, such as the DLL3 binding domain of the DLL3 targeting trispecific proteins comprise a single domain antibody, such as heavy chain only antibodies, such as VH or VHH domains, and comprise three CDRs. Such heavy chain only antibodies, in some embodiments, bind DLL3 as a monomer with no dependency on dimerisation with a VL (light chain variable) region for optimal binding affinity. In some embodiments of this disclosure, the CD3 binding domain of the DLL3 targeting trispecific proteins comprises an scFv. In some embodiments of this disclosure, the albumin binding domain of the DLL3 targeting trispecific proteins comprise a heavy chain only antibody, such as a single domain antibody comprising a VH domain or a VHH domain.

[0089] The assignment of amino acids to each domain, framework region and CDR is, in some embodiments, in accordance with one of the numbering schemes provided by Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest (5th Ed.), US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242; Chothia et al., 1987, PMID: 3681981; Chothia et al., 1989, PMID: 2687698; MacCallum et al., 1996, PMID: 8876650; or Dubel, Ed. (2007) Handbook of Therapeutic Antibodies, 3rd Ed., Wily-VCH Verlag GmbH and Co or AbM (Oxford Molecular/MSI Pharmacopia) unless otherwise noted. It is not intended that CDRs of the present disclosure necessarily correspond to the Kabat numbering convention. In some embodiments of this disclosure, the DLL3 binding proteins comprise single domain antibodies, such as heavy chain only antibodies, such as VH or VHH domains, and comprise three CDRs. Such heavy chain only antibodies, in some embodiments, bind DLL3 as a monomer with no dependency on dimerisation with a VL (light chain variable) region for optimal binding affinity.

[0090] "Variable domain residue numbering as in Kabat" or "amino acid position numbering as in Kabat," and variations thereof, refers to the numbering system used for heavy chain variable domains or light chain variable domains of the compilation of antibodies in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991). Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or CDR of the variable domain. For example, a heavy chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.*, residues 82a, 82b, and 82c, etc according to Kabat) after heavy chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a "standard" Kabat numbered sequence.

[0091] The term "Framework" or "FR" residues (or regions) refer to variable domain residues other than the CDR or hypervariable region residues as herein defined. A "human consensus framework" is a framework which represents the most commonly occurring amino acid residue in a selection of human immunoglobulin VL or VH framework sequences.

[0092] As used herein, the term "Percent (%) amino acid sequence identity" with respect to a sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer softwares such as EMBOSS MATCHER, EMBOSS WATER, EMBOSS STRETCHER, EMBOSS NEEDLE, EMBOSS LALIGN, BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0093] As used herein, "elimination half-time" is used in its ordinary sense, as is described in Goodman and Gillman's The Pharmaceutical Basis of Therapeutics 21-25 (Alfred Goodman Gilman, Louis S. Goodman, and Alfred Gilman, eds., 6th ed. 1980). Briefly, the term is meant to encompass a quantitative measure of the time course of drug elimination. The elimination of most drugs is exponential (i.e., follows first-order kinetics), since drug concentrations usually do not approach those required for saturation of the elimination process. The rate of an exponential process may be expressed by its rate constant, k, which expresses the fractional change per unit of time, or by its half-time, t1/2 the time required for 50% completion of the process. The units of these two constants are time−1 and time, respectively. A first-order rate constant and the half-time of the reaction are simply related ($k \times t1/2 = 0.693$) and may be interchanged accordingly. Since first-order elimination kinetics dictates that a constant fraction of drug is lost per unit time, a plot of the log of drug concentration versus time is linear at all times following the initial distribution phase (i.e. after drug absorption and distribution are complete). The half-time for drug elimination can be accurately determined from such a graph.

[0094] As used herein, the term "binding affinity" refers to the affinity of the proteins described in the disclosure to their binding targets, and is expressed numerically using "Kd" values. If two or more proteins are indicated to have comparable binding affinities towards their binding targets, then the Kd values for binding of the respective proteins towards their binding targets, are within ±2-fold of each other. If two or more proteins are indicated to have comparable

binding affinities towards single binding target, then the Kd values for binding of the respective proteins towards said single binding target, are within ±2-fold of each other. If a protein is indicated to bind two or more targets with comparable binding affinities, then the Kd values for binding of said protein to the two or more targets are within ±2-fold of each other. In general, a higher Kd value corresponds to a weaker binding. In some embodiments, the "Kd" is measured by a radiolabeled antigen binding assay (RIA) or surface plasmon resonance assays using a BIAcore™-2000 or a BIAcore™-3000 (BIAcore, Inc., Piscataway, N.J.). In certain embodiments, an "on-rate" or "rate of association" or "association rate" or "kon" and an "off-rate" or "rate of dissociation" or "dissociation rate" or "koff" are also determined with the surface plasmon resonance technique using a BIAcore™-2000 or a BIAcore™-3000 (BIAcore, Inc., Piscataway, N.J.). In additional embodiments, the "Kd", "kon", and "koff" are measured using the OCTET® Systems (Pall Life Sciences). In an exemplary method for measuring binding affinity using the OCTET® Systems, the ligand, *e.g.*, biotinylated human or cynomolgus DLL3, is immobilized on the OCTET® streptavidin capillary sensor tip surface which streptavidin tips are then activated according to manufacturer's instructions using about 20-50 μg/ml human or cynomolgus DLL3 protein. A solution of PBS/Casein is also introduced as a blocking agent. For association kinetic measurements, DLL3 binding protein variants are introduced at a concentration ranging from about 10 ng/mL to about 100 μg/mL, about 50 ng/mL to about 5 μg/mL, or about 2 ng/mL to about 20 μg/mL. In some embodiments, the DLL3 binding single domain proteins are used at a concentration ranging from about 2 ng/mL to about 20 μg/mL. Complete dissociation is observed in case of the negative control, assay buffer without the binding proteins. The kinetic parameters of the binding reactions are then determined using an appropriate tool, *e.g.*, ForteBio software.

[0095] One embodiment provides a DLL3 binding protein (also referred to herein as an DLL3 binding domain, such as the DLL3 binding domain of a DLL3 trispecific antibody of this disclosure) that comprises a single domain antibody, comprising a CDR1 sequence comprising a sequence selected from the group consisting of SEQ ID Nos. 443-884 and 1887, a CDR2 sequence comprising a sequence selected from the group consisting of SEQ ID Nos. 885-1326 and 1888, and a CDR3 sequence comprising a sequence selected from the group consisting of SEQ ID Nos. 1327-1768 and 1889. It is contemplated that in some embodiments the DLL3 binding protein of this disclosure is fairly small and no more than 25 kD, no more than 20 kDa, no more than 15 kDa, or no more than 10 kDa in some embodiments. In certain instances, the EGFR binding is 5 kDa or less if it is a peptide or a small molecule entity.

[0096] In one aspect, the DLL3 targeting trispecific protein (also referred to herein as a DLL3 binding trispecific protein, a DLL3 trispecific protein, or a DLL3 TriTAC™) comprises (a) a

first domain (A) which specifically binds to human CD3; (b) a second domain (B) which is a half-life extension domain; and (c) a third domain (C) which specifically binds to DLL3.The three domains in DLL3 targeting trispecific proteins are arranged in any order. Thus, it is contemplated that the domain order of the DLL3 targeting trispecific proteins are:

H_2N-(A)-(B)-(C)-COOH,
H_2N-(A)-(C)-(B)-COOH,
H_2N-(B)-(A)-(C)-COOH,
H_2N-(B)-(C)-(A)-COOH,
H_2N-(C)-(B)-(A)-COOH, or
H_2N-(C)-(A)-(B)-COOH.

[0097] In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(A)-(B)-(C)-COOH. In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(A)-(C)-(B)-COOH. In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(B)-(A)-(C)-COOH. In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(B)-(C)-(A)-COOH. In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(C)-(B)-(A)-COOH. In some embodiments, the DLL3 targeting trispecific proteins have a domain order of H_2N-(C)-(A)-(B)-COOH.

[0098] In some embodiments, the DLL3 targeting trispecific proteins have the HSA (also referred to herein as ALB) binding domain as the middle domain, such that the domain order is H_2N-(A)-(B)-(C)-COOH or H_2N-(C)-(B)-(A)-COOH. It is contemplated that in such embodiments where the HSA binding domain as the middle domain, the CD3 and DLL3 binding domains are afforded additional flexibility to bind to their respective targets.

[0099] In some embodiments, the trispecific binding protein comprises a third domain that specifically binds DLL3, which third domain is in some cases a DLL3 binding single domain antibody, which binds to DLL3 with equivalent or better affinity as that of a reference DLL3 binding parental molecule. The third domain in some embodiments comprises an affinity matured DLL3 binding molecule (*e.g.*, an affinity matured DLL3 binding single domain antibody), and is derived from the DLL3 binding parental molecule, comprising one or more amino acid mutations (*e.g.*, a stabilizing mutation, a destabilizing mutation) with respect to the DLL3 binding parental molecule. In some embodiments, the affinity matured DLL3 binding molecule has superior stability with respect to selected destabilizing agents, as that of a reference DLL3 binding parental molecule. In some embodiments, the affinity matured DLL3 binding molecule is identified in a process comprising panning of one or more pre-candidate DLL3 binding molecules derived from one or more DLL3 binding parental molecule, expressed

in a phage display library, against a DLL3 protein, such as a human DLL3 protein. The pre-candidate DLL3 binding molecule comprises, in some embodiments, amino acid substitutions in the variable regions, CDRs, or framework residues, relative to a parental molecule.

[00100] As used herein, "Phage display" refers to a technique by which variant polypeptides are displayed as fusion proteins to at least a portion of a coat protein on the surface of phage, filamentous phage, particles. A utility of phage display lies in the fact that large libraries of randomized protein variants can be rapidly and efficiently selected for those sequences that bind to a target molecule with high affinity. Display of peptide and protein libraries on phage has been used for screening millions of polypeptides for ones with specific binding properties. Polyvalent phage display methods have been used for displaying small random peptides and small proteins through fusions to either gene III or gene VIII of filamentous phage. Wells and Lowman, Curr. Opin. Struct. Biol, 3:355-362 (1992), and references cited therein. In monovalent phage display, a protein or peptide library is fused to a gene III or a portion thereof, and expressed at low levels in the presence of wild type gene III protein so that phage particles display one copy or none of the fusion proteins. Avidity effects are reduced relative to polyvalent phage so that selection is on the basis of intrinsic ligand affinity, and phagemid vectors are used, which simplify DNA manipulations. Lowman and Wells, Methods: A companion to Methods in Enzymology, 3:205-0216 (1991).

[00101] In some embodiments, the panning comprises using varying binding times and concentrations to identify DLL3 binding molecules with increased or decreased on-rates, from pre-candidate DLL3 binding molecules. In some embodiments, the panning comprises using varying wash times to identify DLL3 binding molecules with increased or decreased off-rates, from pre-candidate DLL3 molecules. In some embodiments, the panning comprises using both varying binding times and varying wash times. In some embodiments, one or more stabilizing mutations are combined to increase the stability of the affinity matured DLL3 binding molecule, for example, by shuffling to create a second-stage combinatorial library from such mutants and conducting a second round of panning followed by a binding selection.

[00102] In some embodiments, the affinity matured DLL3 binding molecule comprises an equivalent or better affinity to a DLL3 protein (such as human DLL3 protein) as that of a DLL3 binding parental molecule, but that has reduced cross reactivity, or in some embodiments, increased cross reactivity, with selected substances, such as ligands, proteins, antigens, or the like, other than the DLL3 epitope for which the DLL3 binding parental molecule is specific, or is designed to be specific for. In regard to the latter, an affinity matured DLL3 binding molecule, in some embodiments, is more successfully tested in animal models if the affinity matured DLL3 binding molecule is reacted with both human DLL3 and the corresponding target of the

animal model, mouse DLL3 or cynomolgus DLL3. In some embodiments, the parental DLL3 binding molecule binds to human DLL3 with an affinity of about 10 nM or less, and to cynomolgus DLL3 with an affinity of about 15 nM or less. In some embodiments, the affinity matured DLL3 binding molecule, identified after one round of panning, binds to human DLL3 with an affinity of about 5 nM or less, and to cynomolgus DLL3 with an affinity of about 7.5 nM or less. In some embodiments, the affinity matured DLL3 binding molecule, identified after two rounds of panning, binds to human DLL3 with an affinity of about 2.5 nM or less, and to cynomolgus DLL3 with an affinity of about 3.5 nM or less.

[00103] In some embodiments, domain A, domain B, and domain C of the trispecific binding protein of this disclosure, are independently antigen-specific binding domain polypeptides that specifically bind to targets, such as targets on diseased cells, or targets on other cells that support the diseased state, such as targets on stromal cells that support tumor growth or targets on immune cells that support disease-mediated immunosuppression. In some examples, the antigen-specific binding domains include antibodies, heavy chain only antibodies, including single chain antibodies, Fabs, Fv, T-cell receptor binding domains, ligand binding domains, receptor binding domains, domain antibodies, single domain antibodies, minibodies, nanobodies, peptibodies, or various other antibody mimics (such as affimers, affitins, alphabodies, atrimers, CTLA4-based molecules, adnectins, anticalins, Kunitz domain-based proteins, avimers, knottins, fynomers, darpins, affibodies, affilins, monobodies and armadillo repeat protein-based proteins).

[00104] In some embodiments, the DLL3 targeting trispecific proteins described herein comprise a DLL binding polypeptide having a sequence selected from the group consisting of SEQ ID Nos. 1-442 and 1886, subsequences thereof, and variants thereof. In some embodiments, the trispecific antigen binding protein comprises a DLL3 binding polypeptide (*i.e.*, the third domain (C)) having at least 70%-95% or more homology to a sequence selected from SEQ ID Nos. 1-442 and 1886, subsequences thereof, and variants thereof. In some embodiments, the trispecific antigen binding protein comprises a DLL3 binding polypeptide (*i.e.*, the third domain (C)) having at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more homology to a sequence selected from the group consisting of SEQ ID Nos. 1-442 and 1886, subsequences thereof, and variants thereof. In some embodiments, the trispecific antigen binding protein comprises a DLL3 binding polypeptide (*i.e.*, the third domain (C)) having at least 70%-95% or more identity to a sequence selected from SEQ ID Nos. 1-442 and 1886, subsequences thereof, and variants thereof. In some embodiments, the trispecific antigen binding protein comprises a DLL3 binding polypeptide (*i.e.*, the third domain (C)) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more

identity to a sequence selected from the group consisting of SEQ ID Nos. 1-442 and 1886, subsequences thereof, and variants thereof.

[00105] The DLL3 targeting trispecific proteins described herein are designed to allow specific targeting of cells expressing DLL3 by recruiting cytotoxic T cells. In some embodiments, this improves efficacy compared to ADCC (antibody dependent cell-mediated cytotoxicity), which is using full length antibodies directed to a sole antigen and is not capable of directly recruiting cytotoxic T cells. In contrast, by engaging CD3 molecules expressed specifically on these cells, the DLL3 targeting trispecific proteins can crosslink cytotoxic T cells with cells expressing DLL3 in a highly specific fashion, thereby directing the cytotoxic potential of the T cell towards the target cell. The DLL3 targeting trispecific proteins described herein engage cytotoxic T cells via binding to the surface-expressed CD3 proteins, which form part of the TCR. Simultaneous binding of several DLL3 trispecific antigen-binding protein to CD3 and to DLL3 expressed on the surface of particular cells causes T cell activation and mediates the subsequent lysis of the particular DLL3 expressing cell. Thus, DLL3 targeting trispecific proteins are contemplated to display strong, specific and efficient target cell killing. In some embodiments, the DLL3 targeting trispecific proteins described herein stimulate target cell killing by cytotoxic T cells to eliminate pathogenic cells (*e.g.*, tumor cells expressing DLL3). In some of such embodiments, cells are eliminated selectively, thereby reducing the potential for toxic side effects.

[00106] The DLL3 targeting trispecific proteins described herein confer further therapeutic advantages over traditional monoclonal antibodies and other smaller bispecific molecules. Generally, the effectiveness of recombinant protein pharmaceuticals depends heavily on the intrinsic pharmacokinetics of the protein itself. One such benefit here is that the DLL3 targeting trispecific proteins described herein have extended pharmacokinetic elimination half-time due to having a half-life extension domain such as a domain that specifically binds to a serum albumin protein (*e.g.*, a human serum albumin protein, HSA). In this respect, the DLL3 targeting trispecific proteins described herein have an extended serum elimination half-time of about two, three, about five, about seven, about 10, about 12, or about 14 days in some embodiments. This contrasts to other binding proteins such as BiTE or DART molecules which have relatively much shorter elimination half-times. For example, the BiTE CD19×CD3 bispecific scFv-scFv fusion molecule requires continuous intravenous infusion (i.v.) drug delivery due to its short elimination half-time. The longer intrinsic half-times of the DLL3 targeting trispecific proteins solve this issue thereby allowing for increased therapeutic potential such as low-dose pharmaceutical formulations, decreased periodic administration and/or novel pharmaceutical compositions.

[00107] The DLL3 targeting trispecific proteins described herein also have an optimal size for enhanced tissue penetration and tissue distribution. Larger sizes limit or prevent penetration or distribution of the protein in the target tissues. The DLL3 targeting trispecific proteins described herein avoid this by having a small size that allows enhanced tissue penetration and distribution. Accordingly, the DLL3 targeting trispecific proteins described herein, in some embodiments have a size of about 50 kDa to about 80 kDa, about 50 kDa to about 75 kDa, about 50 kDa to about 70 kDa, or about 50 kDa to about 65 kDa. In some embodiments, the size of the DLL3 targeting trispecific protein is smaller than about 60 kDa. Thus, the size of the DLL3 targeting trispecific proteins is advantageous over IgG antibodies which are about 150 kDa and the BiTE and DART diabody molecules which are about 55 kDa but are not half-life extended and therefore cleared quickly through the kidney.

[00108] In further embodiments, the DLL3 targeting trispecific proteins described herein have an optimal size for enhanced tissue penetration and distribution. In these embodiments, the DLL3 targeting trispecific proteins are constructed to be as small as possible, while retaining specificity toward its targets. Accordingly, in these embodiments, the DLL3 targeting trispecific proteins described herein have a size of about 20 kDa to about 40 kDa or about 25 kDa to about 35 kDa to about 40 kDa, to about 45 kDa, to about 50 kDa, to about 55 kDa, to about 60 kDa, to about 65 kDa. In some embodiments, the DLL3 targeting trispecific proteins described herein have a size of about 50kDa, 49, kDa, 48 kDa, 47 kDa, 46 kDa, 45 kDa, 44 kDa, 43 kDa, 42 kDa, 41 kDa, 40 kDa, about 39 kDa, about 38 kDa, about 37 kDa, about 36 kDa, about 35 kDa, about 34 kDa, about 33 kDa, about 32 kDa, about 31 kDa, about 30 kDa, about 29 kDa, about 28 kDa, about 27 kDa, about 26 kDa, about 25 kDa, about 24 kDa, about 23 kDa, about 22 kDa, about 21 kDa, or about 20 kDa. An exemplary approach to the small size is through the use of single domain antibody (sdAb) fragments for each of the domains. For example, a particular DLL3 trispecific antigen-binding protein has an anti-CD3 sdAb, anti-ALB sdAb and an sdAb for DLL3. This reduces the size of the exemplary DLL3 trispecific antigen-binding protein to under 60 kDa. Thus in some embodiments, the domains of the DLL3 targeting trispecific proteins are all single domain antibody (sdAb) fragments. It is contemplated that in some embodiments the DLL3 binding protein is fairly small and no more than 25 kDa, no more than 20 kDa, no more than 15 kDa, or no more than 10 kDa in some embodiments. In certain instances, the DLL3 binding protein is 5 kDa or less if it is a peptide or small molecule entity.

[00109] In other embodiments, the DLL3 targeting trispecific proteins described herein comprise small molecule entity (SME) binders for ALB , DLL3, CD3, or all. SME binders are small molecules averaging about 500 to 2000 Da in size and are attached to the DLL3 targeting trispecific proteins by known methods, such as sortase ligation or conjugation. In these

instances, one of the domains of DLL3 trispecific antigen-binding protein is a sortase recognition sequence, LPETG (SEQ ID No: 1896). To attach a SME binder to DLL3 trispecific antigen-binding protein with a sortase recognition sequence, the protein is incubated with a sortase and a SME binder whereby the sortase attaches the SME binder to the recognition sequence. In yet other embodiments, the domain which binds to DLL3 of DLL3 targeting trispecific proteins described herein comprise a knottin peptide for binding DLL3. Knottins are disulfide-stabilized peptides with a cysteine knot scaffold and have average sizes about 3.5 kDa. Knottins have been contemplated for binding to certain tumor molecules such as DLL3. In further embodiments, the third domain which binds to DLL3 of DLL3 targeting trispecific proteins described herein comprise a natural DLL3 ligand.

[00110] Another feature of the DLL3 targeting trispecific proteins described herein is that they are of a single-polypeptide design with flexible linkage of their domains. This allows for facile production and manufacturing of the DLL3 targeting trispecific proteins as they can be encoded by single cDNA molecule to be easily incorporated into a vector. Further, because the DLL3 targeting trispecific proteins described herein are a monomeric single polypeptide chain, there are no chain pairing issues or a requirement for dimerization. It is contemplated that the DLL3 targeting trispecific proteins described herein have a reduced tendency to aggregate unlike other reported molecules such as bispecific proteins with Fc-gamma immunoglobulin domains.

[00111] In the DLL3 targeting trispecific proteins described herein, the domains are, in some embodiments,linked by internal linkers L1 and L2, where L1 links the first and second domain of the DLL3 targeting trispecific proteins and L2 links the second and third domains of the DLL3 targeting trispecific proteins. Linkers L1 and L2 have an optimized length and/or amino acid composition. In some embodiments, linkers L1 and L2 are the same length and amino acid composition. In other embodiments, L1 and L2 are different. In certain embodiments, internal linkers L1 and/or L2 are "short," *i.e.*, consist of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues. Thus, in certain instances, the internal linkers consist of about 12 or less amino acid residues. In the case of 0 amino acid residues, the internal linker is a peptide bond. In certain embodiments, internal linkers L1 and/or L2 are "long," *i.e.*, consist of 15, 20 or 25 amino acid residues. In some embodiments, these internal linkers consist of about 3 to about 15, for example 8, 9 or 10 contiguous amino acid residues. Regarding the amino acid composition of the internal linkers L1 and L2, peptides are selected with properties that confer flexibility to the DLL3 targeting trispecific proteins, do not interfere with the binding domains as well as resist cleavage from proteases. For example, glycine and serine residues generally provide protease resistance. Examples of internal linkers suitable for linking the domains in the DLL3 targeting trispecific proteins include but are not limited to $(GS)_n$ (SEQ ID No. 1809), $(GGS)_n$ (SEQ ID

No. 1810), $(GGGS)_n$ (SEQ ID No. 1811), $(GGSG)_n$ (SEQ ID No. 1812), $(GGSGG)_n$ (SEQ ID No. 1813), $(GGGGS)_n$ (SEQ ID No. 1814), $(GGGGG)_n$ (SEQ ID No. 1815), or $(GGG)_n$ (SEQ ID No. 1816), wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In one embodiment, internal linker L1 and/or L2 is $(GGGGS)_4$ (SEQ ID No. 1817) or $(GGGGS)_3$ (SEQ ID No. 1818). In another embodiment, internal linker L1 and/or L2 is GGGGSGGGS (SEQ ID No. 1808).

[00112] In some cases, the domains within the DLL3 targeting trispecific protein are conjugated using an enzymatic site-specific conjugation method which involves the use of a mammalian or bacterial transglutaminase enzyme. Microbial transglutaminases (mTGs) are versatile tools in modern research and biotechnology. The availability of large quantities of relatively pure enzymes, ease of use, and lack of regulation by calcium and guanosine-5'-triphosphate (GTP) has propelled mTG to be the main cross-linking enzyme used in both the food industry and biotechnology. Currently, mTGs are used in many applications to attach proteins and peptides to small molecules, polymers, surfaces, DNA, as well as to other proteins. *See*, , Pavel Strp, Veracity of microbial transglutaminase, Bioconjugate Chem. 25, 5, 855-862).

[00113] In some examples are provided DLL3 targeting trispecific protein wherein one of the domains comprises an acceptor glutamine in a constant region, which can then be conjugated to another domain *via* a lysine-based linker (*e.g.*, any primary amine chain which is a substrate for TGase, comprising an alkylamine, oxoamine) wherein the conjugation occurs exclusively on one or more acceptor glutamine residues present in the targeting moiety outside of the antigen combining site (*e.g.*, outside a variable region, in a constant region). Conjugation thus does not occur on a glutamine, an at least partly surface exposed glutamine, within the variable region. The trispecific protein, in some examples, is formed by reacting one of the domains with a lysine-based linker in the presence of a TGase.

[00114] In some embodiments, where one or more domains within the DLL3 targeting trispecific binding protein are directly joined, a hybrid vector is made where the DNA encoding the directly joined domains are themselves directly ligated to each other. In some embodiments, where linkers are used, a hybrid vector is made where the DNA encoding a first domain out of the three domains is ligated to the DNA encoding one end of a first linker moiety and the DNA encoding a second domain out of the three domains is ligated to the other end of the first linker moiety; further, the DNA encoding the second domain out of the three domains is linked to one end of a second linker moiety and the DNA encoding a third domain out of the three domains is linked to the other end of the second linker moiety, wherein the first domain, the second domain, and the third domain are distinct and wherein the first domain, the second domain, and the third domain are independently selected from domain A, domain B, and domain C. Such ligation is performed, for example, either in series, or as a three way ligation.

CD3 binding domain

[00115] The specificity of the response of T cells is mediated by the recognition of antigen (displayed in context of a major histocompatibility complex, MHC) by the TCR. As part of the TCR, CD3 is a protein complex that includes a CD3γ (gamma) chain, a CD3δ (delta) chain, and two CD3ε (epsilon) chains which are present on the cell surface. CD3 associates with the α (alpha) and β (beta) chains of the TCR as well as CD3 ζ (zeta) altogether to comprise the complete TCR. Clustering of CD3 on T cells, such as by immobilized anti-CD3 antibodies leads to T cell activation similar to the engagement of the T cell receptor but independent of its clone-typical specificity.

[00116] In one aspect, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to CD3. In one aspect, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to human CD3. In some embodiments, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to CD3γ. In some embodiments, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to CD3δ. In some embodiments, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to CD3ε.

[00117] In further embodiments, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds to the TCR. In certain instances, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds the α chain of the TCR. In certain instances, the DLL3 targeting trispecific proteins described herein comprise a domain which specifically binds the β chain of the TCR.

[00118] In certain embodiments, the CD3 binding domain of the DLL3 targeting trispecific proteins described herein exhibit not only potent CD3 binding affinities with human CD3, but show also excellent cross reactivity with the respective cynomolgus monkey CD3 proteins.

[00119] In some embodiments, the CD3 binding domain of the DLL3 trispecific antigen-binding protein can be any domain that binds to CD3 including but not limited to domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody. In some instances, it is beneficial for the CD3 binding domain to be derived from the same species in which the DLL3 trispecific antigen-binding protein will ultimately be used in. For example, for use in humans, it may be beneficial for the CD3 binding domain of the DLL3 trispecific antigen-binding protein to comprise human or humanized residues from the antigen binding domain of an antibody or antibody fragment.

[00120] Thus, in one aspect, the antigen-binding domain comprises a humanized or human antibody or an antibody fragment, or a murine antibody or antibody fragment. In one

embodiment, the humanized or human anti-CD3 binding domain comprises one or more (*e.g.*, all three) light chain complementary determining region 1 (LC CDR1), light chain complementary determining region 2 (LC CDR2), and light chain complementary determining region 3 (LC CDR3) of a humanized or human anti- CD3 binding domain described herein, and/or one or more (*e.g.*, all three) heavy chain complementary determining region 1 (HC CDR1), heavy chain complementary determining region 2 (HC CDR2), and heavy chain complementary determining region 3 (HC CDR3) of a humanized or human anti-CD3 binding domain described herein, , a humanized or human anti-CD3 binding domain comprising one or more, , all three, LC CDRs and one or more, all three, HC CDRs.

[00121] In some embodiments, the humanized or human anti-CD3 binding domain comprises a humanized or human light chain variable region specific to CD3 where the light chain variable region specific to CD3 comprises human or non-human light chain CDRs in a human light chain framework region. In certain instances, the light chain framework region is a λ (lamda) light chain framework. In other instances, the light chain framework region is a κ (kappa) light chain framework.

[00122] In some embodiments, the humanized or human anti-CD3 binding domain comprises a humanized or human heavy chain variable region specific to CD3 where the heavy chain variable region specific to CD3 comprises human or non-human heavy chain CDRs in a human heavy chain framework region.

[00123] In certain instances, the complementary determining regions of the heavy chain and/or the light chain are derived from known anti-CD3 antibodies, such as, for example, muromonab-CD3 (OKT3), otelixizumab (TRX4), teplizumab (MGA031), visilizumab (Nuvion), SP34, TR-66 or X35-3, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, F111-409, CLB-T3.4.2, TR-66, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2, F101.01, UCHT-1 and WT-31.

[00124] In one embodiment, the anti-CD3 binding domain is a single chain variable fragment (scFv) comprising a light chain and a heavy chain of an amino acid sequence provided herein. As used herein, "single chain variable fragment" or "scFv" refers to an antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single polypeptide chain, and wherein the scFv retains the specificity of the intact antibody from which it is derived. In an embodiment, the anti-CD3 binding domain comprises: a light chain variable region comprising an amino acid sequence having at least one, two or three modifications (*e.g.*, substitutions) but not more than 30, 20 or 10 modifications (*e.g.*,

substitutions) of an amino acid sequence of a light chain variable region provided herein, or a sequence with 95-99% identity with an amino acid sequence provided herein; and/or a heavy chain variable region comprising an amino acid sequence having at least one, two or three modifications (*e.g.*, substitutions) but not more than 30, 20 or 10 modifications (*e.g.*, substitutions) of an amino acid sequence of a heavy chain variable region provided herein, or a sequence with 95-99% identity to an amino acid sequence provided herein. In some examples, the anti-CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1793-1807, or a sequence that is at least about 60%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identity to a sequence selected from SEQ ID Nos. 1793-1807. In some examples, the anti-CD3 binding domain comprises three heavy chain CDRs (HC CDR1, HC CDR2, and HC CDR3), and three light chain CDRs. The heavy chain CDR1(HC CDR1) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1820-1831, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1820-1831, or at least about 80% to about 99% . The heavy chain CDR2 (HC CDR2) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1832-1841, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1832-1841. The heavy chain CDR3 (HC CDR3) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1842-1853, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1842-1853. The light chain CDR1 (LC CDR1) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1852-1864, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1852-1864. The light chain CDR2 (LC CDR2) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1865-1877, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1865-1877. The light chain CDR3 (LC CDR3) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1878-1884, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1878-1884. In one embodiment, the humanized or human anti-CD3 binding domain is a scFv, and a light chain variable region comprising an amino acid sequence described herein, is attached to a heavy chain variable region comprising an amino acid sequence described herein, via a scFv linker. The light chain variable region and heavy chain variable region of a scFv can be in any of the following orientations: light chain variable region- scFv linker-heavy chain variable region or heavy chain variable region- scFv linker-light chain variable region.

[00125] In some instances, scFvs which bind to CD3 are prepared according to known methods. For example, scFv molecules can be produced by linking VH and VL regions together using flexible polypeptide linkers. The scFv molecules comprise a scFv linker (*e.g.*,a Ser-Gly linker) with an optimized length and/or amino acid composition. Accordingly, in some embodiments, the length of the scFv linker is such that the VH or VL domain can associate intermolecularly with the other variable domain to form the CD3 binding site. In certain embodiments, such scFv linkers are "short", *i.e.* consist of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues. Thus, in certain instances, the scFv linkers consist of about 12 or less amino acid residues. In the case of 0 amino acid residues, the scFv linker is a peptide bond. In some embodiments, these scFv linkers consist of about 3 to about 15, for example 8, 9 or 10 contiguous amino acid residues. Regarding the amino acid composition of the scFv linkers, peptides are selected that confer flexibility, do not interfere with the variable domains as well as allow inter-chain folding to bring the two variable domains together to form a functional CD3 binding site. For example, scFv linkers comprising glycine and serine residues generally provide protease resistance. In some embodiments, linkers in a scFv comprise glycine and serine residues. The amino acid sequence of the scFv linkers can be optimized, for example, by phage-display methods to improve the CD3 binding and production yield of the scFv. Examples of peptide scFv linkers suitable for linking a variable light domain and a variable heavy domain in a scFv include but are not limited to $(GS)_n$ (SEQ ID No. 1809), $(GGS)_n$ (SEQ ID No. 1810), $(GGGS)_n$ (SEQ ID No. 1811), $(GGSG)_n$ (SEQ ID No. 1812), $(GGSGG)_n$ (SEQ ID No. 1813), $(GGGGS)_n$ (SEQ ID No. 1814), $(GGGGG)_n$ (SEQ ID No. 1815), or $(GGG)_n$ (SEQ ID No. 1816), wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In one embodiment, the scFv linker can be $(GGGGS)_4$ (SEQ ID No. 1817) or $(GGGGS)_3$ (SEQ ID No. 1818). In some embodiments, a linker comprises a sequence composed of any combinations of the linkers as set forth in SEQ ID Nos. 1809 to 1818, and the length of such a linker is in some examples up to 15 amino acids, or longer than 15 amino acids. Variation in the linker length may retain or enhance activity, giving rise to superior efficacy in activity studies.

[00126] In some embodiments, CD3 binding domain of DLL3 targeting trispecific antigen-binding protein has an affinity to CD3 on CD3 expressing cells with a K_D of 1000 nM or less, 500 nM or less, 200 nM or less, 100 nM or less, 80 nM or less, 50 nM or less, 20 nM or less, 10 nM or less, 5 nM or less, 1 nM or less, or 0.5 nM or less. In some embodiments, the CD3 binding domain of DLL3 targeting trispecific antigen-binding protein has an affinity to CD3ε, γ, or δ with a K_D of 1000 nM or less, 500 nM or less, 200 nM or less, 100 nM or less, 80 nM or less, 50 nM or less, 20 nM or less, 10 nM or less, 5 nM or less, 1 nM or less, or 0.5 nM or less.

In further embodiments, CD3 binding domain of DLL3 targeting trispecific antigen-binding protein has low affinity to CD3, *i.e.*, about 100 nM or greater.

[00127] The affinity to bind to CD3 can be determined, for example, by the ability of the DLL3 targeting trispecific antigen-binding protein itself or its CD3 binding domain to bind to CD3 coated on an assay plate; displayed on a microbial cell surface; in solution; etc. The binding activity of the DLL3 targeting trispecific antigen-binding protein itself or its CD3 binding domain of the present disclosure to CD3 can be assayed by immobilizing the ligand (*e.g.*,CD3) or the DLL3 targeting trispecific antigen-binding protein itself or its CD3 binding domain, to a bead, substrate, cell, etc. Agents can be added in an appropriate buffer and the binding partners incubated for a period of time at a given temperature. After washes to remove unbound material, the bound protein can be released with, for example, SDS, buffers with a high pH, and the like and analyzed, for example, by Surface Plasmon Resonance (SPR).

Half-Life extension domain

[00128] Contemplated herein are domains which extend the half-life of an antigen-binding domain. Such domains are contemplated to include but are not limited to Albumin binding domains, Fc domains, small molecules, and other half-life extension domains known in the art.

[00129] Human albumin (ALB) (molecular mass 67 kDa) is the most abundant protein in plasma, present at about 50 mg/ml (600 μM), and has a half-life of around 20 days in humans. ALB serves to maintain plasma pH, contributes to colloidal blood pressure, functions as carrier of many metabolites and fatty acids, and serves as a major drug transport protein in plasma.

[00130] Noncovalent association with albumin extends the elimination half-time of short lived proteins. For example, a recombinant fusion of an albumin binding domain to a Fab fragment resulted in an in vivo clearance of 25- and 58-fold and a half-life extension of 26- and 37-fold when administered intravenously to mice and rabbits respectively as compared to the administration of the Fab fragment alone. In another example, when insulin is acylated with fatty acids to promote association with albumin, a protracted effect was observed when injected subcutaneously in rabbits or pigs. Together, these studies demonstrate a linkage between albumin binding and prolonged action.

[00131] In one aspect, the DLL3 targeting trispecific proteins described herein comprise a half-life extension domain, for example a domain which specifically binds to ALB. In some embodiments, the ALB binding domain of the DLL3 targeting trispecific antigen-binding protein can be any domain that binds to ALB including but not limited to domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody. In some embodiments, the ALB binding domain is a single chain variable fragments (scFv), single-domain antibody such as a heavy chain variable domain (VH), a light

chain variable domain (VL) and a variable domain (VHH) of camelid derived single domain antibody, peptide, ligand or small molecule entity specific for HSA. In certain embodiments, the ALB binding domain is a single-domain antibody. In other embodiments, the HSA binding domain is a peptide. In further embodiments, the HSA binding domain is a small molecule. It is contemplated that the HSA binding domain of DLL3 trispecific antigen-binding protein is fairly small and no more than 25 kD, no more than 20 kDa, no more than 15 kDa, or no more than 10 kDa in some embodiments. In certain instances, the ALB binding is 5 kDa or less if it is a peptide or small molecule entity.

[00132] The half-life extension domain of DLL3 targeting trispecific antigen-binding protein provides for altered pharmacodynamics and pharmacokinetics of the DLL3 targeting trispecific antigen-binding protein itself. As above, the half-life extension domain extends the elimination half-time. The half-life extension domain also alters pharmacodynamic properties including alteration of tissue distribution, penetration, and diffusion of the trispecific antigen-binding protein. In some embodiments, the half-life extension domain provides for improved tissue (including tumor) targeting, tissue distribution, tissue penetration, diffusion within the tissue, and enhanced efficacy as compared with a protein without a half-life extension domain. In one embodiment, therapeutic methods effectively and efficiently utilize a reduced amount of the trispecific antigen-binding protein, resulting in reduced side effects, such as reduced non-tumor cell cytotoxicity.

[00133] Further, the binding affinity of the half-life extension domain can be selected so as to target a specific elimination half-time in a particular trispecific antigen-binding protein. Thus, in some embodiments, the half-life extension domain has a high binding affinity. In other embodiments, the half-life extension domain has a medium binding affinity. In yet other embodiments, the half-life extension domain has a low or marginal binding affinity. Exemplary binding affinities include KD concentrations at 10 nM or less (high), between 10 nM and 100 nM (medium), and greater than 100 nM (low). As above, binding affinities to ALB are determined by known methods such as Surface Plasmon Resonance (SPR). In some embodiments, ALB binding domains described herein comprise a single domain antibody.

[00134] In some embodiments, the half-life extension domain comprises a sequence selected from SEQ ID Nos. 1769-1778, or a sequence that is at least about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% identical to a sequence selected from SEQ ID Nos. 1769-1778. In some examples, the half-life extension comprises three heavy chain CDRs (HC CDR1, HC CDR2, and HC CDR3), and three light chain CDRs. In some examples, the half-life extension comprises three heavy chain CDRs (HC CDR1, HC CDR2, and HC CDR3), or three light chain CDRs. The heavy chain CDR1(HC

CDR1) of the half-life extension domain, in some embodiments, comprises a sequence selected from SEQ ID Nos.. 1782-1784, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1782-1784, or at least about 80% to about 99%. The heavy chain CDR2 (HC CDR2) of the half-life extension domain, in some embodiments, comprises a sequence selected from SEQ ID Nos. 1785-1790, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1785-1790. The heavy chain CDR3 (HC CDR3) of the CD3 binding domain comprises a sequence selected from SEQ ID Nos. 1791 or 1792, or a sequence comprising one or more modifications or substitutions in a sequence selected from SEQ ID Nos. 1791 or 1792.

DLL3 binding domain

[00135] DLL3 (also known as Delta-like Ligand 3 or SCDO1) is a member of the Delta-like family of Notch DSL ligands. Representative DLL3 protein orthologs include, but are not limited to, human (Accession Nos. NP_058637 and NP_982353), chimpanzee (Accession No. XP_003316395), mouse (Accession No. NP_031892), and rat (Accession No. NP_446118). In humans, the DLL3 gene consists of 8 exons spanning 9.5 kbp located on chromosome 19q13. Alternate splicing within the last exon gives rise to two processed transcripts, one of 2389 bases (Accession No. NM_016941) and one of 2052 bases (Accession No. NM_203486). The former transcript encodes a 618 amino acid protein (Accession No. NP_058637), whereas the latter encodes a 587 amino acid protein (Accession No. NP_982353). These two protein isoforms of DLL3 share overall 100% identity across their extracellular domains and their transmembrane domains, differing only in that the longer isoform contains an extended cytoplasmic tail containing 32 additional residues at the carboxy terminus of the protein. The extracellular region of the DLL3 protein, comprises six EGF-like domains, the single DSL domain and the N-terminal domain. Generally, the EGF domains are recognized as occurring at about amino acid residues 216-249 (domain 1), 274-310 (domain 2), 312-351 (domain 3), 353-389 (domain 4), 391-427 (domain 5) and 429-465 (domain 6), with the DSL domain at about amino acid residues 176-215 and the N-terminal domain at about amino acid residues 27-175 of hDLL3. Each of the EGF-like domains, the DSL domain and the N-terminal domain comprise part of the DLL3 protein as defined by a distinct amino acid sequence. The EGF-like domains are termed, in some embodiments, as EGF1 to EGF6 with EGF1 being closest to the N-terminal portion of the protein. In general, DSL ligands are composed of a series of structural domains: a unique N-terminal domain, followed by a conserved DSL domain, multiple tandem epidermal growth factor (EGF)-like repeats, a transmembrane domain, and a cytoplasmic domain not highly conserved across ligands but one which contains multiple lysine residues that are potential sites for ubiquitination by unique E3 ubiquitin ligases. The DSL domain is a degenerate EGF-domain

that is necessary but not sufficient for interactions with Notch receptors. Additionally, the first two EGF-like repeats of most DSL ligands contain a smaller protein sequence motif known as a DOS domain that co-operatively interacts with the DSL domain when activating Notch signaling.

[00136] In some embodiments, the disclosed DLL3 trispecific binding proteins of this disclosure are generated, fabricated, engineered or selected so as to react with a selected domain, motif or epitope within a DLL3 protein. In some embodiments, the DLL3 targeting trispecific protein binds to the DSL domain and, in some embodiments, binds to an epitope comprising G203, R205, P206 within the DSL domain.

[00137] The DLL3 binding domain of the DLL3 targeting trispecific proteins of the present disclosure are, in some embodiments, engineered fabricated and/or selected to react with both isoform(s) of DLL3 or a single isoform of the protein or, conversely, comprise a pan-DLL binding domain that reacts or associates with at least one additional DLL family member in addition to DLL3. In some embodiments, the DLL3 binding domain, such as DLL3 binding domain are engineered, fabricated, and/or selected so that they react with domains (or epitopes therein) that are exhibited by DLL3 only or with domains that are at least somewhat conserved across multiple or all DLL family members.

[00138] In some embodiments the DLL3 binding domain associates or binds to a specific epitope, portion, motif or domain of DLL3. Both DLL3 isoforms incorporate an identical extracellular region comprising at least an N-terminal domain, a DSL (Delta/Serrate/lag-2) domain and six EGF-like domains (*i.e.*, EGF1-EGF6). Accordingly, in certain embodiments the DLL3 binding domain binds or associate with the N-terminal domain of DLL3 (amino acids 27-175 in the mature protein) while in other embodiments the DLL3 binding domain associates with the DSL domain (amino acids 176-215) or epitope therein. In other aspects of the present disclosure the DLL3 binding domain associates or bind to a specific epitope located in a particular EGF-like domain of DLL3. In some embodiments, the DLL3 binding domain associates or binds to an epitope located in EGF1 (amino acids 216-249), EGF2 (amino acids 274-310), EGF3 (amino acids 312-351), EGF4 (amino acids 353-389), EGF5 (amino acids 391.427) or EGF6 (amino acids 429-465). In some embodiments, each of the aforementioned domains comprises more than one epitope and/or more than one bin. In some embodiments the DLL3 binding domain binds, reacts or associates with the DSL domain or an epitope therein. In other embodiments the DLL3 binding domain binds, reacts or associates with a particular EGF-like domain or an epitope therein. In some embodiments the DLL3 binding domain binds, reacts or associates with the N-terminal domain or an epitope therein.

[00139] In some embodiments, the DLL3 binding proteins of this disclosure, such as the DLL3 binding domain of the trispecific proteins of this disclosure binds to the full length DLL3 protein or to a fragment thereof, such as epitope containing fragments within the full length DLL3 protein, as described above. In some cases, the epitope containing fragment comprises antigenic or immunogenic fragments and derivatives thereof of the DLL3 protein. Epitope containing fragments, including antigenic or immunogenic fragments, are, in some embodiments, 12 amino acids or more, 20 amino acids or more, 50 or 100 amino acids or more. The DLL3 fragments, in some embodiments, comprises 95% or more of the length of the full protein, 90% or more, 75% or 50% or 25% or 10% or more of the length of the full protein. In some embodiments, the epitope-containing fragments of DLL3 including antigenic or immunogenic fragments are capable of eliciting a relevant immune response in a patient. Derivatives of DLL3 include, in some embodiments, variants on the sequence in which one or more (*e.g.*, 1-20 such as 15 amino acids, or up to 20% such as up to 10% or 5% or 1% by number of amino acids based on the total length of the protein) deletions, insertions or substitutions have been made to the DLL3 sequence provided in SEQ ID No. 1885 (UniProtKB Accession Q9NYJ7). In some embodiments, substitutions comprise conservative substitutions. Derivatives and variants of DLL3, in some examples, have essentially the same biological function as the DLL3 protein from which they are derived. For instance, derivatives and variants of DLL3 are, in some cases, comparably antigenic or immunogenic to the protein from which they are derived, have either the ligand-binding activity, or the active receptor-complex forming ability, or preferably both, of the protein from which they are derived, and have the same tissue distribution as DLL3.

[00140] The design of the DLL3 targeting trispecific proteins described herein allows the binding domain to DLL3 to be flexible in that the binding domain to DLL3 can be any type of binding domain, including but not limited to, domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody. In some embodiments, the binding domain to DLL3 is a single chain variable fragments (scFv), a single-domain antibody such as a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) of camelid derived single domain antibody. In other embodiments, the binding domain to DLL3 is a non-Ig binding domain, *i.e.*, an antibody mimetic, such as anticalins, affilins, affibody molecules, affimers, affitins, alphabodies, avimers, DARPins, fynomers, kunitz domain peptides, and monobodies. In further embodiments, the binding domain to DLL3 is a ligand or peptide that binds to or associates with DLL3. In yet further embodiments, the binding domain to DLL3 is a knottin. In yet further embodiments, the binding domain to DLL3 is a small molecular entity.

[00141] In some embodiments, the DLL3 binding domain binds to a protein comprising the sequence of SEQ ID No. 1885 (UniProtKB Accession Q9NYJ7). In some embodiments, the DLL3 binding domain binds to a protein comprising a truncated sequence compared to SEQ ID No. 1885 (UniProtKB Accession Q9NYJ7). In some embodiments, the DLL3 binding domain binds to a protein comprising the sequence of SEQ ID No. 1892 or SEQ ID No. 1893 (which is the mature extracellular domain of a DLL3 protein). In some embodiments, the DLL3 binding domain binds to a protein comprising amino acids 47-492 of SEQ ID No. 1892. In some embodiments, the DLL3 binding domain recognizes an epitope within amino acids 47-4492 of SEQ ID No. 1892.

[00142] In some embodiments, the DLL3 binding domain is an anti-DLL3 antibody or an antibody variant. As used herein, the term "antibody variant" refers to variants and derivatives of an antibody described herein. In certain embodiments, amino acid sequence variants of the anti-DLL3 antibodies described herein are contemplated. For example, in certain embodiments amino acid sequence variants of anti-DLL3 antibodies described herein are contemplated to improve the binding affinity and/or other biological properties of the antibodies. Exemplary method for preparing amino acid variants include, but are not limited to, introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody.

[00143] Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, antigen-binding. In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitution mutagenesis include the CDRs and framework regions. Examples of such substitutions are described below. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, retained/improved antigen binding, decreased immunogenicity, or improved T-cell mediated cytotoxicity (TDCC). Both conservative and non-conservative amino acid substitutions are contemplated for preparing the antibody variants.

[00144] In another example of a substitution to create a variant anti-DLL3 antibody, one or more hypervariable region residues of a parent antibody are substituted. In general, variants are then selected based on improvements in desired properties compared to a parent antibody, for example, increased affinity, reduced affinity, reduced immunogenicity, increased pH dependence of binding.

[00145] In some embodiments, the DLL3 binding domain of the DLL3 targeting trispecific protein is a single domain antibody such as a heavy chain variable domain (VH), a variable

domain (VHH) of a llama derived sdAb, a peptide, a ligand or a small molecule entity specific for DLL3. In some embodiments, the DLL3 binding domain of the DLL3 targeting trispecific protein described herein is any domain that binds to DLL3 including but not limited to domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody. In certain embodiments, the DLL3 binding domain is a single-domain antibody. In other embodiments, the DLL3 binding domain is a peptide. In further embodiments, the DLL3 binding domain is a small molecule.

[00146] Generally, it should be noted that the term single domain antibody as used herein in its broadest sense is not limited to a specific biological source or to a specific method of preparation. Single domain antibodies are antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine. For example, in some embodiments, the single domain antibodies of the disclosure are obtained: (1) by isolating the VHH domain of a naturally occurring heavy chain antibody; (2) by expression of a nucleotide sequence encoding a naturally occurring VHH domain; (3) by "humanization" of a naturally occurring VHH domain or by expression of a nucleic acid encoding a such humanized VHH domain; (4) by "camelization" of a naturally occurring VH domain from any animal species, and in particular from a species of mammal, such as from a human being, or by expression of a nucleic acid encoding such a camelized VH domain; (5) by "camelisation" of a "domain antibody" or "Dab," or by expression of a nucleic acid encoding such a camelized VH domain; (6) by using synthetic or semi-synthetic techniques for preparing proteins, polypeptides or other amino acid sequences; (7) by preparing a nucleic acid encoding a single domain antibody using techniques for nucleic acid synthesis known in the field, followed by expression of the nucleic acid thus obtained; and/or (8) by any combination of one or more of the foregoing.

[00147] In one embodiment, a single domain antibody corresponds to the VHH domains of naturally occurring heavy chain antibodies directed against DLL3. As further described herein, such VHH sequences can generally be generated or obtained by suitably immunizing a species of Llama with DLL3, (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against DLL3), by obtaining a suitable biological sample from said Llama (such as a blood sample, serum sample or sample of B-cells), and by generating VHH sequences directed against DLL3, starting from said sample, using any suitable technique known in the field.

[00148] In another embodiment, such naturally occurring VHH domains against DLL3, are obtained from naïve libraries of Camelid VHH sequences, for example by screening such a library using DLL3, or at least one part, fragment, antigenic determinant or epitope thereof using one or more screening techniques known in the field. Such libraries and techniques are for example described in WO 99/37681, WO 01/90190, WO 03/025020 and WO 03/035694. Alternatively, improved synthetic or semi-synthetic libraries derived from naïve VHH libraries are used, such as VHH libraries obtained from naïve VHH libraries by techniques such as random mutagenesis and/or CDR shuffling, as for example described in WO 00/43507.

[00149] In a further embodiment, yet another technique for obtaining VHH sequences directed against DLL3, involves suitably immunizing a transgenic mammal that is capable of expressing heavy chain antibodies (*i.e.*, so as to raise an immune response and/or heavy chain antibodies directed against DLL3), obtaining a suitable biological sample from said transgenic mammal (such as a blood sample, serum sample or sample of B-cells), and then generating VHH sequences directed against DLL3, starting from said sample, using any suitable technique known in the field. For example, for this purpose, the heavy chain antibody-expressing rats or mice and the further methods and techniques described in WO 02/085945 and in WO 04/049794 can be used.

[00150] In some embodiments, an anti-DLL3 single domain antibody of the DLL3 targeting trispecific protein comprises a single domain antibody with an amino acid sequence that corresponds to the amino acid sequence of a naturally occurring VHH domain, but that has been "humanized", *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of said naturally occurring VHH sequence (and in particular in the framework sequences) by one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being (*e.g.*, as indicated above). This can be performed in a manner known in the field, which will be clear to the skilled person, for example on the basis of the further description herein. Again, it should be noted that such humanized anti-DLL3 single domain antibodies of the disclosure are obtained in any suitable manner known per se (*i.e.*, as indicated under points (1)-(8) above) and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VHH domain as a starting material. In some additional embodiments, a single domain anti-DLL3 antibody, as described herein, comprises a single domain antibody with an amino acid sequence that corresponds to the amino acid sequence of a naturally occurring VH domain, but that has been "camelized," *i.e.*, by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring VH domain from a conventional 4-chain antibody by one or more of the amino acid residues that occur at the corresponding position(s) in a VHH domain of

a heavy chain antibody. Such "camelizing" substitutions are preferably inserted at amino acid positions that form and/or are present at the VH-VL interface, and/or at the so-called Camelidae hallmark residues (see for example WO 94/04678 and Davies and Riechmann (1994 and 1996)). Preferably, the VH sequence that is used as a starting material or starting point for generating or designing the camelized single domain is preferably a VH sequence from a mammal, more preferably the VH sequence of a human being, such as a VH3 sequence. However, it should be noted that such camelized anti-DLL3 single domain antibodies of the disclosure, in certain embodiments, are obtained in any suitable manner known in the field (*i.e.*, as indicated under points (1)-(8) above) and thus are not strictly limited to polypeptides that have been obtained using a polypeptide that comprises a naturally occurring VH domain as a starting material. For example, as further described herein, both "humanization" and "camelization" is performed by providing a nucleotide sequence that encodes a naturally occurring VHH domain or VH domain, respectively, and then changing, one or more codons in said nucleotide sequence in such a way that the new nucleotide sequence encodes a "humanized" or "camelized" single domain antibody, respectively. This nucleic acid can then be expressed, so as to provide a desired anti-DLL3 single domain antibody of the disclosure. Alternatively, in other embodiments, based on the amino acid sequence of a naturally occurring VHH domain or VH domain, respectively, the amino acid sequence of the desired humanized or camelized anti-DLL3 single domain antibody of the disclosure, respectively, are designed and then synthesized *de novo* using known techniques for peptide synthesis. In some embodiments, based on the amino acid sequence or nucleotide sequence of a naturally occurring VHH domain or VH domain, respectively, a nucleotide sequence encoding the desired humanized or camelized anti-DLL3 single domain antibody of the disclosure, respectively, is designed and then synthesized *de novo* using known techniques for nucleic acid synthesis, after which the nucleic acid thus obtained is expressed in using known expression techniques, so as to provide the desired anti-DLL3 single domain antibody of the disclosure.

[00151] Other suitable methods and techniques for obtaining the anti-DLL3 single domain antibody of the disclosure and/or nucleic acids encoding the same, starting from naturally occurring VH sequences or VHH sequences for example comprises combining one or more parts of one or more naturally occurring VH sequences (such as one or more framework (FR) sequences and/or complementarity determining region (CDR) sequences), one or more parts of one or more naturally occurring VHH sequences (such as one or more FR sequences or CDR sequences), and/or one or more synthetic or semi-synthetic sequences, in a suitable manner, so as to provide an anti-DLL3 single domain antibody of the disclosure or a nucleotide sequence or nucleic acid encoding the same.

[00152] In some embodiments, the DLL3 binding domain is an anti-DLL3 specific antibody comprising a heavy chain variable complementarity determining region CDR1, a heavy chain variable CDR2, a heavy chain variable CDR3, a light chain variable CDR1, a light chain variable CDR2, and a light chain variable CDR3. In some embodiments, the DLL3 binding domain comprises any domain that binds to DLL3 including but not limited to domains from a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, or antigen binding fragments such as single domain antibodies (sdAb), Fab, Fab', F(ab)2, and Fv fragments, fragments comprised of one or more CDRs, single-chain antibodies (*e.g.*, single chain Fv fragments (scFv)), disulfide stabilized (dsFv) Fv fragments, heteroconjugate antibodies (*e.g.*, bispecific antibodies), pFv fragments, heavy chain monomers or dimers, light chain monomers or dimers, and dimers consisting of one heavy chain and one light chain. In some embodiments, the DLL3 binding domain is a single domain antibody. In some embodiments, the anti-DLL3 single domain antibody comprises heavy chain variable complementarity determining regions (CDR), CDR1, CDR2, and CDR3.

[00153] In some embodiments, the DLL3 binding domain is a polypeptide comprising an amino acid sequence that is comprised of four framework regions/sequences (f1-f4) interrupted by three complementarity determining regions/sequences, as represented by the formula: f1-r1-f2-r2-f3-r3-f4, wherein r1, r2, and r3 are complementarity determining regions CDR1, CDR2, and CDR3, respectively, and f1, f2, f3, and f4 are framework residues. The framework residues of the DLL3 binding protein of the present disclosure comprise, for example, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, or 94 amino acid residues, and the complementarity determining regions comprise, for example, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 amino acid residues. In some embodiments, the DLL3 binding domain comprises an amino acid sequence selected from SEQ ID Nos. 1-442 and 1886. In some embodiments, CDR1 of the DLL3 binding domain comprises a sequence selected from SEQ ID Nos. 443-884 and 1887, or one or more amino acid substitutions relative to a sequence selected from the group consisting of SEQ ID Nos. 443-884 and 1887. In some embodiments, CDR2 comprises a sequence selected from the group consisting of SEQ ID Nos. 885-1326 and 1888, or one or more amino acid substitutions relative to a sequence selected from the group consisting of SEQ ID Nos. 885-1326 and 1888. In some embodiments, the CDR3 comprises a sequence selected from the group consisting of SEQ ID Nos. 1327-1768 and 1889, or one or more substitutions relative to a sequence selected from SEQ ID Nos. 1327-1768 and 1889.

[00154] In some embodiments, the CDR1 comprises an amino acid sequence selected from SEQ ID Nos. 443-884 and 1887 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid selected from SEQ ID Nos. 443-884 and 1887.

In some embodiments, the CDR2 comprises an amino acid sequence selected from SEQ ID Nos. 885-1326 and 1888 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid sequence selected from SEQ ID Nos. 885-1326 and 1888. In some embodiments, the CDR3 comprises an amino acid sequence selected from SEQ ID Nos. 1327-1768 and 1889 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in a sequence selected from SEQ ID Nos. 1327-1768 and 1889.

[00155] In some embodiments, the CDR1 comprises an amino acid sequence selected from SEQ ID Nos. 495-528 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid selected from SEQ ID Nos. 495-528. In some embodiments, the CDR2 comprises an amino acid sequence selected from SEQ ID Nos. 937-970 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid sequence selected from SEQ ID Nos. 937-970. In some embodiments, the CDR3 comprises an amino acid sequence selected from SEQ ID Nos. 1379-1412 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in a sequence selected from SEQ ID Nos. 1379-1412.

[00156] In some embodiments, the CDR1 comprises an amino acid sequence selected from SEQ ID Nos. 529-809 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid selected from SEQ ID Nos. 529-809. In some embodiments, the CDR2 comprises an amino acid sequence selected from SEQ ID Nos. 971 to 1251 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid sequence selected from SEQ ID Nos. 971 to 1251. In some embodiments, the CDR3 comprises an amino acid sequence selected from SEQ ID Nos. 1379 to 1412 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in a sequence selected from SEQ ID Nos. 1379-1412.

[00157] In some embodiments, the CDR1 comprises an amino acid sequence selected from SEQ ID Nos. 810-884 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid selected from SEQ ID Nos. 810-884. In some embodiments, the CDR2 comprises an amino acid sequence selected from SEQ ID Nos. 1252 to 1326 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in an amino acid sequence selected from SEQ ID Nos. 1252 to 1326. In some embodiments, the CDR3 comprises an amino acid sequence selected from SEQ ID Nos. 1692 to 1768 or a variant having one, two, three, four, five, six, seven, eight, nine, or ten amino acid substitutions in a sequence selected from SEQ ID Nos. 1692 to 1768.

[00158] In various embodiments, the DLL3 binding domain of the present disclosure is at least about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identical to an amino acid sequence selected from SEQ ID Nos. 1-442 and 1886.In various embodiments, the DLL3 binding domain of the present disclosure is at least about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identical to an amino acid sequence selected from SEQ ID Nos. 53-86.

[00159] In various embodiments, the DLL3 binding domain of the present disclosure is at least about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identical to an amino acid sequence selected from SEQ ID Nos. 87-367.

[00160] In various embodiments, the DLL3 binding domain of the present disclosure is at least about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identical to SEQ ID No.68, or a sequence derived from SEQ ID No.68.

[00161] In various embodiments, the DLL3 binding domain of the present disclosure is at least about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identical to SEQ ID No.75, or a sequence derived from SEQ ID No.75.

[00162] In some embodiments, the DLL3 binding domain of the DLL3 targeting trispecific binding protein is cross-reactive with human and cynomolgus DLL3. In some embodiments, the DLL3 binding domain is specific for human DLL3. In certain embodiments, the DLL3 binding domain disclosed herein binds to human DLL3 with a human Kd (hKd). In certain embodiments, the DLL3 binding domain disclosed herein binds to cynomolgus DLL3 with a cynomolgus Kd (cKd). In certain embodiments, the DLL3 binding domain disclosed herein

binds to both cynomolgus DLL3 and a human DLL3,with a cyno Kd (cKd) and a human Kd, respectively (hKd). In some embodiments, the DLL3 binding protein binds to human and cynomolgus DLL3 with comparable binding affinities (*i.e.*, hKd and cKd values do not differ by more than ± 10%). In some embodiments, the hKd and the cKd range from about 0.001 nM to about 500 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 450 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 400 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 350 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 300 nM . In some embodiments, the hKd and the cKd range from about 0.001 nM to about 250 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 200 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 150 nM. In some embodiments, the hKd and the cKd range from about 0.001 nM to about 100 nM. In some embodiments, the hKd and the cKd range from about 0. 1 nM to about 90 nM. In some embodiments, the hKd and the cKd range from about 0. 2 nM to about 80 nM. In some embodiments, the hKd and the cKd range from about 0. 3 nM to about 70 nM. In some embodiments, the hKd and the cKd range from about 0. 4 nM to about 50 nM. In some embodiments, the hKd and the cKd range from about 0.5 nM to about 30 nM. In some embodiments, the hKd and the cKd range from about 0.6 nM to about 10 nM. In some embodiments, the hKd and the cKd range from about 0.7 nM to about 8 nM. In some embodiments, the hKd and the cKd range from about 0.8 nM to about 6 nM. In some embodiments, the hKd and the cKd range from about 0.9 nM to about 4 nM. In some embodiments, the hKd and the cKd range from about 1 nM to about 2 nM.

[00163] In certain embodiments, the DLL3 binding domains of the present disclosure preferentially bind membrane bound DLL3 over soluble DLL3. Membrane bound DLL3 refers to the presence of DLL3 in or on the cell membrane surface of a cell that expresses DLL3. Soluble DLL3 refers to DLL3 that is no longer on in or on the cell membrane surface of a cell that expresses or expressed DLL3. In certain instances, the soluble DLL3 is present in the blood and/or lymphatic circulation in a subject. In one embodiment, the DLL3 binding proteins bind membrane-bound DLL3 at least 5 fold, 10 fold, 15 fold, 20 fold, 25 fold, 30 fold, 40 fold, 50 fold, 100 fold, 500 fold, or 1000 fold greater than soluble DLL3. In one embodiment, the antigen binding proteins of the present disclosure preferentially bind membrane-bound DLL3 30 fold greater than soluble DLL3. Determining the preferential binding of an antigen binding protein to membrane bound DLL3 over soluble DLL3 can be readily determined using assays well known in the art.

[00164] In some embodiments, any of the foregoing DLL3 binding domains (*e.g.*, anti-DLL3 single domain antibodies of SEQ ID Nos. 1-442 and 1886) are affinity peptide tagged for ease of purification. In some embodiments, the affinity peptide tag is six consecutive histidine residues, also referred to as 6X-his (SEQ ID No. 1819).

[00165] In some embodiments, any of the foregoing DLL3 binding domains (*e.g.*, anti-DLL3 single domain antibodies of SEQ ID Nos. 1-442 and 1886) are affinity peptide tagged for ease of purification. In some embodiments, the affinity peptide tag is six consecutive histidine residues, also referred to as 6X-his (SEQ ID No. 1819).

Integration into chimeric antigen receptors (CAR)

[00166] The DLL3 targeting trispecific antigen binding proteins of the present disclosure can, in certain examples, be incorporated into a chimeric antigen receptor (CAR). An engineered immune effector cell, a T cell or NK cell, can be used to express a CAR that includes an anti-DLL3 targeting trispecific protein containing an anti-DLL3 single domain antibody as described herein. In one embodiment, the CAR including an anti-DLL3 targeting trispecific protein as described herein is connected to a transmembrane domain via a hinge region, and further a costimulatory domain, a functional signaling domain obtained from OX40, CD27, CD28, CD5, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278), or 4-1BB. In some embodiments, the CAR further comprises a sequence encoding an intracellular signaling domain, such as 4-1BB and/or CD3 zeta.

Tumor growth reduction properties

[00167] In certain embodiments, the DLL3 targeting trispecific proteins of the disclosure reduce the growth of tumor cells in vivo when administered to a subject who has tumor cells that express DLL3. Measurement of the reduction of the growth of tumor cells can be determined by multiple different methodologies well known in the art. Non-limiting examples include direct measurement of tumor dimension, measurement of excised tumor mass and comparison to control subjects, measurement via imaging techniques (*e.g.*,CT or MRI) that may or may not use isotopes or luminescent molecules (*e.g.* luciferase) for enhanced analysis, and the like.

[00168] In specific embodiments, administration of the trispecific proteins of the disclosure results in a reduction of *in vivo* growth of tumor cells as compared to a control antigen binding agent by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, with an about 100% reduction in tumor growth indicating a complete response and disappearance of the tumor. In further embodiments, administration of the trispecific proteins of the disclosure results in a reduction of in vivo growth of tumor cells as compared to a control antigen binding agent by about 50-100%, about 75-100% or about 90-100%. In further embodiments, administration of the trispecific proteins of the disclosure results in a reduction of in vivo growth of tumor cells as

compared to a control antigen binding agent by about 50-60%, about 60-70%, about 70-80%, about 80-90%, or about 90-100%.

DLL3 Targeting Trispecific Protein Modifications

[00169] The DLL3 targeting trispecific proteins described herein encompass derivatives or analogs in which (i) an amino acid is substituted with an amino acid residue that is not one encoded by the genetic code, (ii) the mature polypeptide is fused with another compound such as polyethylene glycol, or (iii) additional amino acids are fused to the protein, such as a leader or secretory sequence or a sequence for purification of the protein.

[00170] Typical modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

[00171] Modifications are made anywhere in DLL3 targeting trispecific proteins described herein, including the peptide backbone, the amino acid side-chains, and the amino or carboxyl termini. Certain common peptide modifications that are useful for modification of DLL3 targeting trispecific proteins include glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation, blockage of the amino or carboxyl group in a polypeptide, or both, by a covalent modification, and ADP-ribosylation.

[00172] In some embodiments, a derivative of the DLL3 targeting trispecific protein as described herein comprises immunoreactive modulator derivatives and antigen binding molecules comprising one or more modifications.

[00173] In some embodiments, the trispecific DLL3 binding molecules of the disclosure are monovalent or multivalent, bivalent, trivalent, etc. As used herein, the term "valency" refers to the number of potential target binding sites associated with an antibody. Each target binding site specifically binds one target molecule or specific position or locus on a target molecule. When an antibody is monovalent, each binding site of the molecule will specifically bind to a single antigen position or epitope. When an antibody comprises more than one target binding site (multivalent), each target binding site may specifically bind the same or different molecules (*e.g.*, may bind to different ligands or different antigens, or different epitopes or positions on the same antigen).

[00174] In some embodiments, the DLL3 targeting trispecific proteins of this disclosure contain *inter alia* one or more additional amino acid residue substitutions, mutations and/or modifications which result in a compound with preferred characteristics including, but not limited to: altered pharmacokinetics, increased serum half-life, increase binding affinity, reduced immunogenicity, increased production, altered Fc ligand binding to an Fc receptor (FcR), enhanced or reduced "ADCC" (antibody-dependent cell mediated cytotoxicity) or "CDC" (complement-dependent cytotoxicity) activity, altered glycosylation and/or disulfide bonds and modified binding specificity. In some cases these DLL3 targeting trispecific protein variants are advantageously used to enhance the effective anti-neoplastic properties of the disclosed DLL3 targeting trispecific proteins.

[00175] In some embodiments, the DLL3 targeting trispecific proteins of the disclosure have half-lives in a mammals, such as in a human, or in a cynomolgus monkey of less than about 5 days, about 5 days, greater than about 5 days, greater than 10 days, greater than about 15 days, greater than about 20 days, greater than about 25 days, greater than about 30 days, greater than about 35 days, greater than about 40 days, greater than about 45 days, greater than about 2 months, greater than about 3 months, greater than about 4 months, or greater than about 5 months. The increased half-life, in some cases, results in a higher serum titer which thus reduces the frequency of the administration of the DLL3 targeting trispecific proteins, reduces the concentration of the antibodies to be administered, or both.

[00176] Still other embodiments comprise one or more engineered glycoforms, *i.e.*, a DLL3 targeting trispecific binding protein comprising an altered glycosylation pattern or altered carbohydrate composition that is covalently attached to the protein. Engineered glycoforms are useful, in some cases, for a variety of purposes, including but not limited to enhancing or reducing effector function, increasing the affinity of the trispecific protein for a target or facilitating production of the trispecific protein. In certain embodiments where reduced effector function is desired, the molecule is engineered to express an aglycosylated form. Substitutions that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site, are included in some embodiments. Conversely, enhanced effector functions or improved binding is imparted to the Fc containing trispecific proteins of this disclosure by engineering in one or more additional glycosylation sites, in some cases.

[00177] The DLL3 targeting trispecific proteins, in some cases, are differentially modified during or after production, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications are carried out

by techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH4, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin etc.

[00178] Various post-translational modifications also encompassed by the disclosure include, for example, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends, attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. Moreover, the DLL3 targeting trispecific binding proteins are, in some cases, modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for detection and isolation of the modulator.

Polynucleotides Encoding DLL3 targeting trispecific proteins

[00179] Also provided, in some embodiments, are polynucleotide molecules encoding an anti-DLL3 trispecific binding protein described herein. In some embodiments, the polynucleotide molecules are provided as a DNA construct. In other embodiments, the polynucleotide molecules are provided as a messenger RNA transcript.

[00180] The polynucleotide molecules are constructed by known methods such as by combining the genes encoding the three binding domains either separated by peptide linkers or, in other embodiments, directly linked by a peptide bond, into a single genetic construct operably linked to a suitable promoter, and optionally a suitable transcription terminator, and expressing it in bacteria or other appropriate expression system such as, for example CHO cells. In the embodiments where the DLL3 binding domain is a small molecule, the polynucleotides contain genes encoding the CD3 binding domain and the half-life extension domain. In the embodiments where the half-life extension domain is a small molecule, the polynucleotides contain genes encoding the domains that bind to CD3 and DLL3. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. The promoter is selected such that it drives the expression of the polynucleotide in the respective host cell.

[00181] In some embodiments, the polynucleotide is inserted into a vector, preferably an expression vector, which represents a further embodiment. This recombinant vector can be constructed according to known methods. Vectors of particular interest include plasmids, phagemids, phage derivatives, virii (*e.g.*, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, lentiviruses, and the like), and cosmids.

[00182] A variety of expression vector/host systems may be utilized to contain and express the polynucleotide encoding the polypeptide of the described trispecific antigen-binding protein.

Examples of expression vectors for expression in E.coli are pSKK (Le Gall *et al.*, J Immunol Methods. (2004) 285(1):111-27) or pcDNA5 (Invitrogen) for expression in mammalian cells.

[00183] Thus, the DLL3 targeting trispecific proteins as described herein, in some embodiments, are produced by introducing a vector encoding the protein as described above into a host cell and culturing said host cell under conditions whereby the protein domains are expressed, may be isolated and, optionally, further purified.

Pharmaceutical Compositions

[00184] Also provided, in some embodiments, are pharmaceutical compositions comprising an anti-DLL3 trispecific binding protein described herein, a vector comprising the polynucleotide encoding the polypeptide of the DLL3 targeting trispecific proteins or a host cell transformed by this vector and at least one pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" includes, but is not limited to, any carrier that does not interfere with the effectiveness of the biological activity of the ingredients and that is not toxic to the patient to whom it is administered. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Such carriers can be formulated by conventional methods and can be administered to the subject at a suitable dose. Preferably, the compositions are sterile. These compositions may also contain adjuvants such as preservative, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents. A further embodiment provides one or more of the above described DLL3 targeting trispecific proteins packaged in lyophilized form, or packaged in an aqueous medium.

[00185] In some embodiments of the pharmaceutical compositions, the DLL3 targeting trispecific proteins described herein are encapsulated in nanoparticles. In some embodiments, the nanoparticles are fullerenes, liquid crystals, liposome, quantum dots, superparamagnetic nanoparticles, dendrimers, or nanorods. In other embodiments of the pharmaceutical compositions, the DLL3 targeting trispecific protein is attached to liposomes. In some instances, the DLL3 targeting trispecific proteins are conjugated to the surface of liposomes. In some instances, the DLL3 trispecific antigen-binding protein are encapsulated within the shell of a liposome. In some instances, the liposome is a cationic liposome.

[00186] The DLL3 targeting trispecific proteins described herein are contemplated for use as a medicament. Administration is effected by different ways, by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration. In some embodiments, the route of administration depends on the kind of therapy and the kind of compound contained in the pharmaceutical composition. The dosage regimen will be determined by the attending

physician and other clinical factors. Dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind of therapy, general health and other drugs being administered concurrently. An "effective dose" refers to amounts of the active ingredient that are sufficient to affect the course and the severity of the disease, leading to the reduction or remission of such pathology and may be determined using known methods.

[00187] In some embodiments, the DLL3 targeting trispecific proteins of this disclosure are administered at a dosage of up to 10 mg/kg at a frequency of once a week. In some cases, the dosage ranges from about 1 ng/kg to about 10 mg/kg. In some embodiments, the dose is from about 1 ng/kg to about 10 ng/kg, about 5 ng/kg to about 15 ng/kg, about 12 ng/kg to about 20 ng/kg, about 18 ng/kg to about 30 ng/kg, about 25 ng/kg to about 50 ng/kg, about 35 ng/kg to about 60 ng/kg, about 45 ng/kg to about 70 ng/kg, about 65 ng/kg to about 85 ng/kg, about 80 ng/kg to about 1 μg/kg, about 0.5 μg/kg to about 5 μg/kg, about 2 μg/kg to about 10 μg/kg, about 7 μg/kg to about 15 μg/kg, about 12 μg/kg to about 25 μg/kg, about 20 μg/kg to about 50 μg/kg, about 35 μg/kg to about 70 μg/kg, about 45 μg/kg to about 80 μg/kg, about 65 μg/kg to about 90 μg/kg, about 85 μg/kg to about 0.1 mg/kg, about 0.095 mg/kg to about 10 mg/kg. In some cases, the dosage is about 0.1 mg/kg to about 0.2 mg/kg; about 0.25 mg/kg to about 0.5 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.75 mg/kg to about 3 mg/kg, about 2.5 mg/kg to about 4 mg/kg, about 3.5 mg/kg to about 5 mg/kg, about 4.5 mg/kg to about 6 mg/kg, about 5.5 mg/kg to about 7 mg/kg, about 6.5 mg/kg to about 8 mg/kg, about 7.5 mg/kg to about 9 mg/kg, or about 8.5 mg/kg to about 10 mg/kg. The frequency of administration, in some embodiments, is about less than daily, every other day, less than once a day, twice a week, weekly, once in 7 days, once in two weeks, once in two weeks, once in three weeks, once in four weeks, or once a month. In some cases, the frequency of administration is weekly. In some cases, the frequency of administration is weekly and the dosage is up to 10 mg/kg. In some cases, duration of administration is from about 1 day to about 4 weeks or longer.

[00188] In some embodiments, the DLL3 targeting trispecific proteins of this disclosure are administered at a dosage of about 1μg to about 100μg, about 1 μg to about 500 μg, about 1 μg to about 1mg, about 1 μg to about 2mg, about 1 μg to about 5mg, about 1 μg to about 10mg, about 1 μg to about 100mg, about 100 μg to about 500 μg, about 100 μg to about 1mg, about 100 μg to about 2mg, about 100 μg to about 5mg, about 100 μg to about 10mg, about 100 μg to about 100mg, about 500 μg to about 1mg, about 500 μg to about 2mg, about 500 μg to about 5mg, about 500 μg to about 10mg, about 500 μg to about 100mg, about 1mg to about 2mg, about 1mg to about 5mg, about 1 mg to about 10 mg, about 1mg to about 100 mg, about 2mg to about 5mg, about 2 mg to about 10 mg, about 2mg to about 100 mg, about 5 mg to about 10 mg, about 5mg

to about 100 mg, or about 10 mg to about 100 mg. In some embodiments, the DLL3 targeting trispecific proteins of this disclosure are administered at a dosage of about 15 μg to about 45 μg, about 15 μg to about 135 μg, about 15 μg to about 405 μg, about 15 μg to about 1215 μg, about 15 μg to about 3600 μg, about 45 μg to about 135 μg, about 45 μg to about 405 μg, about 45 μg to about 1215 μg, about 45 μg to about 3600 μg, about 135 μg to about 405 μg, about 135 μg to about 1215 μg, about 135 μg to about 3600 μg, about 405 μg to about 1215 μg, about 405 μg to about 3600 μg, or about 1215 μg to about 3600 μg. In some embodiments, the first dose is about 5 mg. In some embodiments, the dose is about 7 mg. In some embodiments, the dose is about 10 mg. In some embodiments, the dose is about 12 mg. In some embodiments, the dose is about 15 mg. In some embodiments, the dose is about 20 mg. In some embodiments, the dose is about 30 mg. In some embodiments, the dose is about 40 mg. In some embodiments, the dose is about 50 mg. In some embodiments, the dose is about 70 mg. In some embodiments, the dose is about 100 mg.

[00189] The DLL3 targeting trispecific protein described herein can be administered using different dosages. In some embodiments, the DLL3 targeting trispecific protein of this disclosure is administered according to a schedule comprising the following steps: (i) administration of a first dose of the DLL3 targeting trispecific protein, and (ii) administration of a second dose of the DLL3 targeting trispecific protein, wherein the second dose is higher than the first dose. In some embodiments, the schedule further comprises step (iii) administration of a third dose of the DLL3 targeting trispecific protein, wherein the third dose is higher than the second dose. In some embodiments, the schedule further comprises step (iv) administration of a fourth dose of the DLL3 targeting trispecific protein, wherein the fourth dose is higher than the third dose. In some embodiments, the schedule further comprises step (v) administration of a fifth dose of the DLL3 targeting trispecific protein, wherein the fifth dose is higher than the fourth dose.

[00190] In some embodiments, the first dose is about 1 μg to about 100 μg, about 1 μg to about 500 μg, about 1 μg to about 1 mg, about 1 μg to about 2 mg, about 1 μg to about 5 mg, about 1 μg to about 5 mg, about 1 μg to about 8 mg, about 1 μg to about 10 mg, about 1 μg to about 50 mg, about 1 μg to about 100 mg about 100 μg to about 500 μg, about 100 μg to about 1 mg, about 100 μg to about 2 mg, about 100 μg to about 5 mg, about 100 μg to about 5 mg, about 100 μg to about 8 mg, about 100 μg to about 10 mg, about 100 μg to about 50 mg, about 100 μg to about 100 mg, about 500 μg to about 1 mg, about 500 μg to about 2 mg, about 500 μg to about 5 mg, about 500 μg to about 5 mg, about 500 μg to about 8 mg, about 500 μg to about 10 mg, about 500 μg to about 50 mg, about 500 μg to about 100 mg, about 1 mg to about 2 mg, about 1 mg to about 5 mg, about 1 mg to about 8 mg, about 1 mg to about 10 mg, about 1 mg to about

50 mg, about 1 mg to about 100 mg, about 2 mg to about 5 mg, about 2 mg to about 8 mg, about 2 mg to about 10 mg, about 2 mg to about 50 mg, about 2 mg to about 100 mg, about 5 mg to about 8 mg, about 5 mg to about 10 mg, about 5 mg to about 50 mg, about 5 mg to about 100 mg, about 8 mg to about 10 mg, about 8 mg to about 50 mg, about 8 mg to about 100 mg, about 10 mg to about 50 mg, or about 50 mg to about 100 mg. In some embodiments, the first dose is about 5 μg. In some embodiments, the first dose is about 15 μg. In some embodiments, the first dose is about 45 μg. In some embodiments, the first dose is about 135 μg. In some embodiments, the first dose is about 405 μg. In some embodiments, the first dose is about 1215 μg. In some embodiments, the first dose is about 1500 μg. In some embodiments, the first dose is about 2000 μg. In some embodiments, the first dose is about 2500 μg. In some embodiments, the first dose is about 3600 μg. In some embodiments, the first dose is about 3 mg. In some embodiments, the first dose is about 4 mg. In some embodiments, the first dose is about 5 mg. In some embodiments, the first dose is about 6 mg. In some embodiments, the first dose is about 7 mg. In some embodiments, the first dose is about 8 mg. In some embodiments, the first dose is about 9 mg. In some embodiments, the first dose is about 10 mg. In some embodiments, the first dose is about 11 mg. In some embodiments, the first dose is about 12 mg. In some embodiments, the first dose is about 15 mg. In some embodiments, the first dose is about 20 mg. In some embodiments, the first dose is about 30 mg. In some embodiments, the first dose is about 40 mg. In some embodiments, the first dose is about 50 mg. In some embodiments, the first dose is about 70 mg. In some embodiments, the first dose is about 100 mg.

[00191] In some embodiments, the first dose is administered for about 1 week to about 5 weeks, about 1 week to about 10 weeks, about 1 week to about 20 weeks, about 1 week to about 50 weeks, about 1 week to about 80 weeks, about 1 week to about 100 weeks, about 5 weeks to about 10 weeks, about 5 weeks to about 20 weeks, about 5 weeks to about 50 weeks, about 5 weeks to about 80 weeks, about 5 weeks to about 100 weeks, about 10 weeks to about 20 weeks, about 10 weeks to about 50 weeks, about 10 weeks to about 80 weeks, about 10 weeks to about 100 weeks, about 20 weeks to about 50 weeks, about 20 weeks to about 80 weeks, about 20 weeks to about 100 weeks, about 50 weeks to about 80 weeks, about 50 weeks to about 100 weeks, about 80 weeks to about 100 weeks, about 1 week to about 9 weeks, about 1 week to about 18 weeks, about 1 week to about 27 weeks, about 1 week to about 36 weeks, about 9 weeks to about 18 weeks, about 9 weeks to about 27 weeks, about 9 weeks to about 36 weeks, about 18 weeks to about 27 weeks, about 18 weeks to about 36 weeks, or about 27 weeks to about 36 weeks.

[00192] In some embodiments, the first dose is administered once per day, twice per day, three times per day, four times per day, five times per day, six times per day, seven times per day,

eight times per day, nine times per day or ten times per day. In some embodiments, the first dose is administered once per week, twice per week, three times per week, four times per week, five times per week, six times per week, once every other week, once every three weeks, once every four week or once every five weeks.

[00193] In some embodiments, the second dose is about 1 μg to about 100 μg, about 1 μg to about 500 μg, about 1 μg to about 1 mg, about 1 μg to about 2 mg, about 1 μg to about 5 mg, about 1 μg to about 5 mg, about 1 μg to about 8 mg, about 1 μg to about 10 mg, about 1 μg to about 50 mg, about 1 μg to about 100 mg about 100 μg to about 500 μg, about 100 μg to about 1 mg, about 100 μg to about 2 mg, about 100 μg to about 5 mg, about 100 μg to about 5 mg, about 100 μg to about 8 mg, about 100 μg to about 10 mg, about 100 μg to about 50 mg, about 100 μg to about 100 mg, about 500 μg to about 1 mg, about 500 μg to about 2 mg, about 500 μg to about 5 mg, about 500 μg to about 5 mg, about 500 μg to about 8 mg, about 500 μg to about 10 mg, about 500 μg to about 50 mg, about 500 μg to about 100 mg, about 1 mg to about 2 mg, about 1 mg to about 5 mg, about 1 mg to about 8 mg, about 1 mg to about 10 mg, about 1 mg to about 50 mg, about 1 mg to about 100 mg, about 2 mg to about 5 mg, about 2 mg to about 8 mg, about 2 mg to about 10 mg, about 2 mg to about 50 mg, about 2 mg to about 100 mg, about 5 mg to about 8 mg, about 5 mg to about 10 mg, about 5 mg to about 50 mg, about 5 mg to about 100 mg, about 8 mg to about 10 mg, about 8 mg to about 50 mg, about 8 mg to about 100 mg, about 10 mg to about 50 mg, or about 50 mg to about 100 mg. In some embodiments, the second dose is about 1.2 mg. In some embodiments, the second dose is about 2 mg. In some embodiments, the second dose is about 3 mg. In some embodiments, the second dose is about 4 mg. In some embodiments, the second dose is about 5 mg. In some embodiments, the second dose is about 6 mg. In some embodiments, the second dose is about 7 mg. In some embodiments, the second dose is about 8 mg. In some embodiments, the second dose is about 9 mg. In some embodiments, the second dose is about 10 mg. In some embodiments, the second dose is about 11 mg. In some embodiments, the second dose is about 12 mg. In some embodiments, the second dose is about 13 mg. In some embodiments, the second dose is about 14 mg. In some embodiments, the second dose is about 15 mg. In some embodiments, the second dose is about 20 mg. In some embodiments, the second dose is about 30 mg. In some embodiments, the second dose is about 40 mg. In some embodiments, the second dose is about 50 mg. In some embodiments, the second dose is about 70 mg. In some embodiments, the second dose is about 100 mg. In some embodiments, the second dose is about 3.6 mg. In some embodiments, the second dose is about 7.2 mg. In some embodiments, the second dose is about 12 mg. In some embodiments, the second dose is about 24 mg. In some embodiments, the second dose is about 36 mg. In some embodiments, the second dose is about 48 mg. In some

embodiments, the second dose is about 60 mg. In some embodiments, the second dose is about 72 mg. In some embodiments, the second dose is about 84 mg. In some embodiments, the second dose is about 96 mg.

[00194] In some embodiments, the second dose is administered for about 1 week to about 5 weeks, about 1 week to about 10 weeks, about 1 week to about 20 weeks, about 1 week to about 50 weeks, about 1 week to about 80 weeks, about 1 week to about 100 weeks, about 5 weeks to about 10 weeks, about 5 weeks to about 20 weeks, about 5 weeks to about 50 weeks, about 5 weeks to about 80 weeks, about 5 weeks to about 100 weeks, about 10 weeks to about 20 weeks, about 10 weeks to about 50 weeks, about 10 weeks to about 80 weeks, about 10 weeks to about 100 weeks, about 20 weeks to about 50 weeks, about 20 weeks to about 80 weeks, about 20 weeks to about 100 weeks, about 50 weeks to about 80 weeks, about 50 weeks to about 100 weeks, about 80 weeks to about 100 weeks, about 1 week to about 9 weeks, about 1 week to about 18 weeks, about 1 week to about 27 weeks, about 1 week to about 36 weeks, about 9 weeks to about 18 weeks, about 9 weeks to about 27 weeks, about 9 weeks to about 36 weeks, about 18 weeks to about 27 weeks, about 18 weeks to about 36 weeks, or about 27 weeks to about 36 weeks.

[00195] In some embodiments, the second dose is administered once per day, twice per day, three times per day, four times per day, five times per day, six times per day, seven times per day, eight times per day, nine times per day or ten times per day. In some embodiments, the first dose is administered once per week, twice per week, three times per week, four times per week, five times per week, six times per week, once every other week, once every three weeks, once every four week or once every five weeks.

[00196] In some embodiments, the first dose is about 3.6 mg and the second dose is about 7.2 mg. In some embodiments, the first dose is about 3 mg and the second dose is about 14 mg, which is administered weekly. In some embodiments, the first dose is about 3 mg and the second dose is about 7 mg, which is administered weekly. In some embodiments, the first dose is about 3 mg and the second dose is about 7 mg, which is administered every other week.

Methods of treatment

[00197] In some embodiments, the DLL3 binding proteins, or DLL3 targeting trispecific proteins of the present disclosure is administered to treat a neoplastic condition. Neoplastic conditions, in some embodiments, are benign or malignant; solid tumors or other blood neoplasia; and, in some embodiments, are selected from the group including, but not limited to: adrenal gland tumors, AIDS-associated cancers, alveolar soft part sarcoma, astrocytic tumors, autonomic ganglia tumors, bladder cancer (squamous cell carcinoma and transitional cell carcinoma), blastocoelic disorders, bone cancer (adamantinoma, aneurismal bone cysts,

osteochondroma, osteosarcoma), brain and spinal cord cancers, metastatic brain tumors, breast cancer including triple negative breast cancer, carotid body tumors, cervical cancer, chondrosarcoma, chordoma, chromophobe renal cell carcinoma, clear cell carcinoma, colon cancer, colorectal cancer, cutaneous benign fibrous histiocytomas, desmoplastic small round cell tumors, ependymomas, epithelial disorders, Ewing's tumors, extraskeletal myxoid chondrosarcoma, fibrogenesis imperfecta ossium, fibrous dysplasia of the bone, gallbladder and bile duct cancers, gastric cancer, gastrointestinal, gestational trophoblastic disease, germ cell tumors, glandular disorders, head and neck cancers, hypothalamic, intestinal cancer, islet cell tumors, Kaposi's Sarcoma, kidney cancer (nephroblastoma, papillary renal cell carcinoma), leukemias, lipoma/benign lipomatous tumors, liposarcoma/malignant lipomatous tumors, liver cancer (hepatoblastoma, hepatocellular carcinoma), lymphomas, lung cancers (small cell carcinoma, adenocarcinoma, squamous cell carcinoma, large cell carcinoma etc.), macrophagal disorders, medulloblastoma, melanoma, meningiomas, multiple endocrine neoplasia, multiple myeloma, myelodysplastic syndrome, neuroblastoma, neuroendocrine tumors, ovarian cancer, pancreatic cancers, papillary thyroid carcinomas, parathyroid tumors, pediatric cancers, peripheral nerve sheath tumors, phacochromocytoma, pituitary tumors, prostate cancer, posterious unveal melanoma, rare hematologic disorders, renal metastatic cancer, rhabdoid tumor, rhabdomysarcoma, sarcomas, skin cancer, soft-tissue sarcomas, squamous cell cancer, stomach cancer, stromal disorders, synovial sarcoma, testicular cancer, thymic carcinoma, thymoma, thyroid metastatic cancer, and uterine cancers (carcinoma of the cervix, endometrial carcinoma, and leiomyoma).

[00198] In certain embodiments the DLL3 binding proteins, or the DLL3 targeting trispecific proteins of the present disclosure is used as a front line therapy and administered to subjects who have not previously been treated for the cancerous condition. In other embodiments the DLL3 targeting trispecific proteins of the present disclosure are used to treat subjects that have previously been treated (with a DLL3 targeting trispecific protein of this disclosure or with other anti-cancer agent) and have relapsed or determined to be refractory to the previous treatment. In some embodiments the DLL3 targeting trispecific proteins of the present disclosure are used to treat subjects that have recurrent tumors.

[00199] In some aspects, the DLL3 binding proteins, or the DLL3 targeting trispecific proteins of the present disclosure are administered to treat a proliferative disorder comprising a solid tumor including, but not limited to, adrenal, liver, kidney, bladder, breast, gastric, ovarian, cervical, uterine, esophageal, colorectal, prostate, pancreatic, lung (both small cell and non-small cell), thyroid, carcinomas, sarcomas, glioblastomas and various head and neck tumors.

[00200] In some embodiments, the DLL3 binding proteins, or the DLL3 targeting trispecific proteins of the present disclosure are administered to a subject suffering from melanoma. In some embodiments, the DLL3 targeting trispecific proteins of the present disclosure are used to diagnose, monitor, treat or prevent melanoma. The term "melanoma," as used herein, includes all types of melanoma including, but not limited to, primary melanoma, malignant melanoma, cutaneous melanoma, extracutaneous melanoma, superficial spreading melanoma, polypoid melanoma, melanocarcinomas, melanoepitheliomas, melanosarcomas, melanoma in situ, nodular malignant melanoma, lentigo maligna melanoma, lentiginous melanoma, lentiginous malignant melanoma, mucosal lentiginous melanoma, mucosal melanoma, acral lentiginous melanoma, soft tissue melanoma, ocular melanoma, invasive melanoma, familial atypical mole and melanoma (FAM-M) syndrome, desmoplastic malignant melanoma or uveal melanoma.

[00201] DLL3 is an effective tumor marker that is expressed on a number of different cancers and has been found to be associated with cancer stem cells. Thus, in some embodiments where the DLL3 binding proteins, or the DLL3 targeting trispecific proteins of the disclosure are incorporated in a chimeric antigen receptor expressed on lymphocytes, the resulting "DLL3 sensitized lymphocytes" (*e.g.*, natural killer cells or T cells that immunospecifically recognize a DLL3 determinant) are able to effectively mount an immune response directed to aberrant DLL3 positive cells including cancer stem cells. This ability to effectively eliminate tumorigenic "seed" cells is often critical in reducing the possibility of tumor recurrence or metastasis. In some embodiments, such DLL3 sensitized lymphocytes are used in combination with other therapeutic agents or as part of a maintenance regimen following standard of care treatments.

[00202] More generally a chimeric antigen receptor is an artificially constructed hybrid protein or polypeptide containing or comprising an antigen binding domain of an antibody linked to a signaling domain (*e.g.*, T-cell signaling or T-cell activation domains). In some embodiments, CARs comprising the DLL3 targeting trispecific binding protein of the present disclosure have the ability to redirect the specificity and reactivity of sensitized lymphocytes (*e.g.*, T-cells) toward DLL3 positive target cells in a non-MHC-restricted manner by exploiting the antigen-binding properties of antibodies or antigen binding fragments thereof. The non-MHC-restricted antigen recognition gives T-cells expressing DLL3 CARs the ability to recognize tumorigenic DLL3 independent of antigen processing, thus bypassing a major mechanism of tumor escape. Moreover, when expressed in T-cells, CARs advantageously do not dimerize with endogenous T cell receptor (TCR) alpha and beta chains.

[00203] In selected aspects the DLL3 binding proteins, or the DLL3 targeting trispecific proteins of the disclosure is incorporated into a chimeric antigen receptor (CAR) and the DLL3 CAR is administered in a CAR based therapy effective at treating lung cancer, including the following

subtypes: small cell lung cancer, non-small cell lung cancer (*e.g.*, squamous cell non-small cell lung cancer or squamous cell small cell lung cancer) and large cell neuroendocrine carcinoma (LCNEC).

[00204] In some embodiments, the DLL3 binding proteins, or the DLL3 sensitive lymphocytes are administered to patients exhibiting limited stage disease or extensive stage disease. In other embodiments the disclosed DLL3 targeting trispecific antibodies are administered to refractory patients (*i.e.*, those whose disease recurs during or shortly after completing a course of initial therapy); sensitive patients (*i.e.*, those whose relapse is longer than 2-3 months after primary therapy); or patients exhibiting resistance to a platinum based agent (*e.g.*, carboplatin, cisplatin, oxaliplatin) and/or a taxane (*e.g.*, docetaxel, paclitaxel, larotaxel or cabazitaxel). In another embodiment the disclosed DLL3 CAR treatments are effective at treating ovarian cancer, including ovarian-serous carcinoma and ovarian-papillary serous carcinoma.

[00205] The disclosed DLL3 binding proteins, or the DLL3 targeting trispecific binding proteins, in some embodiments, are used to prevent, treat or diagnose tumors with neuroendocrine features or phenotypes including neuroendocrine tumors. True or canonical neuroendocrine tumors (NETs) arising from the dispersed endocrine system are relatively rare, with an incidence of 2-5 per 100,000 people, but highly aggressive. Neuroendocrine tumors occur in the kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (colon, stomach), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma and large cell neuroendocrine carcinoma). These tumors may secrete several hormones including serotonin and/or chromogranin A that can cause debilitating symptoms known as carcinoid syndrome. Such tumors can be denoted by positive immunohistochemical markers such as neuron-specific enolase (NSE, also known as gamma enolase, gene symbol=ENO2), CD56 (or NCAM1), chromogranin A (CHGA), and synaptophysin (SYP) or by genes known to exhibit elevated expression such as ASCL1. Traditional chemotherapies have not been particularly effective in treating neuroendocrine tumors and liver metastasis is a common outcome. In some embodiments the disclosed DLL3 targeting trispecific antibodies are advantageously used to treat neuroendocrine tumors, and in some embodiments they are used to treat, prevent or diagnose pseudo neuroendocrine tumors (pNETs) that genotypically or phenotypically mimic, resemble or exhibit common traits with canonical neuroendocrine tumors. Pseudo neuroendocrine tumors or tumors with neuroendocrine features are tumors that arise from cells of the diffuse neuroendocrine system or from cells in which a neuroendocrine differentiation cascade has been aberrantly reactivated during the oncogenic process. Such pNETs commonly share certain phenotypic or biochemical characteristics with traditionally defined neuroendocrine tumors, including the ability to produce subsets of biologically active

amines, neurotransmitters, and peptide hormones. Histologically, such tumors (NETs and pNETs) share a common appearance often showing densely connected small cells with minimal cytoplasm of bland cytopathology and round to oval stippled nuclei. In some embodiments of the present disclosure commonly expressed histological markers or genetic markers that are used to define neuroendocrine and pseudo neuroendocrine tumors include, but are not limited to, chromogranin A, CD56, synaptophysin, PGP9.5, ASCL1 and neuron-specific enolase (NSE). Accordingly, in some embodiments, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof, of the present disclosure, are beneficially used to treat both pseudo neuroendocrine tumors and canonical neuroendocrine tumors, such as to treat neuroendocrine tumors (both NET and pNET) arising in the kidney, genitourinary tract (bladder, prostate, ovary, cervix, and endometrium), gastrointestinal tract (colon, stomach), thyroid (medullary thyroid cancer), and lung (small cell lung carcinoma and large cell neuroendocrine carcinoma). Moreover, in some embodiments, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are used to treat tumors expressing one or more markers such as NSE, CD56, synaptophysin, chromogranin A, ASCL1, or PGP9.5 (UCHL1). In some embodiments, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are used to treat a subject suffering from a tumor that is NSE+ or CD56+ or PGP9.5+ or ASCL1+ or SYP+ or CHGA+ or any combination thereof.

[00206] In another embodiment the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are used in maintenance therapy to reduce or eliminate the chance of tumor recurrence following the initial presentation of the disease. In some cases, the disorder has been treated and the initial tumor mass eliminated, reduced or otherwise ameliorated so the patient is asymptomatic or in remission. At such time the subject is administered pharmaceutically effective amounts of the disclosed the DLL3 binding proteins, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof one or more times regardless of if there is little or no indication of disease using standard diagnostic procedures. In some embodiments, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof is administered on a regular schedule over a period of time, such as weekly, every two weeks, monthly, every six weeks, every two months, every three months every six months or annually, for example, to reduce the potential of disease recurrence. Moreover such treatments are in some embodiments continued

for a period of weeks, months, years or even indefinitely depending on the patient response and clinical and diagnostic parameters.

[00207] In yet another embodiment the DLL3 binding proteins, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are used to prophylactically or as an adjuvant therapy to prevent or reduce the possibility of tumor metastasis following a debulking procedure. As used in the present disclosure a "debulking procedure" is defined broadly and means any procedure, technique or method that eliminates, reduces, treats or ameliorates a tumor or tumor proliferation. Exemplary debulking procedures include, but are not limited to, surgery, radiation treatments (*i.e.*, beam radiation), chemotherapy, immunotherapy or ablation. In some embodiments, at appropriate times, the DLL3 binding proteins, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are administered as suggested by clinical, diagnostic or theranostic procedures to reduce tumor metastasis. In some embodiments, the dosing regimen is accompanied by appropriate diagnostic or monitoring techniques that allow it to be modified.

[00208] Yet other embodiments of the disclosure comprise administering the DLL3 binding proteins, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof to subjects that are asymptomatic but at risk of developing a proliferative disorder. That is, in some embodiments, the DLL3 binding proteins, the DLL3 targeting trispecific protein of the disclosure, the DLL3 CAR, or the DLL3 sensitized lymphocytes, or any combination thereof are used in preventative sense and given to patients that have been examined or tested and have one or more noted risk factors (*e.g.*, genomic indications, family history, *in vivo* or *in vitro* test results, etc.) but have not developed neoplasia. In such cases those skilled in the art would be able to determine an effective dosing regimen through empirical observation or through accepted clinical practices.

[00209] As used herein, in some embodiments, "treatment" or "treating" or "treated" refers to therapeutic treatment wherein the object is to slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (*i.e.*, not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes

prolonging survival as compared to expected survival if not receiving treatment. In other embodiments, "treatment" or "treating" or "treated" refers to prophylactic measures, wherein the object is to delay onset of or reduce severity of an undesired physiological condition, disorder or disease, such as, for example is a person who is predisposed to a disease (*e.g.*, an individual who carries a genetic marker for a disease such as breast cancer).

[00210] In some embodiments of the methods described herein, the DLL3 binding proteins, the DLL3 targeting trispecific proteins, or compositions as described herein are administered in combination with an agent for treatment of the particular disease, disorder or condition. Agents include but are not limited to, therapies involving antibodies, small molecules (*e.g.*, chemotherapeutics), hormones (steroidal, peptide, and the like), radiotherapies (γ-rays, X-rays, and/or the directed delivery of radioisotopes, microwaves, UV radiation and the like), gene therapies (*e.g.*, antisense, retroviral therapy and the like) and other immunotherapies. In some embodiments, an anti-DLL3 binding protein, or an anti-DLL3 targeting trispecific protein as described herein is administered in combination with anti-diarrheal agents, anti-emetic agents, analgesics, opioids and/or non-steroidal anti-inflammatory agents. In some embodiments, an anti-DLL3 binding protein, or an anti-DLL3 targeting trispecific protein as described herein is administered in combination with anti-cancer agents. Non-limiting examples of anti-cancer agents that can be used in the various embodiments of the disclosure, including pharmaceutical compositions and dosage forms and kits of the disclosure, include: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or

rIL2), interferon alpha-2a; interferon alpha-2b; interferon alpha-n1 interferon alpha-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinzolidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride. Other examples of anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix;

chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9–; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-I receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4–; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; HMG-CoA reductase inhibitor (such as but not limited to, Lovastatin, Pravastatin, Fluvastatin, Statin, Simvastatin, and Atorvastatin); loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase;

nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; Vitaxin®; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Additional anti-cancer drugs are 5-fluorouracil and leucovorin. These two agents are particularly useful when used in methods employing thalidomide and a topoisomerase inhibitor. In some

embodiments, the DLL3 targeting trispecific protein of the present disclosure is used in combination with gemcitabine. In some embodiments, the DLL3 targeting trispecific protein as described herein is administered before, during, or after surgery.

Methods of detection of DLL3 expression and diagnosis of DLL3 associated cancer

[00211] According to another embodiment of the disclosure, kits for detecting expression of DLL3 *in vitro* or *in vivo* are provided. The kits include the foregoing DLL3 binding proteins, DLL3 targeting trispecific proteins (*e.g.*, a trispecific protein containing a labeled anti-DLL3 single domain antibody or antigen binding fragments thereof), and one or more compounds for detecting the label. In some embodiments, the label is selected from the group consisting of a fluorescent label, an enzyme label, a radioactive label, a nuclear magnetic resonance active label, a luminescent label, and a chromophore label.

[00212] In some cases, DLL3 expression is detected in a biological sample. The sample can be any sample, including, but not limited to, tissue from biopsies, autopsies and pathology specimens. Biological samples also include sections of tissues, for example, frozen sections taken for histological purposes. Biological samples further include body fluids, such as blood, serum, plasma, sputum, spinal fluid or urine. A biological sample is typically obtained from a mammal, such as a human or non-human primate.

[00213] In one embodiment, provided is a method of determining if a subject has cancer by contacting a sample from the subject with an anti-DLL3 single domain antibody or an anti-DLL3 trispecific protein as disclosed herein; and detecting binding of the single domain antibody to the sample. An increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having cancer.

[00214] In another embodiment, provided is a method of confirming a diagnosis of cancer in a subject by contacting a sample from a subject diagnosed with cancer with an anti-DLL3 single domain antibody or an anti-DLL3 trispecific protein as disclosed herein; and detecting binding of the antibody to the sample. An increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample confirms the diagnosis of cancer in the subject.

[00215] In some examples of the disclosed methods, the DLL3 binding protein, or the DLL3 binding single domain antibody of the trispecific protein is directly labeled. In some examples, the methods further include contacting a second antibody that specifically binds an anti-DLL3 single domain antibody or an anti-DLL3 trispecific protein with the sample; and detecting the binding of the second antibody. An increase in binding of the second antibody to the sample as compared to binding of the second antibody to a control sample detects cancer in the subject or confirms the diagnosis of cancer in the subject. In some cases, the cancer is a neuroendocrine cancer, prostate cancer, lung cancer, stomach cancer, squamous cell carcinoma, pancreatic

cancer, cholangiocarcinoma, triple negative breast cancer or ovarian cancer, or any other type of cancer that expresses DLL3. In some examples, the control sample is a sample from a subject without cancer. In particular examples, the sample is a blood or tissue sample.

[00216] In some cases, the antibody that binds (for example specifically binds) DLL3 is directly labeled with a detectable label. In another embodiment, the antibody that binds (for example, specifically binds) DLL3 (the first antibody) is unlabeled and a second antibody or other molecule that can bind the antibody that specifically binds DLL3 is labeled. A second antibody is chosen such that it is able to specifically bind the specific species and class of the first antibody. For example, if the first antibody is a llama IgG, then the secondary antibody may be an anti-llama-IgG. Other molecules that can bind to antibodies include, without limitation, Protein A and Protein G, both of which are available commercially. Suitable labels for the antibody or secondary antibody are described above, and include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, magnetic agents and radioactive materials. Non-limiting examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase. Non-limiting examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin. Non-limiting examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin. A non-limiting exemplary luminescent material is luminol; a non-limiting exemplary a magnetic agent is gadolinium, and non-limiting exemplary radioactive labels include 125I, 131I, 35S or 3H.

[00217] In an alternative embodiment, DLL3 can be assayed in a biological sample by a competition immunoassay utilizing DLL3 standards labeled with a detectable substance and an unlabeled antibody that specifically binds DLL3. In this assay, the biological sample, the labeled DLL3 standards and the antibody that specifically bind DLL3 are combined and the amount of labeled DLL3 standard bound to the unlabeled antibody is determined. The amount of DLL3 in the biological sample is inversely proportional to the amount of labeled DLL3 standard bound to the antibody that specifically binds DLL3.

[00218] The immunoassays and method disclosed herein can be used for a number of purposes. In one embodiment, the antibody that specifically binds DLL3 may be used to detect the production of DLL3 in cells in cell culture. In another embodiment, the antibody can be used to detect the amount of DLL3 in a biological sample, such as a tissue sample, or a blood or serum sample. In some examples, the DLL3 is cell-surface DLL3. In other examples, the DLL3 is soluble DLL3 (*e.g.*, DLL3 in a cell culture supernatant or soluble DLL3 in a body fluid sample, such as a blood or serum sample).

[00219] In one embodiment, a kit is provided for detecting DLL3 in a biological sample, such as a blood sample or tissue sample. For example, to confirm a cancer diagnosis in a subject, a biopsy can be performed to obtain a tissue sample for histological examination. Alternatively, a blood sample can be obtained to detect the presence of soluble DLL3 protein or fragment. Kits for detecting a polypeptide will typically comprise a single domain antibody, according to the present disclosure, that specifically binds DLL3. In some embodiments, an antibody fragment, such as an scFv fragment, a VH domain, or a Fab is included in the kit. In a further embodiment, the antibody is labeled (for example, with a fluorescent, radioactive, or an enzymatic label).

[00220] In one embodiment, a kit includes instructional materials disclosing means of use of an antibody that binds DLL3. The instructional materials may be written, in an electronic form (such as a computer diskette or compact disk) or may be visual (such as video files), or provided through an electronic network, for example, over the internet, World Wide Web, an intranet, or other network. The kits may also include additional components to facilitate the particular application for which the kit is designed. Thus, for example, the kit may additionally contain means of detecting a label (such as enzyme substrates for enzymatic labels, filter sets to detect fluorescent labels, appropriate secondary labels such as a secondary antibody, or the like). The kits may additionally include buffers and other reagents routinely used for the practice of a particular method. Such kits and appropriate contents are well known to those of skill in the art.

[00221] In one embodiment, the diagnostic kit comprises an immunoassay. Although the details of the immunoassays may vary with the particular format employed, the method of detecting DLL3 in a biological sample generally includes the steps of contacting the biological sample with an antibody which specifically reacts, under immunologically reactive conditions, to a DLL3 polypeptide. The antibody is allowed to specifically bind under immunologically reactive conditions to form an immune complex, and the presence of the immune complex (bound antibody) is detected directly or indirectly.

[00222] Methods of determining the presence or absence of a cell surface marker are well known in the art. For example, the antibodies can be conjugated to other compounds including, but not limited to, enzymes, magnetic beads, colloidal magnetic beads, haptens, fluorochromes, metal compounds, radioactive compounds or drugs. The antibodies can also be utilized in immunoassays such as but not limited to radioimmunoassays (RIAs), ELISA, or immunohistochemical assays. The antibodies can also be used for fluorescence activated cell sorting (FACS). FACS employs a plurality of color channels, low angle and obtuse light-scattering detection channels, and impedance channels, among other more sophisticated levels of detection, to separate or sort cells (see U.S. Patent No. 5,061,620). Any of the single domain antibodies that bind DLL3, as disclosed herein, can be used in these assays. Thus, the antibodies

can be used in a conventional immunoassay, including, without limitation, an ELISA, an RIA, FACS, tissue immunohistochemistry, Western blot or imunoprecipitation.

EXAMPLES

Example 1: Screening of Phage Display Library for Identification of DLL3 Binding Domains

[00223] Llamas were immunized with purified DLL3 protein expressed in EXPI293™ cells. A phage display library for expression of heavy chain variable antibody domains was constructed from circulating B cells (*see* van der Linden , de Geus , Stok , Bos ,van Wassenaar, Verrips, and Frenken. 2000. J Immunol Methods 240:185–195). Phage clones were screening for binding to DLL3 by expressing the clones in *E coli*, preparing periplasmic extracts, and screening the clones for DLL3 binding activity by ELISA. Fifty-two unique heavy chain only single domain antibodies were identified that produced a signal in the ELISA screening (SEQ ID Nos. 1 to 52). The CDR1, CDR2, and CDR3 sequences for these heavy variable domains were, respectively, SEQ ID Nos. 443 to 494, SEQ ID Nos.885 to 936, and SEQ ID Nos.1327 to 1378.

Example 2: Humanization of DLL3 Binding Single Domain Antibodies and T Cell Dependent Cellular Cytotoxicity Assay

[00224] Thirty-four (SEQ ID Nos. 53 to 86) exemplary llama anti-DLL3 heavy chain only single domain antibodies from **Example 1** were humanized. The CDR1, CDR2, and CDR3 sequences for the 34 heavy chain only single domain antibodies were, respectively, SEQ ID Nos. 495 to 528, SEQ ID Nos. 937 to 970, and SEQ ID Nos. 1379 to 1412.

[00225] The humanized anti-DLL3 sequences were cloned into an expression vector, in an expression construct comprising a signal domain followed by an anti-DLL3 heavy chain only variable domain followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by anti-human albumin single domain antibody 10G (SEQ ID No. 1774) followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by anti-human CD3 antibody 2B2 (SEQ ID No.1793) followed by a HHHHHH tag (SEQ ID No. 1819), to generate anti-DLL3 trispecific constructs.

[00226] The anti-DLL3 trispecific constructs containing the humanized anti-DLL3 binding sequences were then transfected into EXPI293™ cells. These anti-DLL3 trispecific constructs have an engineered with a protein A binding site, and the amount of anti-DLL3 trispecific construct in the conditioned media from the transfected EXPI293™ cells was quantitated using an Octet instrument with protein A tips. A trispecific protein of similar molecular weight as the anti-DLL3 trispecific proteins was used as a standard.

[00227] Using conditioned media containing known concentrations of anti-DLL3 trispecific proteins, the binding affinities of the anti-DLL3 trispecific proteins toward human and

cynomolgus monkey DLL3 proteins were measured, using a method where the DLL3 proteins were expressed as human IgG1-Fc fusions and the measurements were carried out using an Octet instrument with anti-human Fc tips. The K_D measurements were made using a single 50 nM concentration of the anti-DLL3 trispecific proteins, which allowed for rank ordering based on potency. The relative affinities, measured as described above, are listed in **Table 1**. All of the sequences were found to bind human DLL3, with relative affinities (K_D) ranging from 0.5 to 42 nM. Some of the sequences were found to bind cynomolgus DLL3 with similar affinities to human DLL3, and the relative affinities for the binding of those sequences to cynomolgus DLL3 are also shown in **Table 1**.

[00228] The conditioned media were also tested in a T-cell dependent cellular cytotoxicity assay (*see* Nazarian AA, Archibeque IL, Nguyen YH, Wang P, Sinclair AM, Powers DA. 2015. J Biomol Screen. 20:519-27). In this assay, luciferase labelled DMS-153 cells (small-cell lung carcinoma cell line; ATCC No. ATCC® CRL-2064™) were combined with purified human T cells, from a donor, and a titration of the anti-DLL3 trispecific proteins being tested.

[00229] It was hypothesized that if an anti-DLL3 trispecific protein directed T cells to kill the DLL3-expressing DMS-153 cells, then the viability of the DMS-153 cells, as determined by running a luciferase assay at 48 hours after starting the experiment, should decrease.

[00230] As illustrated in **Figs. 2-6**, which show graphs of representative TDCC data, several exemplary anti-DLL3 trispecific proteins were able to decrease the viability of the DMS-153 cells. **Fig. 2** shows results of the TDCC assay for anti-DLL3 trispecific proteins comprising DLL3 binding domains DH18 (SEQ ID No. 59), DH11 (SEQ ID No. 55), DH67 (SEQ ID No. 42), and DH56 (SEQ ID No. 73). **Fig. 3** shows results of the TDCC assay for anti-DLL3 trispecific proteins comprising DLL3 binding domains DH2 (SEQ ID No. 60), DH43 (SEQ ID No. 68), DH10 (SEQ ID No. 54), and DH6 (SEQ ID No. 75). **Fig. 4** shows results of the TDCC assay for DLL3 trispecific protein comprises DLL3 binding domains DH82 (SEQ ID No. 81), DH23 (SEQ ID No. 62), DH89 (SEQ ID No. 84), and DH17 (SEQ ID No. 58). **Fig. 5** shows results of the TDCC assay for DLL3 trispecific protein comprises DLL3 binding domains DH83 (SEQ ID No. 82), DH12 (SEQ ID No. 56), DH61 (SEQ ID No. 76), and DH29 (SEQ ID No. 64). **Fig. 6** shows results of the TDCC assay for DLL3 trispecific protein comprises DLL3 binding domains DH58 (SEQ ID No. 74) and DH70 (SEQ ID No. 79). A negative control for the TDCC assays was a trispecific protein targeting GFP instead of DLL3 (as shown in **Fig. 6**) which did not direct the T cells to kills the DMS-153 cells. EC_{50} values from the TDCC assay are also listed in **Table 1**. These values ranged from 69 pM to 11 nM.

Table 1: Activity of Humanized Anti-DLL3 Trispecific Proteins in DMS-153 TDCC Assays and Their Affinities for Human and Cynomolgus DLL3 Protein. The K_D measurements were made using a single concentration of anti-DLL3 trispecific protein. The TDCC assay was performed using human T cells. n/d indicates binding was not detected.

DLL3 binder	DMS-153 TDCC EC50 (M)	huDLL3 KD (nM)	cyDLL3 KD (nM)
DH43	6.9E-11	4.3	5.5
DH12	7.8E-11	1.3	n/d
DH11	9.3E-11	5.3	5.6
DH58	1.1E-10	3.3	27.9
DH6	1.2E-10	6.1	6.8
DH83	1.5E-10	4.7	n/d
DH10	1.6E-10	3.9	25.0
DH17	1.6E-10	7.0	n/d
DH67	2.0E-10	8.4	8.2
DH2	2.6E-10	6.5	14.6
DH56	3.4E-10	8.1	8.0
DH70	3.4E-10	16.2	86.2
DH61	3.8E-10	10.6	30.8
DH89	4.0E-10	6.9	n/d
DH23	4.0E-10	9.9	n/d
DH29	4.2E-10	5.6	n/d
DH5	5.2E-10	0.5	5.5
DH18	6.4E-10	1.0	5.9
DH45	6.9E-10	1.9	2.8
DH82	8.4E-10	6.6	n/d
DH80	1.0E-09	0.8	5.5
DH27	1.2E-09	2.1	11.3
DH69	1.4E-09	1.2	7.0
DH92	1.7E-09	18.0	17.5
DH94	1.8E-09	2.6	9.6
DH42	1.8E-09	4.3	11.7
DH1	2.0E-09	3.5	10.7
DH38	2.9E-09	11.9	n/d
DH51	3.8E-09	5.1	18.2
DH54	4.5E-09	20.6	42.4
DH3	6.2E-09	41.9	n/d
DH15	2.0E-08	17.4	n/d
DH22	2.8E-08	6.8	16.4
DH84	1.1E-08	15.2	17.9

Example 3: Screening of Phage Display Library for Identification of DLL3 Binding Domains with Higher Binding Affinities, Using Two Humanized DLL3 Single Domain Antibodies from Previous Example

[00231] Two of the humanized antibody sequences, DH43 (SEQ ID No. 68) and DH6 (SEQ ID No. 75), were used as a starting point for making phage display libraries (following a method as described in WO2016187101A2). The anti-DLL3 sequences from this panning were subsequently cloned into an expression vector, in an expression construct comprising a signal domain followed by an anti-DLL3 heavy chain only variable domain followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by an anti-human albumin single domain antibody domain followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by an anti-human CD3 antibody fragment followed by a HHHHHH tag (SEQ ID No. 1819), to generate anti-DLL3 trispecific proteins. These constructs were transfected into EXPI293™ cells, and the expressed anti-DLL3 trispecific proteins were quantitated as described in **Example 2**. The sequences of the clones identified from the panning are SEQ ID Nos. 87 to 367. **Table 2** provides CDR variations obtained in the DH43 DLL3 binder sequences after phage display selection. Three of the clones identified from the panning, SEQ ID Nos. 199 (2E05), 330 (4D09), and 365 (4H011) were engineered to generate variants, where each variant had a single amino acid change from the parental sequence, for example, to remove potential metabolic liabilities of the parental sequence. In particular, the DLL3 binding domains comprising SEQ ID Nos. 227 (2E05-M106Y), 228 (2E05-M106Q) were engineered variants of SEQ ID No. 199 (2E05); SEQ ID No. 366 (4D09-M34L) was an engineered variant of SEQ ID No. 330 (4D09); and SEQ ID No. 367 (4H11-M34L) was an engineered variant of SEQ ID No. 365 (4H011). The CDR1 sequences of these DLL3 binding clones identified by the panning are SEQ ID Nos. 529 to 809, the CDR2 sequences of the clones identified by the panning are SEQ ID Nos. 971 to 1251, and the CDR3 sequences of the clones identified by the panning are SEQ ID Nos. 1413 to 1691.

Table 2: Variants in CDR sequences by amino acid position of DH43 and its derivatives

CDR	Amino acid position	CDR Amino acid Variants
CDR1	26	G
	27	A, E, F, G, I, K, L, N, Q, R, S, T, V, Y
	28	A, G, I, K, P, R, S, T, V
	29	A, D, F, K, L, N, P, Q, R, S, T, Y
	30	A, D, F, H, I, K, L, M, N, P, R, S, T, V, Y
	31	F, I, K, L, M, N, R, S, T, V
	32	N
	33	A, G
	34	F, I, L, M, T, V, Y
	35	A, G
	36	W
CDR2	50	G
	51	I, V

CDR	Amino acid position	CDR Amino acid Variants
	52	S
	53	A, K, P, R, S
	54	D, N
	55	D, E, G, K, N, Q, R, S, T, Y
	56	S, T
	57	A, E, F, H, I, K, L, N, Q, R, S, T, V, Y
	58	A, I, L, M, V, Y
	59	D, F, H, I, L, N, S, T, V, Y
	60	A, D, E, F, G, I, K, L, N, Q, R, S, T, V, Y
	61	A, D, E, G, K, Q, S, V
	62	S
	63	A, V
	64	K
	65	G, V
CDR3	98	F, Y
	99	G, H, I, K, N, R, S, T
	100	A, F, H, I, K, L, M, N, P, Q, R, S, T, Y
	101	A, E, F, G, H, I, K, L, M, N, Q, R, S, T, V, Y
	102	A, C, D, E, G, H, I, K, L, N, P, Q, R, S, T, W, Y
	103	G, K, L, R, T
	104	A, G, H, L, Q, R, S, T, V, Y
	105	A, D, E, G, H, P, Q, S, T, W, Y
	106	A, G, I, K, L, M, N, Q, R, S, T, V, Y
	107	A, G, K, P, R, S, T, V
	108	A, F, S, Y

[00232] Using the conditioned medium with known concentrations of the anti-DLL3 trispecific proteins, the binding affinities of the anti-DLL3 trispecific proteins toward human DLL3 protein were measured using a method where biotinylated version of human DLL3 protein were expressed as a human IgG1 fusion protein, and the binding affinity measurement was carried out in an Octet instrument with streptavidin tips. The K_D measurements were made using a single 50 nM concentration of the anti-DLL3 trispecific proteins, which allowed for rank ordering potency. In this experiment, the relative K_D values of the affinity matured clones ranged from 2.3 nM to 64 nM, as listed in **Table 3**. The parental binders DH43 and DH6, respectively, had K_D values of 7.7 ± 0.6 nM and 9.9± 0.3 nM based on four samples of conditioned medium from four transfections.

[00233] For select DLL3 binder molecules identified in this round of panning, as well as for the parental DLL3 binders DH43 and DH6, more precise affinity measurements for human DLL3 were made using 60 nM, 20 nM, 6.67 nM, and 2.22 nM concentrations of the anti-DLL3 trispecific proteins. In addition, relative affinity measurements were made using only 60 nM of

the anti-DLL3 trispecific proteins. Binding affinities determined from the more precise measurements of certain anti-DLL3 binding molecules are listed in **Table 4** [1H012 (SEQ ID No. 162); 1A011 (SEQ ID No. 95); 2E05 (SEQ ID No. 199); 4H011 (SEQ ID No. 365); 3C04 (SEQ ID No. 251); 2E02 (SEQ ID No. 198); 2H02 (SEQ ID No. 221); 3A011(SEQ ID No. 238) ; 3A02 (SEQ ID No. 230); 4D09 (SEQ ID No. 330); DH43 (SEQ ID No. 68); and DH6(SEQ ID No. 75)]. In this study, the parental binder, DH43, had a K_D value of 8.9 nM, whereas the highest affinity daughter molecule, 1H012 (SEQ ID No. 162), had an affinity of 2.9 nM. Furthermore, 1H012 (SEQ ID No. 162) retained an ability to bind to cynomolgus DLL3 as well. Also in this study, the parental binder, DH6, had a K_D value of 9.0 nM, whereas the highest affinity daughter molecule, 4H011 (SEQ ID No. 365), had an affinity of 3.9 nM. Furthermore, 4H011(SEQ ID No. 365) retained an ability to bind to cynomolgus DLL3 as well.

[00234] Twenty-two DLL3 binder molecules identified in this round of panning were selected for testing in a TDCC assay with DMS-153 cells, using the same protocol as described in **Example 2**. Exemplary TDCC data are plot as graphs in **Figs. 7-11**, and a summary of the EC_{50} values are listed in **Table 5**. In this experiment, the parental DLL3 molecules, DH43 and DH6, had EC_{50} values of 200 nM and 340 nM, respectively. The most potent daughter molecule of DH43 was 1H012 (SEQ ID No. 162), with an EC_{50} value of 28 nM, demonstrating greater than 7-fold increase in TDCC potency compared to the parental DLL3 binder DH43. The most potent daughter molecule of DH6 was 4H011 (SEQ ID No. 365) with an EC_{50} value of 36 nM, thereby showing greater than 8-fold increase in TDCC potency, compared to the parental DLL3 binder molecule. A control trispecific protein targeting GFP, used as a control, had no activity in this assay (as shown in **Fig. 11**).

Table 3: Relative Affinities of Anti-DLL3 Trispecific Proteins

Name	KD(M)
4A010	2.3E-09
2E011	2.4E-09
1C010	2.5E-09
3H011	2.7E-09
1E011	2.7E-09
1H012	3.5E-09
4G01	3.6E-09
1A011	3.7E-09
4D01	3.7E-09
4E02	3.8E-09
2E05	3.9E-09
4B011	3.9E-09
1F02	4.0E-09
1A05	4.0E-09
2A011	4.0E-09
2E010	4.0E-09
2C02	4.1E-09
2E01	4.1E-09
2G08	4.1E-09
1C01	4.3E-09
4B07	4.3E-09
1E09	4.4E-09
2H02	4.4E-09
3F010	4.4E-09
1D011	4.4E-09
3C04	4.5E-09
4H011	4.5E-09
4D09	4.7E-09
1A012	4.9E-09
2D012	4.9E-09
3C03	4.9E-09
1F011	5.0E-09
2H011	5.0E-09
1D010	5.0E-09
4C01	5.1E-09
1B01	5.2E-09
1D09	5.2E-09
1E012	5.3E-09
3D011	5.3E-09
1C05	5.3E-09
2H03	5.3E-09
1B09	5.4E-09
4B09	5.4E-09
2D011	5.4E-09
2A04	5.6E-09
1A06	5.6E-09
4A011	5.6E-09

Name	KD(M)
2G03	5.6E-09
2B07	5.7E-09
1B011	5.7E-09
1H01	5.7E-09
1E010	5.7E-09
4F010	5.8E-09
1D01	5.8E-09
1F05	5.8E-09
1D03	5.8E-09
4D011	5.8E-09
1F012	5.8E-09
3C08	5.9E-09
2F03	5.9E-09
4D08	5.9E-09
3D07	5.9E-09
2D07	6.0E-09
2E02	6.0E-09
4C011	6.0E-09
2C08	6.1E-09
1C03	6.1E-09
2H07	6.1E-09
4H04	6.1E-09
1C02	6.2E-09
2C07	6.2E-09
1H011	6.2E-09
1H07	6.2E-09
2D04	6.2E-09
3A09	6.3E-09
2H04	6.3E-09
1F010	6.3E-09
1A03	6.3E-09
2C09	6.4E-09
2H010	6.4E-09
4D05	6.5E-09
2G07	6.5E-09
1A010	6.5E-09
2F09	6.5E-09
2B02	6.6E-09
4C03	6.6E-09
1A09	6.6E-09
2D06	6.6E-09
1G01	6.6E-09
2C06	6.7E-09
4C02	6.8E-09
2C04	6.8E-09
3A011	6.8E-09
1G011	6.8E-09

Name	KD(M)
4C06	6.8E-09
2D03	6.8E-09
1B010	6.8E-09
1D06	6.8E-09
3G010	6.9E-09
4C010	7.0E-09
1E02	7.0E-09
1A01	7.0E-09
4B02	7.1E-09
1C07	7.1E-09
3F011	7.1E-09
1E07	7.1E-09
4E08	7.2E-09
3B05	7.2E-09
2B012	7.3E-09
3G09	7.3E-09
3B07	7.3E-09
2D010	7.3E-09
2B05	7.4E-09
4D06	7.5E-09
4G011	7.5E-09
4C07	7.5E-09
3F05	7.5E-09
2C010	7.6E-09
2B03	7.6E-09
4G08	7.6E-09
1C011	7.6E-09
2A08	7.7E-09
1A04	7.8E-09
3C09	7.8E-09
2H06	7.9E-09
2G09	8.0E-09
2F07	8.0E-09
1B05	8.0E-09
2A01	8.0E-09
3H06	8.0E-09
1E04	8.1E-09
1C04	8.1E-09
3A02	8.1E-09
2A03	8.2E-09
3G01	8.2E-09
4F011	8.2E-09
2D09	8.2E-09
3C05	8.2E-09
4C05	8.3E-09
1C06	8.3E-09
2D05	8.3E-09

Name	KD(M)
1G07	8.3E-09
1H010	8.4E-09
2E09	8.5E-09
1C012	8.5E-09
1A07	8.6E-09
3H010	8.6E-09
4D04	8.6E-09
1B03	8.7E-09
4F09	8.8E-09
4G09	8.8E-09
3G04	8.8E-09
2A05	8.9E-09
2A06	8.9E-09
1F06	8.9E-09
1B07	8.9E-09
4H08	8.9E-09
4A02	9.0E-09
4F08	9.0E-09
4E010	9.0E-09
3H01	9.0E-09
3B011	9.0E-09
4A09	9.0E-09
4E09	9.1E-09
3C02	9.1E-09
2F01	9.2E-09
3A04	9.2E-09
1D012	9.3E-09
1E08	9.4E-09
4A05	9.4E-09
1F01	9.4E-09
2F02	9.6E-09
1D04	9.7E-09
4G05	9.7E-09
4F04	9.8E-09
4A07	9.8E-09
4G010	9.9E-09
4D010	9.9E-09
3H03	9.9E-09
3F06	9.9E-09
1D08	1.0E-08
2B010	1.0E-08
3B01	1.0E-08
3D01	1.0E-08
4A01	1.0E-08
2B01	1.0E-08
3C06	1.0E-08
1H02	1.0E-08

Name	K_D(M)
1G09	1.0E-08
4E06	1.0E-08
2F06	1.0E-08
2A09	1.0E-08
3E09	1.0E-08
1F04	1.0E-08
4B08	1.0E-08
2G04	1.1E-08
4B01	1.1E-08
1B02	1.1E-08
1B04	1.1E-08
2E06	1.1E-08
3E011	1.1E-08
4E01	1.1E-08
3D03	1.1E-08
4E07	1.1E-08
1G04	1.1E-08
3E04	1.1E-08
2B011	1.1E-08
3E02	1.2E-08
3D02	1.2E-08
3A010	1.2E-08
2C01	1.2E-08
3G06	1.2E-08
3B010	1.2E-08
3A03	1.2E-08
3F09	1.2E-08
4B04	1.2E-08
3G08	1.2E-08
3A08	1.2E-08
3B02	1.2E-08
4F03	1.2E-08
1B08	1.2E-08
2G011	1.3E-08
3G07	1.3E-08
4E011	1.3E-08
3H07	1.3E-08
1F07	1.3E-08
4H03	1.3E-08
4A06	1.3E-08
3F03	1.3E-08
3C011	1.4E-08
1D02	1.4E-08
1H06	1.4E-08
2D02	1.4E-08
1E05	1.4E-08
1G05	1.4E-08

Name	K_D(M)
3D010	1.4E-08
3F08	1.4E-08
3H09	1.4E-08
3C01	1.4E-08
3A05	1.5E-08
4F02	1.5E-08
4G02	1.5E-08
3B06	1.5E-08
4C08	1.6E-08
3A06	1.6E-08
3D05	1.6E-08
4H09	1.6E-08
4H07	1.6E-08
3A01	1.6E-08
3E01	1.6E-08
4B06	1.6E-08
1H08	1.7E-08
3G011	1.7E-08
3D08	1.7E-08
2E08	1.7E-08
4H06	1.8E-08
2H08	1.8E-08
4B05	1.8E-08
4G07	1.8E-08
3G02	2.0E-08
3E03	2.0E-08
2F08	2.0E-08
4G03	2.0E-08
3B09	2.0E-08
4H01	2.1E-08
3B04	2.4E-08
4A08	2.4E-08
1C08	2.5E-08
4D03	2.6E-08
1G06	2.6E-08
4D02	3.0E-08
1F08	3.1E-08
3D09	3.2E-08
4A04	3.5E-08
1F09	3.5E-08
4H05	6.4E-08

Table 4: Binding constants for human DLL3 determined using three different concentrations of anti-DLL3 Trispecific proteins and binding constants for cynomolgus DLL3 determine using a single concentration of anti-DLL3 Trispecific proteins

Name	Human K_D (nM)	Cynomolgus K_D (nM)
1H012	2.9	4.3
1A011	3.5	3.6
2E05	3.5	4.8
4H011	3.9	5.7
3C04	4.0	5.7
2E02	4.4	3.4
2H02	4.4	5.2
3A011	7.3	8.8
3A02	7.8	9.5
4D09	8.1	8.2
DH43	8.9	8.5
DH6	9.0	10

Table 5: DMS-153 TDCC values of affinity matured anti-DLL3 Trispecific protein in conditioned medium tested in triplicate using human T cells

Name	EC_{50} (M)
1H012	2.8E-11
2H02	3.1E-11
2E010	3.1E-11
2E05	3.3E-11
2E01	3.3E-11
4H011	3.6E-11
4E02	4.1E-11
4B011	4.8E-11
2F11	4.9E-11
4H04	5.1E-11
1A011	5.1E-11
4D09	5.2E-11
3C04	5.2E-11
2E02	5.9E-11
3D07	6.1E-11
4B07	6.7E-11
4C06	6.8E-11
2A04	8.1E-11
1C03	9.6E-11
3H06	1.2E-10
3H011	1.2E-10
2E011	1.9E-10
DH43	2.0E-10
DH6	3.4E-10

Example 4: Cloning of Select DLL3 Binding Molecules from Example 3 into Mammalian Cells

[00235] Anti-DLL3 trispecific proteins described in **Example 3**, as well as the parental DLL3 binder molecules were subcloned into a CHO cell expression vector and were stably transfected in CHO cells (*see,* , Running Deer and Allison 2004. Biotechnol. Prog. 20: 880-889). The DLL3 binder molecules were: 2E05-M106Q (SEQ ID No. 228); 2C04 (SEQ ID No. 181); 4D09-M34L(SEQ ID No. 366); 4D09 (SEQ ID No. 330); 2E05-M106Y (SEQ ID No. 227); 1H012 (SEQ ID No.162) (also referred to herein as 1H12); 2E05 (SEQ ID No. 199) ; 2H02 (SEQ ID No. 221); 4D011 (SEQ ID No. 332) (also referred to herein as 4D11); 2E02 (SEQ ID No. 198); 4H11-M34L (SEQ ID No. 367); 1A011 (SEQ ID No. 95) (also referred to herein as 1A11); DH6 (SEQ ID No. 75); and DH43 (SEQ ID No. 68). The anti-DLL3 trispecific proteins were purified after expression in CHO cells, in conditioned medium from pools of stable clones, using protein A and ion exchange chromatography. The purified proteins were tested in TDCC assay using the same method as described in **Example 2.** The EC_{50} values from the TDCC assay of the instant example are listed in **Table 6**, and the graphs of the data are in **Figs. 12-15**. The most potent molecule, 2E05-M106Q (SEQ ID No. 228), had an EC_{50} value of 41 nM, which is 6.6 fold more potent than the parental molecule, DH43. The most potent molecule derived from DH6 was 4D09-M34L (SEQ ID No. 366), which had an EC_{50} value of 54 nM and is 4.4 fold more potent than the parental molecule, DH6.

Table 6: TDCC Activity of CHO Expressed and Purified Affinity Matured Anti-DLL3 Trispecific Proteins

Name	EC_{50} (M)
2E05-M106Q	4.10E-11
2C04	4.30E-11
4D09-M34L	5.40E-11
4D09	6.00E-11
2E05-M106Y	6.30E-11
1H12	6.30E-11
2E05	7.20E-11
2H02	9.60E-11
4D11	9.80E-11
2E02	1.20E-10
4H11-M34L	1.30E-10
1A11	1.70E-10
DH6	2.40E-10
DH43	2.70E-10

Example 5: Affinity Maturation to Obtain Anti-DLL3 Binders of Improved Affinity

[00236] To obtain more potent anti-DLL3 binders, a second round of affinity maturation was performed. Phage display libraries were created based on the DH6 (SEQ ID No. 75) and DH58 (SEQ ID No. 74) parental sequences. The sequences for the binders from this round of affinity maturation are provided in SEQ ID Nos. 368 to 442. The CDR1 sequences of DLL3 binders identified in this round of affinity maturation are SEQ ID Nos. 810 to 884, the CDR2 sequences of DLL3 binders identified in this round of affinity maturation are SEQ ID Nos. 1252 to 1326, and the CDR3 sequences of DLL3 binders identified in this round of affinity maturation are SEQ ID Nos. 1692 to 1768. **Table 7** provides CDR variations obtained in the DH6 DLL3 binder sequences after phage display selection.

[00237] The affinity matured anti-DLL3 sequences identified as above were cloned into an expression vector, in an expression construct comprising a signal domain followed by an anti-DLL3 sequence followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by anti-human albumin single domain antibody 10G (SEQ ID No. 1774) followed by a GGGGSGGGS linker (SEQ ID No. 1808) followed by anti-human CD3 antibody 2B2 (SEQ ID No.1793) followed by a HHHHHH tag (SEQ ID No. 1819), to generate anti-DLL3 trispecific constructs.

[00238] The anti-DLL3 trispecific constructs containing the affinity matured anti-DLL3 binding sequences were then transfected into EXPI293™ cells. These anti-DLL3 trispecific constructs were subsequently engineered with a protein A binding site, and the amount of anti-DLL3 trispecific construct in the conditioned media from the transfected EXPI293™ cells was quantitated using an Octet instrument with protein A tips. A control trispecific protein of similar molecular weight as the anti-DLL3 trispecific proteins was used as a standard.

[00239] Using the conditioned medium with known concentrations of the anti-DLL3 trispecific proteins, the relative binding affinities of the anti-DLL3 trispecific proteins toward human DLL3 protein were measured using a method where biotinylated version of human DLL3 protein were expressed as a human IgG1 fusion protein, and the binding affinity measurement was carried out in an Octet instrument with streptavidin tips. The K_D measurements were made using a single 50 nM concentration of anti-DLL3 trispecific protein, which allowed for rank ordering potency. The measured affinities are listed in **Table 8**. All of the tested sequences were found to bind human DLL3, with K_D values ranging from 0.3 nM to 34 nM.

[00240] The conditioned medium was also tested in a T-cell dependent cellular cytotoxicity assay (*see* Nazarian AA, Archibeque IL, Nguyen YH, Wang P, Sinclair AM, Powers DA. 2015. J Biomol Screen. 20:519-27). In this assay, luciferase labelled DMS-153 cells were combined with purified human T cells and a titration of anti-DLL3 trispecific proteins. It was hypothesized that if an anti-DLL3 trispecific protein directed T cells to kill the DLL3-expression DMS-153

cells, then the viability of the DMS-153 cells, as determined by running a luciferase assay at 48 hours after starting the experiment, should decrease. **Fig. 16** illustrates a graph of representative TDCC data for anti-DLL3 trispecific proteins containing the following DLL3 binding domains: 51A02 (SEQ ID No. 409), 51G02 (SEQ ID No. 425), 52B01 (SEQ ID No. 430), 52C04 (SEQ ID No.431), 51A05 (SEQ ID No. 411), 52D04 (SEQ ID No. 432), 51E05 (SEQ ID No. 420), 51H05 (SEQ ID No. 429), and for purified DH43 protein (SEQ ID No. 68), and purified DH6 protein (SEQ ID No. 75). EC_{50} values from the TDCC assay are listed in **Table 9**. The values ranged from 4.2 pM to 1.5 nM. A negative control for the TDCC assays was a trispecific protein targeting GFP (as shown in **Fig. 16**) which did not direct the T cells to kills the DMS-153 cells.

Table 7: Variants in CDR sequences by amino acid position of DH6 and its derivatives

CDR	Amino acid position	CDR Amino acids
CDR1	26	A, D, E, F, G, H, K, L, M, N, Q, R, S, V, W, Y
	27	D, E, H, K, M, P, R, S, T, Y
	28	A, D, G, H, K, N, P, Q, R, S, T, V, Y
	29	K, S, V
	30	A, F, G, H, K, L, M, N, Q, R, S, T, V, W, Y
	31	D, F, H, I, K, L, M, N, Q, R, S, V, Y
	32	L, M
	33	S
	34	I, L, M, S, T, V
	35	A
CDR2	50	G
	51	I, V
	52	S
	53	A, D, E, G, H, I, K, L, N, P, Q, R, S, T, V, Y
	54	A, D, E, G, H, N, R, T
	55	G
	56	H, P, R, S
	57	A, H, I, K, M, N, Q, R, T, V
	58	A, D, G, H, I, L, M, N, S, T, V, Y
	59	Y
	60	A, F, I, L, M, R, S, T, V, Y
	61	A, D, E, G, H, K, L, N, R, S, V
	62	S
	63	V
	64	K
	65	G
CDR3	98	L, Y
	99	D, E, G, H, K, N, Q, R, S, T, V, Y
	100	Q, W
	101	A, D, E, G, H, I, K, L, M, P, R, S, T, V

CDR	Amino acid position	CDR Amino acids
	102	A, D, E, G, N, R, S, T, Y
	103	A, P, R, S
	104	A, D, F, G, H, L, M, N, Q, R, S, T, V, Y
	105	A, G, I, K, P, Q, R, S, T
	106	F, H, Y

Table 8: Binding constants for human DLL3 determined using a single concentration of anti-DLL3 Trispecific proteins

Name	K_D (nM)
53A05	3.1E-10
53A04	4.2E-10
53C04	5.0E-10
52D04	5.0E-10
53B05	6.0E-10
51G10	6.0E-10
52B01	6.1E-10
51H05	6.7E-10
53B06	7.1E-10
54B05	7.6E-10
52C04	8.2E-10
42C03	8.8E-10
51A01	9.2E-10
51E05	9.7E-10
53A09	9.7E-10
51H04	1.0E-09
42A06	1.0E-09
41H03	1.0E-09
51A05	1.1E-09
42E05	1.2E-09
51A02	1.2E-09
42D08	1.3E-09
51G02	1.3E-09

Name	K_D (nM)
42B10	1.3E-09
42G07	1.3E-09
41D01	1.4E-09
51F03	1.4E-09
42D06	1.5E-09
41H04	1.5E-09
51B01	1.6E-09
42C08	1.8E-09
42A03	1.9E-09
42A11	2.0E-09
42H08	2.1E-09
51A03	2.2E-09
42C11	2.3E-09
41C02	2.4E-09
51B11	2.4E-09
51F02	2.4E-09
42H05	2.7E-09
41D02	2.7E-09
42D05	2.7E-09
42E02	2.9E-09
42H11	3.1E-09
42A07	3.2E-09
42C10	3.2E-09
42B06	3.2E-09
42F08	3.2E-09
51D03	3.3E-09
41E02	3.4E-09
42G05	3.4E-09
51E02	3.5E-09
42C01	3.6E-09
42A08	3.6E-09
42E06	3.8E-09

Name	K_D (nM)
42E07	3.9E-09
41G01	4.0E-09
42E01	4.0E-09
41D03	4.8E-09
41E01	5.3E-09
42D07	5.3E-09
42F01	5.5E-09
42C07	6.4E-09
51F04	6.7E-09
51E03	7.2E-09
51C02	7.5E-09
51D01	7.9E-09
41B11	9.9E-09
51B04	1.6E-08
51F01	1.6E-08
42F10	1.7E-08
51G04	2.1E-08
41F07	2.5E-08
41D07	3.4E-08

Table 9: DMS-153 TDCC values of affinity matured anti-DLL3 Trispecific Proteins in conditioned medium tested in triplicate using human T cells

Name	TDCC EC_{50} (M)
52D04	4.2E-12
51H05	5.3E-12
52B01	5.5E-12
54B05	6.2E-12
53C04	6.2E-12
51G10	6.6E-12
51G02	6.8E-12
53B06	7.7E-12

Name	TDCC EC_{50} (M)
52C04	8.2E-12
53A04	8.2E-12
51A02	9.5E-12
51A05	9.6E-12
53A09	9.7E-12
51E05	1.1E-11
51F03	1.1E-11
51H04	1.2E-11
53B05	1.2E-11
53H04	1.3E-11
53A05	1.6E-11
51B01	1.8E-11
42D08	1.9E-11
51A01	1.9E-11
41E02	2.1E-11
41D01	2.3E-11
42C03	2.5E-11
42A03	2.5E-11
42F10	2.5E-11
51B11	2.7E-11
42A07	2.8E-11
42G07	2.8E-11
42A06	2.8E-11
42F08	3.1E-11
42E05	3.4E-11
42C01	3.5E-11
42D05	3.6E-11
41C02	3.6E-11
51D03	3.8E-11
42H05	3.8E-11
51E02	3.8E-11
42C10	3.9E-11
42D06	4.0E-11

Name	TDCC EC_{50} (M)
42H08	4.0E-11
42A11	4.2E-11
41D02	4.4E-11
42A08	4.5E-11
42E02	4.7E-11
41D03	4.8E-11
41G01	5.0E-11
42C11	5.3E-11
51A03	5.4E-11
42G05	5.9E-11
42B10	6.6E-11
42D07	8.5E-11
42F01	8.9E-11
42C08	9.4E-11
42E07	1.0E-10
42E01	1.0E-10
51C02	1.0E-10
42B06	1.1E-10
41E01	1.1E-10
51F04	1.2E-10
51F02	1.2E-10
42C07	1.3E-10
51D01	1.3E-10
42E06	1.8E-10
51F01	5.5E-10
51E03	1.4E-09
51B04	1.5E-09

Example 6: Affinity Maturation to Obtain Anti-DLL3 Binders of Improved Affinity

[00241] Certain anti-DLL3 trispecific proteins containing DLL-3 binding sequences that had the most potent TDCC activity in the assay described in Example 5, and an anti-DLL3 trispecific protein containing the parental DLL3 binder DH6, were subcloned into a CHO cell expression vector and were stably transfected in CHO cells (*see* Running Deer and Allison 2004.

Biotechnol. Prog. 20: 880-889). The DLL3 binding sequences were: DH6 (SEQ ID No. 75); 51A2 (SEQ ID No. 408); 51A5 (SEQ ID No. 411); 51F3 (SEQ ID No. 423); 51G2 (SEQ ID No. 425); 51G10 (SEQ ID No. 427); 51H5 (SEQ ID No. 429); 51X5 (SEQ ID No. 1886); 52B1 (SEQ ID No. 430); 52C4 (SEQ ID No. 431); and 52D4 (SEQ ID No. 432). The trispecific proteins were purified into conditioned medium from pools of stable clones using protein A and ion exchange chromatography. An SDS-PAGE image of the purified proteins is provided in **Fig. 17**.

[00242] The affinity measurements for human and cynomolgus DLL3 were made using 60 nM, 20 nM, 6.67 nM, and 2.22 nM concentrations of biotinylated DLL3 targeting trispecific proteins immobilized on Octet streptavidin tips. The affinities determined from the measurements are listed in **Table 10**. In this experiment, anti-DLL3 trispecific containing DH6, the parental DLL3 binder sequence to the affinity matured DLL3 binder sequences, had K_D values of 13.5 nM for human DLL3 and 11 nM for cynomolgus DLL3. In comparison, the ten anti-DLL3 trispecific proteins containing the affinity matured DLL3 binder molecules tested in this experiment had K_D values ranging from 0.9 to 2.2 nM for human DLL3 and 1.4 to 3.4 nM for cynomolgus DLL3. Thus, the improvements in affinity range from 6.1 to 15 fold for human DLL3 and from 3.2 to 7.9 fold for cynomolgus DLL3.

[00243] The purified proteins were tested in TDCC assays, using the same method as described in **Example 2** except that two additional DLL3 expressing cell lines were included in the assay, DMS-53 and NCI-H510A. The EC_{50} values from these TDCC assays are listed in **Table 11**, and the graphs of the DMS-53 and DMS-153 TDCC data are provided, respectively, in **Figs. 18-19**. A trispecific molecule targeting GFP had no activity in these assays (as shown in **Figs. 18-19**). Compared to the parental molecule DH6, the EC_{50} values improved 2.3 to 12.1 fold in DMS-153 cells, 4.5 to 31.5 fold in NCI-H510A cells, and 8.1 to 26.1 fold in DMS-153 cells.

Table 10: Affinities of purified CHO expressed affinity matured anti-DLL3 trispecific proteins for human and cynomolgus DLL3 protein in vitro

Name	huDLL3 K_D (nM)	cyDLL3 K_D (nM)
DH6	13.5	11.0
51A2	1.2	2.0
51A5	1.2	1.6
51F3	1.4	2.0
51G2	2.0	3.4

Name	huDLL3 K_D (nM)	cyDLL3 K_D (nM)
51G10	0.9	1.4
51H5	0.9	1.6
51X5	1.0	1.5
52B1	1.1	1.9
52C4	2.2	3.0
52D4	0.9	1.7

Table 11: TDCC Activity of purified CHO expressed affinity matured anti-DLL3 trispecific proteins with DMS153, NCI-H510A, and DMS53 cell lines and human T cells

Name	DMS153 EC_{50} (pM)	NCI-H510A EC_{50} (pM)	DMS53 EC_{50} (pM)
51A2	16.7	9.1	9.8
51G2	37.7	3.7	15.9
51G10	11.0	2.3	9.6
51H5	6.0	2.4	5.4
51X5	9.0	2.8	8.3
52B1	9.1	1.3	6.5
52C4	17.9	2.0	15.9
52D4	7.2	2.5	4.9

Example 7: T Cell Dependent Cellular Cytotoxicity Assay using Exemplary DLL3 Targeting Trispecific Proteins comprising a DLL3 Binding Protein of this Disclosure

[00244] Several exemplary DLL3 trispecific proteins containing a DLL3 binding domain of this disclosure, 52D04 (SEQ ID NO. 432), were tested in a T cell dependent cellular cytotoxicity (TDCC) assay (*see*Nazarian AA, Archibeque IL, Nguyen YH, Wang P, Sinclair AM, Powers DA. 2015. J Biomol Screen. 20:519-27), the results are shown in Figs. **22-24**. The trispecific proteins contained a DLL3 binding domain, an albumin binding domain (anti-ALB), and a CD3 binding domain (anti-CD3), in an anti-DLL3:anti-ALB:anti-CD3 configuration (TAC), as shown in **Fig. 20**, or in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, as shown in **Fig. 21**. The TDCC assay was carried out in the presence or absence of 15 mg/ml human serum albumin

(HSA). In this assay, luciferase labelled NCI-H2171 (**Fig. 22**), DMS-79 (**Fig. 23**), SHP77 (**Fig. 24**), or WM2664 (**Fig. 25**) cells were combined with purified human T cells and a titration of the exemplary DLL3 binding trispecific proteins, in the presence or absence of albumin. It was hypothesized that if an DLL3 binding trispecific protein directed T cells to kill the DLL3-expression NCI-H2171, DMS-79, SHP77, or WM2664 cells, then the viability of those cells, as determined by running a luciferase assay at 48 hours after starting the experiment, should decrease. **Fig. 22** illustrates a graph of representative TDCC data, using NCI-H2171 cells, for the DLL3 binding trispecific proteins in the TAC or CAT configurations, containing the following DLL3 binding domains. **Fig. 23** illustrates a graph of representative TDCC data, using DMS-79 cells, for the DLL3 binding trispecific proteins in the TAC or CAT configurations, containing the following DLL3 binding domains. **Fig. 24** illustrates a graph of representative TDCC data, using SHP77 cells, for the DLL3 binding trispecific proteins in the TAC or CAT configurations, containing the following DLL3 binding domains. **Fig. 25** illustrates a graph of representative TDCC data, using WM2664 cells, for the DLL3 binding trispecific proteins in the TAC or CAT configurations, containing the following DLL3 binding domains. EC_{50} values from the TDCC assay are listed in **Table 12**. As shown in the graphs and indicated by the EC_{50} values, in the presence of human serum albumin (HSA) the DLL3 binding trispecific proteins having the CAT orientation (**Fig. 21**) were more potent in the TDCC assays than the DLL3 binding trispecific proteins having the TAC configuration.

Table 12: TDCC Activity of exemplary anti-DLL3 trispecific proteins with NCI-H2171, DMS-79, SHP77, and cell lines and human T cells

Cell Line		EC_{50} (pM) no HSA	EC_{50} (pM) with HSA
NCI-H2171	αDLL3:αALB:αCD3	3	224
	αCD3:αALB:αDLL3	2	84
DMS-79	αDLL3:αALB:αCD3	1.1	115
	αCD3:αALB:αDLL3	0.7	41
SHP77	αDLL3:αALB:αCD3	21*	3953
	αCD3:αALB:αDLL3	11*	821
WM2664	αDLL3:αALB:αCD3	9*	855
	αCD3:αALB:αDLL3	10*	422
* 15 mg/ml bovine serum albumin (BSA) was included in these no HSA assays; the αALB domain did not bind BSA (data not shown)			

Example 8: Binding of exemplary DLL3 targeting trispecific proteins to human T cells

[00245] In a cell binding study, human T cells were incubated in the presence or absence of an exemplary DLL3 targeting trispecific protein (in either anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration (SEQ ID No. 1891; or anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration (SEQ ID No. 1890). The human T cells were further incubated with a secondary antibody (anti-trispecific antibody), which is able to recognize the anti-albumin domain in the exemplary trispecific molecules, conjugated to Alexa Fluor 647. Binding of the anti-trispecific antibody was measured by flow cytometry. Robust binding of anti-trispecific antibody was seen in the presence of the exemplary DLL3 trispecific protein in the anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration (right peaks in the plots in **Fig. 26**) compared to cells incubated with secondary antibody alone or cells incubated without exemplary trispecific proteins or secondary antibody (left peaks in the plots in **Fig. 26**). Robust binding of anti-trispecific antibody was also seen in the presence of the exemplary DLL3 trispecific protein in the anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration (right peaks in the plots in **Fig. 27**) compared to cells incubated with secondary antibody alone or cells incubated without exemplary trispecific proteins or secondary antibody (left peaks in the plots in **Fig. 27**).

Example 9: Binding of exemplary DLL3 targeting trispecific proteins to DLL3 expressing cancer cell lines

[00246] In another binding study, DLL3 expressing cancer cells [NCI-H82 (lung cancer cell line), SHP77 (lung cancer cell line), DMS53 (lung carcinoma), or NCI-H2171 (lung cancer cell line)] were incubated with exemplary DLL3 targeting trispecific molecules (in CAT or TAC configuration; SEQ ID No. 1890 and SEQ ID No. 1891) or a control trispecific molecule that targets GFP. Following incubation, the cells were washed to remove unbound trispecific molecules and further incubated with a secondary antibody, which is able to recognize the anti-albumin domain in the trispecific molecules, conjugated to Alexa Fluor 647 or FITC. Binding of the exemplary DLL3 targeting trispecific molecules or that of the control trispecific molecules to the cells was measured by flow cytometry. Robust binding of DLL3 targeting trispecific (in TAC configuration) to each cell line was observed (right peaks in the plots in **Fig. 28**) compared to cells incubated with a control trispecific molecule targeting GFP (left peaks in the plots in **Fig. 28**). Robust binding of DLL3 targeting trispecific (in CAT configuration) to each cell line was also observed (right peaks in the plots in **Fig. 29**) compared to cells incubated with a control trispecific molecule targeting GFP (left peaks in the plots in **Fig. 29**). In control experiments with cell lines that lack DLL3 expression, HCTI16 (colon cancer cell line) and NCI-H292 (lung cancer cell line), similar amount of anti-trispecific antibody were bound to cells incubated with

the exemplary DLL3 targeting trispecific proteins or GFP-targeting control trispecific molecules (*data not shown*), indicating the exemplary DLL3-targting trispecific molecules did not bind to cells lacking DLL3 expression.

Example 10: Ability of exemplary DLL3 targeting trispecific proteins to direct T cell mediated killing of DLL3 expressing cancer cell lines

[00247] The aim of this study was to assess if exemplary DLL3 targeting trispecific molecules were able to direct T cells to kill the DLL3-expressing cell lines NCI-H82, SHP77, DMS53, and NCI-H2171. The DLL3-expressing cells used in this study were engineered to express luciferase.

[00248] For the TDCC assay (T cell dependent cellular cytotoxicity assay) T cells from four healthy donors (donor 2; donor 47; donor 81; donor 86) and the DLL3-expressing cells were mixed and varying amounts of exemplary DLL3 targeting trispecific proteins (in CAT or TAC configurations; SEQ ID No. 1890 and SEQ ID No. 1891) was added to the mixture. The mixture was incubated for 48 hours at 37 °C. As a control, parallel experiments were performed using a control trispecific molecule targeting GFP. After 48 hours, the remaining viable DLL3-expressing cells were quantified using a luminescence assay. It was observed that the DLL3-targeting trispecific molecules (in both TAC and CAT configurations) were able to efficiently direct T cells from all four healthy donors to kill all four DLL3 expressing cell lines (*see* **Figs. 30, 31, 32, and 33** for results using the TAC configuration; *see* **Figs. 34, 35, 36, and 37** for results using the CAT configuration**)** whereas the control GFP TriTAC molecule was not able to do that (also shown in **Figs. 30-37**). The EC_{50} values are presented in **Table 13 and Table 14.** Further TDCC assays were carried out with DLL3-targeting TriTAC and cell lines that lack DLL3 expression, NCI-H292 and HCT116. It was observed that the DLL3-targeting TriTAC was not able to direct T cells to kill these two cell lines lack DLL3 expression (*data not shown*).

Table 13: EC_{50} values for TDCC assays performed using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-DLL3:anti-ALB:anti-CD3 (TAC) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

	EC_{50} (M)			
Cell Line	**Donor 02**	**Donor 47**	**Donor 81**	**Donor 86**
NCI-H82	3.6E-11	3.3E-11	8.0E-11	1.4E-10
SHP77	2.7E-10	1.4E-10	3.8E-10	7.0E-10
DMS53	2.3E-10	2.8E-10	2.8E-10	7.7E-10
NCI-2171	4.0E-10	2.4E-10	7.5E-10	1.0E-09

Table 14: EC_{50} values for TDCC assays performed using exemplary DLL3 targeting trispecific proteins containing DLL3 binding domain of this disclosure, 52D04, in an anti-CD3:anti-ALB:anti-DLL3 (CAT) configuration, tested in the presence of human serum albumin (HSA), using T cells from four different donors.

	EC_{50} (M)			
Cell Line	**Donor 02**	**Donor 47**	**Donor 81**	**Donor 86**
NCI-H82	2.0E-11	1.6E-11	4.5E-11	5.9E-11
SHP77	6.3E-11	3.6E-11	8.4E-11	1.9E-10
DMS53	7.0E-11	7.2E-11	8.0E-11	2.2E-10
NCI-2171	1.6E-10	7.6E-11	2.9E-10	3.2E-10

Example 11: DLL3 dependent activation of T cells by exemplary DLL3 targeting trispecific proteins

[00249] In this assay, T cells from 4 different healthy donors (donor 2; donor 35; donor 47; and donor 86) and NCI-H82 or DMS53 cells were incubated with exemplary DLL3 targeting trispecific proteins (in CAT or TAC configurations; SEQ ID No. 1890 and SEQ ID No. 1891) for 48 hours at 37 °C. T cells from the same donors were also incubated for 48 hours at 37 °C with a control trispecific molecule, GFP TriTAC, which targets GFP and NCI-H82 or DMS53 cells. After 48 hours, T cells were collected, and CD69 and CD25 expression on the T cells was measured by flow cytometry. Increased CD69 or CD25 expression was detected on T cells from all 4 healthy donors in presence of NCI-H82 or SHP77 cells and DLL3 targeting trispecific molecules but not in presence of the negative control GFP TriTAC, as seen in **Figs. 38-45**. A parallel experiment was performed with HCT116 cells, which lack DLL3 expression. No increase CD69 or CD25 expression was observed with DLL3 trispecific molecules tested using HCT116 cells (*data not shown*).

Example 12: DLL3 dependent cytokine production by T cells induced by exemplary DLL3 targeting trispecific proteins

[00250] In this assay, T cells from a healthy donor and NCI-H82 or SHP77 cells were incubated with exemplary DLL3 targeting trispecific molecules (in CAT or TAC configuration; SEQ ID No. 1890 and SEQ ID No. 1891) for 48 hours at 37 °C. T cells from the same donor were also incubated for 48 hours at 37 °C with a control trispecific molecule, GFP TriTAC, which targets GFP and NCI-H82 or DMS53 cells. After 48 hours, conditioned media were collected, and the amount of various cytokines present in the conditioned media were measured using an electrochemiluminscent assay (Meso Scale Discovery). It was observed that IFNγ, IL-2, and TNFα were secreted into the medium in presence of NCI-H82 or SHP77 cells and DLL3 targeting trispecific molecules but not in presence the control GFP-targeting TriTAC molecule.

For the DLL3 targeting trispecific molecule in TAC configuration: IFNγ production is shown in **Figs. 46** and **47**; IL-2 production is shown in **Figs. 48** and **49**; TNFα production is shown in **Figs. 50** and **51**. For the DLL3 targeting trispecific molecule in CAT configuration: IFNγ production is shown in **Figs. 52** and **53**; IL-2 production is shown in **Figs. 54** and **55**; TNFα production is shown in **Figs. 56** and **57.**

Example 13: Inhibition of growth of NCI-H82 xenografts by exemplary DLL3 targeting trispecific proteins

[00251] For this study, 5 x 10^6 human T cells and 5 x 10^6 NCI-H82 small cell lung cancer cells were injected into mice at day 0. On days 1 to 10, mice were injected daily intraperitoneally (i.p.) with exemplary DLL3 targeting trispecific molecules (in CAT or TAC configurations; SEQ ID No. 1890 and SEQ ID No. 1891) at doses of 20, 100, or 500 μg/kg or negative control GFP-targeting TriTAC at a dose of 500 μg/kg. Tumor volumes were measured after every few days starting at day 7 and ending on day 24. Significant inhibition of tumor growth was observed in the mice injected with the DLL3-targeting trispecific proteins at all doses compared to mice dosed with the GFP-targeting TriTAC dosed at 500 μg/kg, as shown in **Fig. 58.**

Example 14: Elimination NCI-H82 xenografts by exemplary DLL3 targeting trispecific proteins

[00252] For this study, 5 x 10^6 NCI-H82 small cell lung cancer cells were injected subcutaneously on day 0. Mice were randomized on day 8, and 2 x 10^7 human T cells were injected per mouse. On days 9 to 18, mice were injected daily i.p. with the exemplary DLL3 targeting trispecific molecules (in CAT configuration; SEQ ID No. 1890) at doses of 1, 10, or 100 μg/kg or negative control GFP-targeting TriTAC at a dose of 100 μg/kg. Tumor volumes were measured after every few days starting at day 8 and ending at day 29. Significant inhibition of tumor growth was observed in the mice injected with DLL3 targeting trispecific molecules at doses of 10 and 100 μg/kg compared to mice dosed with the GFP targeting TriTAC dosed at 100 μg/kg, as shown in **Fig. 59**.

Example 15: Inhibition of growth of SHP77 xenografts by exemplary DLL3 targeting trispecific proteins

[00253] For this study, 5 x 10^6 human T cells and 1 x 10^7 SHP77 small cell lung cancer cells were injected into mice at day 0. On days 1 to 10, mice were injected daily i.p. with DLL3 targeting trispecific molecules (in CAT configuration; SEQ ID No. 1890) at doses of 1, 10, or 100 μg/kg or negative control GFP-targeting TriTAC at a dose of 100 μg/kg. Tumor volumes were measured after every few days starting at day 6 and ending on day 28. Significant

inhibition of tumor growth was observed in the mice injected with DLL3-targeting trispecific molecules at doses of 10 and 100 µg/kg compared to mice dosed with the GFP-targeting TriTAC dosed at 100 µg/kg, as shown in **Fig. 60.**

Example 16: Pharmacokinetic profile of exemplary DLL3 targeting trispecific proteins

[00254] *DLL3-targeting trispecific proteins have a half-life of ~ 3 to ~3.9 days in cynomolgus monkeys when dosed at 0.3 mg/kg*

[00255] For this study, cynomolgus monkeys were injected with 0.3 mg/kg doses of exemplary DLL3-targeting trispecific molecules (in CAT or TAC configurations; SEQ ID No. 1890 and SEQ ID No. 1891), intravenously, and serum samples were collected at various time points after the injection. Two monkeys were injected for each dose. The amount of DLL3 targeting trispecific molecule in the serum was measured using anti-idiotype antibodies recognizing the trispecific molecule, in an electrochemiluminescient assay. **Fig. 61** shows a plot for the serum DLL3 targeting trispecific molecule levels at various time points. The data was then used to calculate the pharmacokinetic properties of the DLL3 targeting trispecific molecules, as provided in **Table 15**. Human dosing schedule of once or twice a week is contemplated based on the pharmacokinetic data.

Table 15: Pharmacokinetics of exemplary DLL3 targeting trispecific molecules

ID	Half life (h)	AUC 0-inf (h*nM)	CL (L/h/kg)	Vss (l/kg)
1	93.1	7210	0.000832	0.0869
2	72.4	6690	0.000896	0.0731
3	82.6	7900	0.00076	0.0767
4	77	7890	0.00076	0.0712

[00256] *DLL3 targeting trispecific protein has a half-life of ~ 2.8 to ~3.3 days in cynomolgus monkeys when dosed at 1 or 10 mg/kg:*

[00257] For this study, cynomolgus monkeys were injected with 1 mg/kg or 10 mg/kg dose of exemplary DLL3 targeting trispecific molecules, intravenously, and serum samples were collected at various time points after the injection. Two monkeys were injected for each dose. The amount of DLL3-targeting TriTAC in the serum was measured using anti-idiotype antibodies recognizing the TriTAC molecule, in an electrochemiluminescient assay. **Fig. 62** shows a plot for the serum DLL3 targeting trispecific molecule levels at various time points. The data was then used to calculate the pharmacokinetic properties of the TriTAC molecule, as

provided in **Table 16**. The pharmacokinetic data suggest that once or twice weekly dosing in humans.

Table 16: Pharmacokinetics of exemplary DLL3 targeting trispecific molecules

Dose (mg/kg)	Half life (h)	C_{max} (nM)	AUC 0-inf (h*nM)	CL (mL/h/kg)	Vss (l/kg)
1	67.5	493	23,800	0.79	63.8
10	78.6	4,492	236,500	0.80	71.9

[00258] *Exemplary DLL3 targeting trispecific proteins were tolerated in cynomolgus monkeys when given as a single dose up to 10 mg/kg:*

[00259] A transient increase in serum cytokine levels were observed, mainly at 10 mg/kg dosage of administration of exemplary DLL3 targeting trispecific protein (in CAT configuration) (**Fig. 63; IFNγ-Fig. 63** top panel, **IL-6** Fig. 63 second panel**; IL-10** Fig. 63 third panel). Transient T cell margination and T cell activation were also observed (*data not shown*). At terminal and recovery euthanasia, no DLL3 trispecific protein-related macroscopic findings or organ weight differences were observed, and at recovery euthanasia, no DLL3 trispecific protein -related microscopic findings were observed.

[00260] To demonstrate the DLL3-targeting TriTAC retained cell directed killing activity after being administered to a cynomolgus monkey, a serum sample form the 10 mg/kg dose group collected at 168 h after dosing was tested in a DMS53 TDCC assay and was compared to DLL3-targeting TriTAC that was freshly thawed. Identical cell DMS53 cell killing was observed with the serum sample and the freshly thawed protein (**Fig. 64**), indicating the DLL3-targeting TriTAC retains the ability to direct T cells to kill target cells 1 week after being dosed in a cynomolgus monkey.

Example 17: Xenograft Tumor Model

[00261] An exemplary anti-DLL3 targeting trispecific protein of this disclosure is evaluated in a xenograft model.

[00262] Female immune-deficient NOD/scid mice are sub-lethally irradiated (2 Gy) and subcutaneously inoculated with 1x 10^6 NCI-H28 cells into their right dorsal flank. When tumors reach 100 to 200 mm^3, animals are allocated into 3 treatment groups. Groups 2 and 3 (8 animals each) are intraperitoneally injected with 1.5x10^7 activated human T-cells. Three days later, animals from Group 3 are subsequently treated with a total of 9 intravenous doses of exemplary

DLL3 trispecific antigen-binding protein (such as 1, 10, 50, or 100 μg/kg) (qdx9d). Groups 1 and 2 are only treated with vehicle. Body weight and tumor volume are determined for 30 days.

[00263] It is expected that animals treated with the exemplary DLL3 targeting trispecific proteins of the previous examples have a statistically significant delay in tumor growth in comparison to the respective vehicle-treated control group.

Example 18: Proof-of-Concept clinical trial protocol for administration of an exemplary DLL3 trispecific antigen-binding protein (anti-DLL3 Trispecific Protein) to neuroendocrine cancer patients

[00264] This is a Phase I/II clinical trial for studying an exemplaryDLL3 trispecific antigen-binding protein as a treatment for a Neuroendocrine Cancer.

[00265] Study Outcomes:

[00266] *Primary*: Maximum tolerated dose of the exemplary DLL3 targeting trispecific protein

[00267] *Secondary*: To determine whether *in vitro* response of the exemplary DLL3 targeting trispecific proteins are associated with clinical response

[00268] Phase I

[00269] The maximum tolerated dose (MTD) will be determined in the phase I section of the trial.

1.1 The maximum tolerated dose (MTD) will be determined in the phase I section of the trial.

1.2 Patients who fulfill eligibility criteria will be entered into the trial to evaluate the exemplaryDLL3 targeting trispecific protein.

1.3 The goal is to identify the highest dose of the exemplary anti-DLL3 trispecific protein that can be administered safely without severe or unmanageable side effects in participants. The dose given will depend on the number of participants who have been enrolled in the study prior and how well the dose was tolerated. Not all participants will receive the same dose.

[00270] Phase II

2.1 A subsequent phase II section will be treated at the MTD with a goal of determining if therapy with therapy of the exemplary DLL3 targeting trispecific proteins results in at least a 20% response rate.

Primary Outcome for the Phase II ---To determine if therapy with the exemplary DLL3 targeting trispecific protein trispecific protein results in at least 20% of patients achieving a clinical response (blast response, minor response, partial response, or complete response)

[00271] Eligibility: Biopsy proven neuroendocrine tumor, which is somatostatin receptor positive as demonstrated on somatostatin receptor PET.

[00272] All sites or origin are eligible.

[00273] Functional and nonfunctional tumors are allowed.

[00274] Not a candidate for surgical debulking.

[00275] ECOG performance status 0, 1 or 2

[00276] Age > 18.

[00277] Ability to understand a written informed consent document, and the willingness to sign it.

Example 19: DLL3 trispecific antigen-binding protein Phase 1/2a dose escalation, expansion, safety and pharmacokinetics study

[00278] Target population: Patients with small cell lung cancer (SCLC) relapsed after platinum chemotherapy, or other malignancies with high grade neuroendocrine features relapsed/refractory (R/R) to Standard of Care (SOC) or no SOC available (includes neuroendocrine prostate cancer (NEPC) and other neuroendocrine neoplasms (NENs)).

[00279] Trial Objectives: Assess safety and tolerability at increasing dose levels, determine PK and pharmacodynamic data and evaluate preliminary anti-tumor activity.

[00280] Trial Design: DLL3 trispecific antigen-binding protein Phase 1/2a trial design is shown in **Fig. 65.** Trial objectives are assessing safety and tolerability at increasing dose levels, determining pK and pharmacodynamic data and evaluating preliminary anti-tumor activity

[00281] Dosing and administration: DLL3 trispecific antigen-binding protein (SEQ ID NO: 1890) was administered once weekly through infusion starting at 15 μg (flat dose), which corresponds to the EC50. One cycle is 21 days with three doses. Patients received premedication with dexamethasone, Tylenol, and histamine receptor blockers at initial dose(s). **Table 17** shows the dosing cohorts and number of subjects. The once weekly administration was tolerated and no dose-limiting toxicity (DLT) is observed to date. **Table 18** shows the baseline demographics of these patients. Medium number of prior systemic therapies is 2 and range is 1-5. 77.8% of the patients had prior exposure to an immune checkpoint inhibitor, which includes 100% of SCLC patients).

Table 17: DLL3 trispecific antigen-binding protein dosing cohorts

Cohort	Dose μg	N
Fixed Dose, Single Patient Dose Escalation Cohorts (includes backfill patients)		
1	15	1
2	45	1
3	135	1
4	405	3

5	1215	4
6	3600	1
Step Dosing 3+3 Dose Escalation Cohorts		
7	3600 → 7200	4
8	2000 →12000	3
Total		18

Table 18: Patient baseline demographics

Baseline Characteristic	All Patients (N = 18)
Median age, years (range)	61 (43-73)
Race White Asian	N (%) 17 (94.4%) 1 (5.6%)
ECOG performance status 0 1	N (%) 9 (50%) 9 (50%)
Disease: Small Cell Lung Cancer, n (%) Neuroendocrine Prostate Cancer, n (%) Other Neuroendocrine Tumor (NENs)*, n (%)	 11 (61.1%) 2 (11.1%) 5 (27.8%)
Prior lines of therapy: 1 2 3 4 5	 5 (27.8%) 5 (27.8%) 3 (16.7%) 3 (16.7%) 2 (11.1%)
Immune checkpoint inhibitor (αPD-1/αCTLA4, αPD-L1)	14 (77.8%)

*Other NENs: Retroperitoneal (unknown primary), Colon, Pancreas, Thymic, Bladder

[00282] Time on Treatment: the median treatment duration is 11.6 weeks, which ranges from 4.1 to 41.4 weeks. 6 out of the 10 patients (33%) is on treatment for over 20 weeks. **Fig. 66** demonstrates the patient time on treatment, dose per week, and number of prior treatments.

[00283] Safety and Tolerability: There is no Dose Limiting Toxicities (DLTs) observed. Grade 1-2 CRS were reported in [4 (22%)] of patients, and there is no Grade ≥3 CRS reported. There is no immune effector cell-associated neurotoxicity syndrome (ICANS) reported. No patients were discontinued due to adverse events.

Table 19. Treatment Emergent Adverse Events (TEAEs) by Grade [a]

Adverse Events	All Grades, n (%)	Grade ≥3, n (%)
Any treatment-emergent AE	18 (100%)	10 (55.6%)
Any treatment-related AE	15 (83.3%)	1 (5.6%)

Treatment-Emergent AEs in ≥15% of subjects (MedDRA preferred term)		
Dysgeusia	7 (38.9%)	-
Fatigue	7 (38.9%)	-
Hypotension	7 (38.9%)	1 (5.6%)
Constipation	6 (33.3%)	-
Hyponatraemia	6 (33.3%)	1 (5.6%)
Nausea	6 (33.3%)	-
Vomiting	6 (33.3%)	-
Anaemia	5 (27.8%)	2 (11.1%)
Chills	5 (27.8%)	-
Pyrexia	5 (27.8%)	-
Alanine aminotransferase increased	4 (22.2%)	1 (5.6%)
Aspartate aminotransferase increased	4 (22.2%)	1 (5.6%)
Cytokine release syndrome	4 (22.2%)	-
Diarrhoea	3 (16.7%)	-
Dry skin	3 (16.7%)	-
Dyspnoea	3 (16.7%)	-
Headache	3 (16.7%)	-
Neutrophil count decreased / Neutropenia	3 (16.7%)	2 (11.1%)
Weight decreased	3 (16.7%)	-

[a] Grading per CTCAE v1.0, except Cytokine Release Syndrome (Grading per ASTCT 2019)

[00284] Target Lesion Response: 7 out of 18 patients (38.9%) had any decrease in sum of target lesion diameters, including 5 with SCLC, 1 with NEPC and 1 with NEN [thymic atypical carcinoid]). 1 patient with SCLC, 2L had confirmed partial response and is ongoing treatment at 32 weeks. For patients with SCLC, 3 of 11 (27.3%) across all doses had >30% decrease in sum of target lesion diameters. 6 out of 18 patients (33%) showed best overall response of stable disease, including 1 with SCLC, 1 with NEPC, and 1 with NEN.

[00285] Fig. 67 shows maximum percent target lesion response from baseline in each cohort.

[00286] Patient 102 Profile: Patient 102 is a 71-year-old female, who was diagnosed in September 2020 with SCLC. Treatment was initiated at 45ng/kg, and demonstrated 38% reduction at Week 9, unconfirmed partial response (PR) (**Fig. 68**). Patent 102 does not have treatment-related adverse effects (AEs) observed to-date and remains on study beyond 9 weeks of treatment.

Table 20: Patient 102 baseline Characteristics

Stage	IV	Prior Therapies	(1) Cisplatin + Etoposide + Durvalumab (2) Brain irradiation
ECOG	1	Response to Most Recent Prior Systemic Therapy	Progressive Disease
Location of Metastases	Target Lesion: Lymph Node Non-Target Lesions: Lung, Adrenal, Lymph Nodes	Time on Most Recent Prior Systemic Therapy	6.9 Weeks

[00287] Fig. 69 illustrates the pharmacokinetic data of the DLL3 trispecific antigen-binding protein for the different dosing cohorts. About 70 hours of half-life extension and increased serum Cmax with dose escalation were observed.

[00288] Fig. 70 demonstrates the result of a flow analysis. **Fig. 70A** demonstrates the T cell margination level after treatment. It shows that there is dose-dependent and transient peripheral T-cell margination. **Fig. 70B** demonstrates the activation marker induction after treatment. T cell activation observed in 135 µg/week cohort, which supports *in vivo* T cell activation.

[00289] Patient 111 Profile: Patient 111, a 61-year-old female who was diagnosed in January 2021 with extensive SCLC. Selected target lesion (TL) metastases are one in the lung, two in the liver, and two in the lymph nodes. Non-target lesion (non-TL) metastases are two in the lung two in the liver. Prior systemic treatment includes carboplatin etoposide and atezolizumab for 20.1 weeks. Upon study entry, stable disease was the best response to most recent prior systemic treatment. Treatment was initiated at 1215 µg/week and increased dose to 3600 µg/week starting C3D15 (week 8), later dose escalated to 7000 µg/week. Partial response (PR) was confirmed at week 10 with 53.3% decrease in sum of target lesion diameters, and the patient remains on treatment beyond 32 weeks.

Table 21: Patient 111 baseline Characteristics

Lesions	TLs: Lung, Liver x2, Lymph Nodes x2 Non-TLs: Lung x2, Liver	Time on most recent prior treatment	20.1 weeks
Prior Systemic Treatments	1) Carboplatin + Etoposide + Atezolizumab	Best response to most recent prior treatment	Stable Disease

[00290] Fig. 71A demonstrates the target lesion change over time for patient 111. **Fig. 71B** CT scans illustrate the reduction in sum of target lesion diameters for patient 111. The target lesion diameters were reduced 38.1% at week 6 post-treatment and were reduced 53.3% at week 10 post-treatment.

[00291] Patient 112 Profile: Patient 112, a 67-year-old male who was diagnosed in April 2020 with extensive SCLC. The TL metastases are two in the liver and two in the lymph nodes. The non-TLs are in liver, lymph nodes, spleen, bone and brain. Prior systemic treatment includes carboplatin, etoposide, and toripalimab (anti-PD1) for 4 cycles in a clinical trial, cisplatin and etoposide for 2 cycles, and Lurbinectedin. Time on most recent prior systemic treatment is 10.9 weeks. Upon study entry, partial response was the best response to most recent prior systemic treatment. Patient 112 received step dose (3.600 μg/week followed by 7,200 μg/week) treatment. At week 9, 27% reduction in sum of target lesion diameters was observed which are primarily in lymph nodes and the liver metastases are stable, symptoms are improved and the patient remains on treatment beyond 10 weeks. At week 27, 64.6% decrease from baseline sum of target lesion diameters was observed and Patient 112 remains on treatment beyond 28 weeks.

Table 22: Patient 112 baseline Characteristics

Lesions	TLs: Liver x2, Lymph Nodes x2 Non-TLs: Liver, LN x2, Spleen, Bone, Brain	Time on most recent prior treatment	10.9 weeks
Prior Systemic Treatments	1) Carboplatin + Etoposide + Toripalimab 2) Cisplatin + Etoposide 3) Lurbinectedin	Best response to most recent prior treatment	Partial Response

[00292] Fig. 72A demonstrates the target lesion change over time for patient 112. **Fig. 72B** CT scans illustrate the reduction in sum of target lesion diameters for patient 112.

[00293] Patient 113 Profile: Patient 113, a 65-year-old male who was diagnosed in Nov. 2020 with neuroendocrine prostate cancer. The TL metastases are two in the lungs, one in the liver, and two in the lymph nodes. Non-TLs are in the lung, liver, lymph nodes, and prostate. Prior systemic treatment includes cisplatin and etoposide, and CAV. Time on most recent prior systemic treatment is 4 weeks. Upon study entry, progressive disease was the best response to most recent prior systemic treatment. Patient 113 received step dose (3600 μg/week followed by 7200 μg/week) treatment. At week 9, 15.3% reduction in sum of target lesion diameters was observed with shrinkage in lung lesions and prostate, new lesions identified in liver, with quality of life is improvement with significant decrease in urinary symptoms and pain, and the patient remains on study beyond 10 weeks. **Fig. 73** demonstrates the target lesion change over time for patient 113.

[00294] Pharmacokinetics. The DLL3 trispecific antigen-binding protein used in this study exhibited linear PK, with dose-proportional increases in exposures at 0.135 to 12 mg, and the median half-life is 71 hours.

[00295] Fig. 74 shows the concentration-time profile (**Fig.74A**) and Cmax by dose (**Fig.74B**).

[00296] Pharmacodynamics. T-cell margination was observed and is consistent with target engagement. Small, transient increases in serum IL-6 and MCP-1 were observed up to 24 hours post dose. "First dose" effect observed with less margination and lower median IL-6 and MCP-1 concentrations with repeat or target dose.

[00297] Fig. 75 shows T-cell margination (CD8+, **Fig. 75C**) and peripheral IL-6 (**Fig. 75A**) and MCP-1 (**Fig. 75B**) concentrations after first and repeat or target dose.

[00298] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

SEQ. ID NO.	name	sequence
1	DL1	QVQLQESGGGLVQAGGSLRLSCAASGSIFSIASMGWYRQAPGKQRELVAVITSFSSTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTGVYYCNARYFERTDWGQGTQVTVSS
2	DL74	QVQLQESGGGLVQAGGSLRLSCAAPGSIFSIASMGWYRQAPGKQRELVAVITSFSSTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTGVYYCNARYFERTDWGQGTQVTVSS
3	DL31	QVQLQESGGGLVQAGGSLRLSCAASGSIFSIASMAWYRQAPGKQRELVAAITSFSSTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTGVYYCNARYFERTDWGQGTQVTVSS
4	DL3	QVQLQESGGGLVQAGGSLRLSCAASESIFSINVMAWHRQAPGKQRELVARITSGGSTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTGVYYCGAYQGLYAYWGQGTQVTVSS
5	DL80	QVQLQESGGGLVQAGGSLRLSCVASGSSFSITSMAWYRQAPGKQRDLVAAITSFGSTNYAD SVKDRFTISRDNAKNTVYLQMNSLKPEDTAVYYCNGRVFDHVYWGQGTQVTVSS
6	DL18	QVQLQESGGGLVQAGGSLKLSCAASSSIFSISSMSWYRQAPGKQRELVAAITTFDYTNYAD SVKGRFTISRDNAKNMMYLQMNSLKPEDTAVYLCNARAFGRDYWGQGTQVTVSS
7	DL94	QVQLQESGGGLVQAGGSLKLSCAASSSIFSISSMSWYRQAPGKQRELVAAITSFGSTNYAD SVKGRFTISRDNAKNMMYLQMNSLKPEDTAVYRCNARTMGRDYWGQGTQVTVSS
8	DL17	QVQLQESGGGLVQPGGSLRLSCAASGSTLNIKIMAWHRQAPGKQRELVATLTSGGNTNYAD SVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCGLWDGVGGAYWGRGTQVTVSS
9	DL46	QVQLQESGGGLVQPGGSLRISCAASGSTLNIKIMAWHRQAPGKQRELVATLTSGGNTNYAD SVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCGLWDGVGGAYWGRGTQVTVSS
10	DL15	QVQLQESGGGLVQAGGSLRLSCAASGSTFNIKTMAWHRQAPGNQRELVATLTSGGNTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCGLWNGVGGAYWGRGTQVTVSS
11	DL26	QVQLQDGGGLVQPGGSLRLSCAASGSTFNIKLMAWHRQAPGNQRELVATLTSGGNTNYADS VKGRFTISRDNASNIVYLQMNSLKPEDTAVYYCGLWDGVGGAYWGRGTQVTVSS
12	DL83	QVQLQESGGGLVQAGGSLRLSCAASGSTFNFKIMAWHRQAPGKQRELVASLTSEGLTNYRD SVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCGLWDGVGGAYWGRGTQVTVSS
13	DL5	QVQLQESGGGLVQPGGSLRLSCAASGFMFSSYSMSWYRQAPGKQRELVAAITTWGSTNYAD SVKGRFTISRDNAKNTVWLQMNSLEPEDTAVYFCNARSWNNYWGQGTQVTVSS
14	DL22	QVQLQESGGGLVQVGGSLRLSCAASGFMFSSYSMSWYRQAPGKQRELVAAITSYGSTNYAD SVKGRFTISRDNAKNTVWLQMNSLKPEDTAVYFCNARSWNNYWGQGTQVTVSS
15	DL85	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSHSMSWYRQAPGKQRELVAAITTYGSTNYID SVKGRFTISRDNTKNTVYLQMNSLKPEDTAVYFCNARSWNNYWGQGTQVTVSS

16	DL69	QVQLQESGGGLVQAGGSLRLSCVASGSSFSHNTMGWYRQAPGKQRDLVARITTFGTTNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCNGESFGRIWYNWGQGTQVTVSS
17	DL27	QVQLQESGGGLVQAGASLRLTCTASGGRFSYATMGWSRQAPGKQREMVARITSSGFSTNYA DSVKGRFTISRDNAKNAVYLQMDSLKPEDTAVYYCNAQHFGTDSWGQGTQVTVSS
18	DL51	QVQLQESGGGLVQAGASLRLTCTASGSRFSYATMGWSRQAPGKQRELVARITSSGFSTNYA DSVKGRFTISRDNAKNAVYLQMDSLKPEDTAVYYCNAQQFGTDSWGQGTQVTVSS
19	DL54	QVQLQESGGGLVQAGGSLRLSCAASGSTFTSNVMGWHRQAPGKQRELVANMHSGGSTNYAD SVKGRFTISRDNAKNIVYLQMNNLKIEDTAVYYCRWYGIQRAEGYWGQGTQVTVSS
20	DL11	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTVSRDNAKNTVYLQMNSLQPEDTAVYYCYAYRWVGRDTYWGQGTQVTVSS
21	DL19	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCYAYRWVGRDTYWGQGTQVTVSS
22	DL68	QVQLQESGGGLVVSGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAKNTVYLQMNSLQPEDTAAYYCYAYRWVGRDTYWGQGTQVTVSS
23	DL14	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAENTVYLQMNSLQPEDTAVYYCYAYRWEGRDTYWGQGTQVTVSS
24	DL67	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAENTVYLQMNSLQPEDTAVYYCYAYRWEGRNTYWGQGTQVTVSS
25	DL56	QVQLQESGGGLVQPGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTNYVD SVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCYAYRWVGRYTYWGQGTQVTVSS
26	DL13	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGTTNYVD SVKDRFTISRDNAKNTVYLQMNSLQPEDTAAYYCYAYRWVGRDTYWGQGTQVTVSS
27	DL77	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSIAWYRQAPGKKRELVAGISTDGTTNYVD SVKDRFTISRDNAKNTVYLQMNSLQPEDTAAYYCYAYRWVGRDTYWGQGTQVTVSS
28	DL79	QVQLQESGGGLVQAGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGTTNYVD SVKDRFTISRDNAKNTVYLQMNSLQPEDTAAYYCYAYRWVGRDTYWGQGTQVTVSS
29	DL20	QVQLQESGGGLVQAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTNYAD SVKGRFTISEGNAKNTVDLQMNSLQPEDTAVYYCYAYRWVDRYTYWGQGTQVTVSS
30	DL41	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTNYAD SVKGRFTISEDNAKNTVDLQMNSLQPEDTAVYYCYAYRWIDRYTYWGQGTQVTVSS
31	DL59	QVQLQESGGGLVQPGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTNYAD SVKGRFTISEDNAKNTVDLQMNSLQPEDTAVYYCYAYRWVDRYTYWGQGTQVTVSS
32	DL16	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISSDGSTNYVD SVKGRFTISRDNAKNIVFLQMNSLQPQDTAVYYCYAYRWVGRDTYWGQGTQVTVSS
33	DL6	QVQLQESGGGLVVAGGSLRLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDSANNTMYLQMNSLQPEDTAVYYCYAYRWTTRYTYWGQGTQVTVSS
34	DL84	QVQLQESGGGLVQPGGSLRLSCAASGFTLDYYAIGWYRQAPGKKRELVAGISSDGSTHYVD SVKGRFAISRDNAENTVYLQMNDLQPDDTAVYYCYAYRWVGGYTYWGQGTQVTVSS
35	DL2	QVQLQESGGGLVQAGGSLRLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKNYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCYYFRTVAASSMQYWGQGTQVTVSS
36	DL43	QVQLQESGGGLVQAGGSLRLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTAVFYCYYFRTVSGSSMRYWGQGTQVTVSS
37	DL92	QVQLQESGGGLVQAGGSLRLSCAASGITSSVYSMGWYRQAPGKQRELVAGSSSDGSTHYVD SVRGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCYANRGFAGAPSYWGQGTQVTVSS
38	DL10	QVQLQESGGGLVQAGGSLRLSCAASGRTSMFNSMGWHRQAPGKQRELVAIIRSGGSSNYAD TVKGRFTISRDNTKNTVYLQMNDLKPEDTAVYYCFYYFQSSYWGQGTQVTVSS
39	DL82	QVQLQESGGGLVQAGGSLRLSCAASGRTSMVNSMGWHRQAPGKQRELVALITSGGSSNYAD TVKGRFTISRDNTKNTVYLQMNDLKPEDTAVYYCFYYFQSSYWGQGTQVTVSS
40	DL23	QVQLQESGGGLVQAGGSLRLSCAASGSVSMFNSMGWHRQPPGKQRELVAIITSGGSSNYAD TVKGRFTISRDNTKNTVYLQMNDLKPEDTAVYYCFYYFQSSYWGQGTQVTVSS
41	DL42	QVQLQESGGGLVQAGGSLRLSCTASGSIFSIAVMGWYRQVPGKRREWVATIFDGSYTNYAD SVKGRFTISRDNARNKVYLQMNNLKPEDTAVYYCQTHWTQGSVPKESWGQGTQVTVSS
42	DL45	QVQLQESGGGLVQAGGSLRLSCVASSGIFSDMSMVWYRQAPGKQRELVASITTFGSTNYAD PVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCSGRSYSSDYWGRGTQVTVSS
43	DL58	QVQLQESGGGLVQAGGSLRLSCVASGSISSIIVMGWSRQAPGKQRESVATITRDGTRNYAD SLKGRFTISRDNAKNTSYLQINSLKPEDTAVYSCYARYGDINYWGKGTQVTVSS
44	DL70	QVQLQESGGGLVQAGGSLRLSCVASGSISSIIVMGWSRQAPGKQRESLATISRGGTRTYAD SVKGRFTISRDNAKNTSYLQMNSLKPEDTAVYSCYARYGDINYWGKGTQVTVSS
45	DL89	QVQLQESGGGLVQAGGSLRLSCVASGSIFTTNSMGWHRQGPGKQRELVALIGSAGSTKYAD SVKGRFTISRDNAKNTVSLQMDSLKPEDTAVYYCFYYDSRSYWGQGTQVTVSS
46	DL38	QVQLQESGGGMVQPGGSLRLSCAASGSREISTMGWHRQAPGKQRELAARITSGGITKYADS VKGRFTISRDNAKKTVYLQMNSLKSEDTAVYYCFAYDNINAYWGQGTQVTVSS

47	DL52	QVQLQESGGGWVQAGGSLRLSCAASGSREISTMGWHRQAPGKQRELAARITSGGITKYADS VKGRFTISRDNAKKTVYLQMNSLKSEDTAVYYCFAYDNINAYWGQGTQVTVSS
48	DL64	QVQLQESGGGWVQAGGSLRLSCTASGSREISTMGWHRQAPGKQRELAARITSGGITKYADS VKGRFTISRDNAKKTVYLQMDSLKSEDTAVYYCFAYDNINAYWGQGTQVTVSS
49	DL33	QVQLQESGGGSVQAGRSLGLSCAASGSREISTMGWHRQAPGKQRELAARITSGGITKYADS VKGRFTISRDNAKKTVYLQMNSLKSEDTAVYYCFAYDNINAYWGQGTQVTVSS
50	DL12	QVQLQESGGGLVQAGGSLRLSCTASGSIFRGAAMYWHRQAPGKQRELVAAITTSGNTSYAD SVKGRFTISRDNAKNTMYLQIISLKPEDTAVYYCAFWIAGKAYWGQGTQVTVSS
51	DL29	QVQLQESGGGLVQPGGSLRLSCAASGSISSFNFMSWHRQAPGKERELAGVITRGGATNYAD SVKGRFTISRDNVKNTVYLQMNGLKPEDTAVYYCHGRSQLGSTWGQGTQVTVSS
52	DL61	QVQLQESGGGLVQAGGSLRLSCLASGTIFTASTMGWHRQPPGKQRELVASIAGDGRTNYAE STEGRFTISRDDAKNTMYLQMNSLKPEDTAVYYCYAYYLDTYAYWGQGTQVTVSS
53	DH1	EVQLVESGGGLVQPGGSLTLSCAASGSIFSIASMGWYRQAPGKQRELVAVITSFSSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNARYFERTDWGQGTLVTVSS
54	DH10	EVQLVESGGGLVQPGGSLTLSCAASGRTSMFNSMGWHRQAPGKQRELVAIIRSGGSSNYAD TVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCFYYFQSSYWGQGTLVTVSS
55	DH11	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWVGRDTYWGQGTLVTVSS
56	DH12	EVQLVESGGGLVQPGGSLTLSCTASGSIFRGAAMYWHRQAPGKQRELVAAITTSGNTSYAD SVKGRFTISRDNAKNSMYLQMNSLRAEDTAVYYCAFWIAGKAYWGQGTLVTVSS
57	DH15	EVQLVESGGGLVQPGGSLTLSCAASGSTFNIKTMAWHRQAPGNQRELVATLTSGGNTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCGLWNGVGGAYWGQGTLVTVSS
58	DH17	EVQLVESGGGLVQPGGSLTLSCAASGSTLNIKIMAWHRQAPGKQRELVATLTSGGNTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCGLWDGVGGAYWGQGTLVTVSS
59	DH18	EVQLVESGGGLVQPGGSLTLSCAASSSIFSISSMSWYRQAPGKQRELVAAITTFDYTNYAD SVKGRFTISRDNAKNSMYLQMNSLRAEDTAVYYCNARAFGRDYWGQGTLVTVSS
60	DH2	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVAASSMQYWGQGTLVTVSS
61	DH22	EVQLVESGGGLVQPGGSLTLSCAASGFMFSSYSMSWYRQAPGKQRELVAAITSYGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNARSWNNYWGQGTLVTVSS
62	DH23	EVQLVESGGGLVQPGGSLTLSCAASGSVSMFNSMGWHRQPPGKQRELVAIITSGGSSNYAD TVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCFYYFQSSYWGQGTLVTVSS
63	DH27	EVQLVESGGGLVQPGGSLTLSCTASGGRFSYATMGWSRQAPGKQREMVARITSSGFSTNYA DSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNAQHFGTDSWGQGTLVTVSS
64	DH29	EVQLVESGGGLVQPGGSLTLSCAASGSISSFNFMSWHRQAPGKERELAGVITRGGATNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCHGRSQLGSTWGQGTLVTVSS
65	DH3	EVQLVESGGGLVQPGGSLTLSCAASESIFSINVMAWHRQAPGKQRELVARITSGGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCGAYQGLYAYWGQGTLVTVSS
66	DH38	EVQLVESGGGLVQPGGSLTLSCAASGSREISTMGWHRQAPGKQRELAARITSGGITKYADS VKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCFAYDNINAYWGQGTLVTVSS
67	DH42	EVQLVESGGGLVQPGGSLTLSCTASGSIFSIAVMGWYRQVPGKRREWVATIFDGSYTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCQTHWTQGSVPKESWGQGTLVTVSS
68	DH43	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
69	DH45	EVQLVESGGGLVQPGGSLTLSCVASSGIFSDMSMVWYRQAPGKQRELVASITTFGSTNYAD PVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCSGRSYSSDYWGQGTLVTVSS
70	DH5	EVQLVESGGGLVQPGGSLTLSCAASGFMFSSYSMSWYRQAPGKQRELVAAITTWGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNARSWNNYWGQGTLVTVSS
71	DH51	EVQLVESGGGLVQPGGSLTLSCTASGSRFSYATMGWSRQAPGKQRELVARITSSGFSTNYA DSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNAQQFGTDSWGQGTLVTVSS
72	DH54	EVQLVESGGGLVQPGGSLTLSCAASGSTFTSNVMGWHRQAPGKQRELVANMHSGGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCRWYGIQRAEGYWGQGTLVTVSS
73	DH56	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTNYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWVGRYTYWGQGTLVTVSS
74	DH58	EVQLVESGGGLVQPGGSLTLSCVASGSISSIIVMGWSRQAPGKQRESVATITRDGTRNYAD SLKGRFTISRDNAKNSSYLQMNSLRAEDTAVYYCYARYGDINYWGQGTLVTVSS
75	DH6	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
76	DH61	EVQLVESGGGLVQPGGSLTLSCLASGTIFTASTMGWHRQPPGKQRELVASIAGDGRTNYAE STEGRFTISRDNAKNSMYLQMNSLRAEDTAVYYCYAYYLDTYAYWGQGTLVTVSS
77	DH67	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWEGRNTYWGQGTLVTVSS

78	DH69	EVQLVESGGGLVQPGGSLTLSCVASGSSFSHNTMGWYRQAPGKQRDLVARITTFGTTNYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNGESFGRIWYNWGQGTLVTVSS
79	DH70	EVQLVESGGGLVQPGGSLTLSCVASGSISSIIVMGWSRQAPGKQRESLATISRGGTRTYAD SVKGRFTISRDNAKNSSYLQMNSLRAEDTAVYYCYARYGDINYWGQGTLVTVSS
80	DH80	EVQLVESGGGLVQPGGSLTLSCVASGSSFSITSMAWYRQAPGKQRDLVAAITSFGSTNYAD SVKDRFTISRDNAKNSVYLQMNSLRAEDTAVYYCNGRVFDHVYWGQGTLVTVSS
81	DH82	EVQLVESGGGLVQPGGSLTLSCAASGRTSMVNSMGWHRQAPGKQRELVALITSGGSSNYAD TVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCFYYFQSSYWGQGTLVTVSS
82	DH83	EVQLVESGGGLVQPGGSLTLSCAASGSTFNFKIMAWHRQAPGKQRELVASLTSEGLTNYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCGLWDGVGGAYWGQGTLVTVSS
83	DH84	EVQLVESGGGLVQPGGSLTLSCAASGFTLDYYAIGWYRQAPGKKRELVAGISSDGSTHYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWVGGYTYWGQGTLVTVSS
84	DH89	EVQLVESGGGLVQPGGSLTLSCVASGSIFTTNSMGWHRQGPGKQRELVALIGSAGSTKYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCFYYDSRSYWGQGTLVTVSS
85	DH92	EVQLVESGGGLVQPGGSLTLSCAASGITSSVYSMGWYRQAPGKQRELVAGSSSDGSTHYVD SVRGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYANRGFAGAPSYWGQGTLVTVSS
86	DH94	EVQLVESGGGLVQPGGSLTLSCAASSSIFSISSMSWYRQAPGKQRELVAAITSFGSTNYAD SVKGRFTISRDNAKNSMYLQMNSLRAEDTAVYYCNARTMGRDYWGQGTLVTVSS
87	1A01	EVQLVESGGGLVQPGGSLTLSCVASGFTSSINAMGWYRRAPGKQRELVAGISSDGSFVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRHVSGSSMRYWGQGTLVTVSS
88	1A03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSSRYWGQGTLVTVSS
89	1A04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYED SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
90	1A05	EVQLVESGGGLVQPGGSLTLSCVASGSPSSINAMGWYRRAPGKQRELSAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMSYWGQGTLVTVSS
91	1A06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELAAGISSDGSSVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSKRYWGQGTLVTVSS
92	1A07	EVQLVESGGGLVQPGGSLTLSCVASGSISSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRMVSGSSMRYWGQGTLVTVSS
93	1A09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKLYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVQGSSMRYWGQGTLVTVSS
94	1A010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAYGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVYGSSMRYWGQGTLVTVSS
95	1A011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSYRYWGQGTLVTVSS
96	1A012	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGSSMRYWGQGTLVTVSS
97	1B01	EVQLVESGGGLVQPGGSLTLSCVASGSTSIINAMGWYRRAPGKQRELAAGISSDGSKVIAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRVSGSSMRYWGQGTLVTVSS
98	1B02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKIYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
99	1B03	EVQLVESGGGLVQPGGSLTLSCVASGKTSSINAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSARYWGQGTLVTVSS
100	1B04	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSLVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRIVRGSSMRYWGQGTLVTVSS
101	1B05	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYYRTVSGSSMRYWGQGTLVTVSS
102	1B07	EVQLVESGGGLVQPGGSLTLSCVASGSGSSINAMGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRHVSGSSMRYWGQGTLVTVSS
103	1B08	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRFVSGSSMRYWGQGTLVTVSS
104	1B09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
105	1B010	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTKSGSSMRYWGQGTLVTVSS
106	1B011	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVYGSSMRYWGQGTLVTVSS
107	1C01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMGYWGQGTLVTVSS
108	1C02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRSWGQGTLVTVSS

109	1C03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVGGSSMRYWGQGTLVTVSS
110	1C04	EVQLVESGGGLVQPGGSLTLSCVASGNTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
111	1C05	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSHMRYWGQGTLVTVSS
112	1C06	EVQLVESGGGLVQPGGSLTLSCVASGSTSIINAMGWYRRAPGKQRELVAGISSDGSKVYED SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRAVSGSSMRYWGQGTLVTVSS
113	1C07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
114	1C08	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELPAGISSDGSKVYAV SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSPMRYWGQGTLVTVSS
115	1C010	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGVSSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMSYWGQGTLVTVSS
116	1C011	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYED SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
117	1C012	EVQLVESGGGLVQPGGSLTLSCVASGITSSINAMGWYRRAPGKQRELVAGISSDGSKVYAG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
118	1D01	EVQLVESGGGLVQPGGSLTLSCVASGSTSDINAMGWYRRAPGKQRELVAGISSDKSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
119	1D02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSNGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRQVSGSSMRYWGQGTLVTVSS
120	1D03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVLAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRIVSGSSMGYWGQGTLVTVSS
121	1D04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSKNAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGASMRYWGQGTLVTVSS
122	1D06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVHGSSMRYWGQGTLVTVSS
123	1D08	EVQLVESGGGLVQPGGSLTLSCVASGLTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRMVSGSSMRYWGQGTLVTVSS
124	1D09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTISGSSMRYWGQGTLVTVSS
125	1D010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSNNAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTRSGSSMRYWGQGTLVTVSS
126	1D011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGHSMRYWGQGTLVTVSS
127	1D012	EVQLVESGGGLVQPGGSLTLSCVASGSTSHINAMGWYRRAPGKQRELVAGISSDGSRVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGGSMRYWGQGTLVTVSS
128	1E02	EVQLVESGGGLVQPGGSLTLSCVASGQTSSINAMGWYRRAPGKQRELVAGISSDGSQVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTKSGSSMRYWGQGTLVTVSS
129	1E04	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINGMGWYRRAPGKQRELPAGISSDGSKAYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTASGTSMRYWGQGTLVTVSS
130	1E05	EVQLVESGGGLVQPGGSLTLSCVASGSTSVINAMAWYRRAPGKQRELAAGISSDGSKVYAK SAKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFNTVSGSSMRYWGQGTLVTVSS
131	1E07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSQRYWGQGTLVTVSS
132	1E08	EVQLVESGGGLVQPGGSLTLSCVASGKTSSINAMGWYRRAPGKQRELVAGISSDGSKVIAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGSSMRYWGQGTLVTVSS
133	1E09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTRSGSSMRYWGQGTLVTVSS
134	1E010	EVQLVESGGGLVQPGGSLTLSCVASGSVSSINAMGWYRRAPGKQRELVAGISSDGSKVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGLSMRYWGQGTLVTVSS
135	1E011	EVQLVESGGGLVQPGGSLTLSCVASGNTSSINAMGWYRRAPGKQRELVAGISSDGSKVYYD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSQRYWGQGTLVTVSS
136	1E012	EVQLVESGGGLVQPGGSLTLSCVASGSTSSTNAMGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMVYWGQGTLVTVSS
137	1F01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYGD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSRSSMRYWGQGTLVTVSS
138	1F02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELAAGISSDQSKVYAD SAKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMSYWGQGTLVTVSS
139	1F04	EVQLVESGGGLVQPGGSLTLSCVASGGTSSINAMGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSARYWGQGTLVTVSS

140	1F05	EVQLVESGGGLVQPGGSLTLSCVASGSTRSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVSGSSMRYWGQGTLVTVSS
141	1F06	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVIAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGSSMRYWGQGTLVTVSS
142	1F07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVDAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
143	1F08	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYKD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRNVSGSSMRYWGQGTLVTVSS
144	1F09	EVQLVESGGGLVQPGGSLTLSCVASGNTSSINAMGWYRRAPGKQRELVAGISSNGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVTGSSMRYWGQGTLVTVSS
145	1F010	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYKD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
146	1F011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVKGSSMRYWGQGTLVTVSS
147	1F012	EVQLVESGGGLVQPGGSLTLSCVASGLTSSINAMGWYRRAPGKQRELVAGISSDGSKVYQD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTNSGSSMRYWGQGTLVTVSS
148	1G01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGASMRYWGQGTLVTVSS
149	1G04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSTNAMGWYRRAPGKQRELVAGISSDGSKVLAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVNLSSMRYWGQGTLVTVSS
150	1G05	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKYYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVTGSSMRYWGQGTLVTVSS
151	1G06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYAV SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRKVSGSSARYWGQGTLVTVSS
152	1G07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVVAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTYSGSSMRYWGQGTLVTVSS
153	1G09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSKSSMRYWGQGTLVTVSS
154	1G011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFKTVSGSSMRYWGQGTLVTVSS
155	1H01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELAAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTRSGSSMRYWGQGTLVTVSS
156	1H02	EVQLVESGGGLVQPGGSLTLSCVASGSKSSINAMGWYRRAPGKQRELAAGISSDGSKVYAQ SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTSSGSSMRYWGQGTLVTVSS
157	1H06	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRFLSGSSMRYWGQGTLVTVSS
158	1H07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAFGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
159	1H08	EVQLVESGGGLVQPGGSLTLSCVASGSTFSINAMGWYRRAPGKQRELVAGISSDGSKVLAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRLVSGSSMRYWGQGTLVTVSS
160	1H010	EVQLVESGGGLVQPGGSLTLSCVASGSTRSINAMGWYRRAPGKQRELVAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRFWGQGTLVTVSS
161	1H011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTQSGSSMRYWGQGTLVTVSS
162	1H012	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMPYWGQGTLVTVSS
163	2A01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVVAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTLSGSSMRYWGQGTLVTVSS
164	2A03	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYGD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSAMRYWGQGTLVTVSS
165	2A04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTTSGSSMRYWGQGTLVTVSS
166	2A05	EVQLVESGGGLVQPGGSLTLSCVASGRTSSINAMGWYRRAPGKQRELVAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGTSMRYWGQGTLVTVSS
167	2A06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSRNAMGWYRRAPGKQRELVAGISSDGSKVTAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTRSGSSMRYWGQGTLVTVSS
168	2A08	EVQLVESGGGLVQPGGSLTLSCVASGSTKSINAMGWYRRAPGKQRELVAGISSDGSKVYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTSSGSSMRYWGQGTLVTVSS
169	2A09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSRNAMGWYRRAPGKQRELVAGISSNGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMSYWGQGTLVTVSS
170	2A011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRPVSGSSMRYWGQGTLVTVSS

171	2B01	EVQLVESGGGLVQPGGSLTLSCVASGSTSLINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRHVSGSSMRYWGQGTLVTVSS
172	2B02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTKSGSSMRYWGQGTLVTVSS
173	2B03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSLVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFTTVSGSSMRYWGQGTLVTVSS
174	2B05	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGTKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVSGSSMRYWGQGTLVTVSS
175	2B07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAFGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
176	2B010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSRNAMGWYRRAPGKQRELVAGISSDGSKLYLD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGSSMRYWGQGTLVTVSS
177	2B011	EVQLVESGGGLVQPGGSLTLSCVASGNTSSINAMGWYRRAPGKQRELVAGISSDGSRVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRSWGQGTLVTVSS
178	2B012	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
179	2C01	EVQLVESGGGLVQPGGSLTLSCVASGSTASINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRYVSGSSMRYWGQGTLVTVSS
180	2C02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVYGSSMRYWGQGTLVTVSS
181	2C04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSRNAMGWYRRAPGKQRELVAGISSDGSKLYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGSSMRYWGQGTLVTVSS
182	2C06	EVQLVESGGGLVQPGGSLTLSCVASGSTNSINAMGWYRRAPGKQRELVAGISSDGSKVYKD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYYRTVSGSSMRYWGQGTLVTVSS
183	2C07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRSVSGSSMRYWGQGTLVTVSS
184	2C08	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYQD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRVSGSSMRYWGQGTLVTVSS
185	2C09	EVQLVESGGGLVQPGGSLTLSCVPSGSTSNINAMGWYRRAPGKQRELPAGISSDGTKIYAD SAKVPFTITRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGTSMRYWGQGTLVTVSS
186	2C010	EVQLVESGGGLVQPGGSLTLSCVASGSTSKINAMGWYRRAPGKQRELVAGISSDRSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVAGSSMRYWGQGTLVTVSS
187	2D02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINALGWYRRAPGKQRELVAGISSDGSLVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRIVSGSSMRYWGQGTLVTVSS
188	2D03	EVQLVESGGGLVQPGGSLTLSCVASGKTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGVSMRYWGQGTLVTVSS
189	2D04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSKVYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVQGSSMRYWGQGTLVTVSS
190	2D05	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTASGSSMRYWGQGTLVTVSS
191	2D06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSSRYWGQGTLVTVSS
192	2D07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGTKVYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVQGSSMRYWGQGTLVTVSS
193	2D09	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELAAGISSDGSKVYND SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
194	2D010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTKSGSSMRYWGQGTLVTVSS
195	2D011	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVWGSSMRYWGQGTLVTVSS
196	2D012	EVQLVESGGGLVQPGGSLTLSCVASGKTSSINAMGWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTRSGSSMRYWGQGTLVTVSS
197	2E01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPFKQGELPAGISPDGTKAYAD SAKVRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVCGTSMGYWGQGTLVTVSS
198	2E02	EVQLVESGGGLVQPGGSLTLSCVASGSTSAINAMGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSQRYWGQGTLVTVSS
199	2E05	EVQLVESGGGLVQPGGSLTLSCVASGSPSSINAYGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMSYWGQGTLVTVSS
200	2E06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYAS SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVRGSSMRYWGQGTLVTVSS
201	2E08	EVQLVESGGGLVQPGGSLTLSCVASGSRSSINAMGWYRRAPGKQRELVAGISADGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTQSGSSMRYWGQGTLVTVSS

202	2E09	EVQLVESGGGLVQPGGSLTLSCVASGSVSSINAMGWYRRAPGKQRELVAGISSDGSKVYAS SAKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTLSGSSMRYWGQGTLVTVSS
203	2E010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVSGSSMRYWGQGTLVTVSS
204	2E011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSSVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRVSGSSMRYWGQGTLVTVSS
205	2F01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRLVSGSSMRYWGQGTLVTVSS
206	2F02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSKVYAG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSYMRYWGQGTLVTVSS
207	2F03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELAAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVGGSSMRYWGQGTLVTVSS
208	2F06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAYGWYRRAPGKQRELVAGISSDGSAVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTHSGSSMRYWGQGTLVTVSS
209	2F07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSSVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSTSSMRYWGQGTLVTVSS
210	2F08	EVQLVESGGGLVQPGGSLTLSCVASGSKSSINAMGWYRRAPGKQRELPAGISSNGTKVYAD SAKVRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVLGTSMRYWGQGTLVTVSS
211	2F09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKLYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
212	2F11	EVQLVESGGGLVQPGGSLTLSCVASGSVSSINAMGWYRRAPGKQRELVAGISSDGSKVYKD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMGYWGQGTLVTVSS
213	2G03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSLVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRAWGQGTLVTVSS
214	2G04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSLVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRILSGSSMRYWGQGTLVTVSS
215	2G07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVQGSSMRYWGQGTLVTVSS
216	2G08	EVQLVESGGGLVQPGGSLTLSCVASGSTSYINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGQSMGYWGQGTLVTVSS
217	2G09	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGVSSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSARYWGQGTLVTVSS
218	2G011	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELPAGISRDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRYVSGSSMRYWGQGTLVTVSS
219	2H010	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELAAGISSDGSKLYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSMRYWGQGTLVTVSS
220	2H011	EVQLVESGGGLVQPGGSLTLSCVASGSTSRINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRVSGSSMRYWGQGTLVTVSS
221	2H02	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELAAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVSGSSMRYWGQGTLVTVSS
222	2H03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRQVSGSSMRYWGQGTLVTVSS
223	2H04	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDTSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSYMRYWGQGTLVTVSS
224	2H06	EVQLVESGGGLVQPGGSLTLSCVASGSTSTINAMGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTASGSSMRYWGQGTLVTVSS
225	2H07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSTVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGHSMRYWGQGTLVTVSS
226	2H08	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELAAGISKDGSKVYAD SAKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSSRYWGQGTLVTVSS
227	2E05- M106Y	EVQLVESGGGLVQPGGSLTLSCVASGSPSSINAYGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSYSYWGQGTLVTVSS
228	2E05- M106Q	EVQLVESGGGLVQPGGSLTLSCVASGSPSSINAYGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSQSYWGQGTLVTVSS
229	3A01	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
230	3A02	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSLAWYRQAPGKKRELVAGISADGSTAYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
231	3A03	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
232	3A04	EVQLVESGGGLVQPGGSLTLSCAASGSQVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYIYWGQGTLVTVSS

233	3A05	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISEAGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
234	3A06	EVQLVESGGGLVQPGGSLTLRCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSTDYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
235	3A08	EVQLVESGGGLVQPGGSLTLSCAASGSSVGFLSMAWYRQAPGKKRELVAGISADGSTDYIR SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
236	3A09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSVDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYIYWGQGTLVTVSS
237	3A010	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
238	3A011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSLAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
239	3B01	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISGDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
240	3B02	EVQLVESGGGLVQPGGSLTLSCAASGSSVQFLSMAWYRQAPGKKRELVAGISADGSTDYIN SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
241	3B04	EVQLVESGGGLVQPGGSLTLSCAASGSNVSFLSMAWYRQAPGKKRELVAGISARGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYHWTTRYTYWGQGTLVTVSS
242	3B05	EVQLVESGGGLVQPGGSLTLSCVASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
243	3B06	EVQLVESGGGLVQPGGSLTLSCAASGKSVSFLSMAWYRQAPGKKRELVAGISKDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
244	3B07	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
245	3B09	EVQLVESGGGLVQPGGSLTLSCAASGSHVSFLSMAWYRQAPGKKRELVAGISANGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYAYWGQGTLVTVSS
246	3B010	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWVTRYTYWGQGTLVTVSS
247	3B011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSADYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWVTRYTYWGQGTLVTVSS
248	3C01	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISAHGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
249	3C02	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTIYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
250	3C03	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISRDGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRGTYWGQGTLVTVSS
251	3C04	EVQLVESGGGLVQPGGSLTLSCAASGSHVSFLSMAWYRQAPGKKRELVAGISADGPTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWDTRYTYWGQGTLVTVSS
252	3C05	EVQLVESGGGLVQPGGSLTLSCVASGTSVSFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
253	3C06	EVQLVESGGGLVQPGGSLTLSCAASGTSVSFLSIAWYRQAPGKKRELVAGISADGSTDYIA SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
254	3C08	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISLDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTGRYTYWGQGTLVTVSS
255	3C09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTIYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
256	3C011	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISAHGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
257	3D01	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWITRYTYWGQGTLVTVSS
258	3D02	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWITRYTYWGQGTLVTVSS
259	3D03	EVQLVESGGGLVQPGGSLTLSCAASGSSVVFLSMAWYRQAPGKKRELVAGISADGSMDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
260	3D05	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
261	3D07	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRYTYWGQGTLVTVSS
262	3D08	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISANGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTNRYTYWGQGTLVTVSS
263	3D09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSRLSMAWYRQAPGKKRELVAGISANGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS

264	3D010	EVQLVESGGGLVQPGGSLTLSCAASGSSKSFLSMAWYRQAPGKKRELVAGISADGSTSYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
265	3D011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSRLSMAWYRQAPGKKRELVAGISADGSRDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYKYWGQGTLVTVSS
266	3E01	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTMYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWHTRYTYWGQGTLVTVSS
267	3E02	EVQLVESGGGLVQPGGSLTLSCAASGSGVRFLSMAWYRQAPGKKRELVAGISPDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
268	3E03	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISGDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWMTRYTYWGQGTLVTVSS
269	3E04	EVQLVESGGGLVQPGGSLTLSCAASGSSVHFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS
270	3E09	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
271	3E011	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTFWGQGTLVTVSS
272	3F03	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
273	3F05	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
274	3F06	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTSYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWATRYTYWGQGTLVTVSS
275	3F08	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWHTRYTYWGQGTLVTVSS
276	3F09	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWGTRYTYWGQGTLVTVSS
277	3F010	EVQLVESGGGLVQPGGSLTLSCAASYSSVSRLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRNTYWGQGTLVTVSS
278	3F011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
279	3G01	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYAYWGQGTLVTVSS
280	3G02	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGRTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
281	3G04	EVQLVESGGGLVQPGGSLTLSCVASGTSVSFLSMAWYRQAPGKKRELVAGISADGSTIYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
282	3G06	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
283	3G07	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTSRYTYWGQGTLVTVSS
284	3G08	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISKDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRVTYWGQGTLVTVSS
285	3G09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSVLSMAWYRQAPGKKRELVAGISADGSTDYIG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRTTYWGQGTLVTVSS
286	3G010	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISVDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
287	3G011	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTGYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWATRYTYWGQGTLVTVSS
288	3H01	EVQLVESGGGLVQPGGSLTLSCVASGSSVKFLSMAWYRQAPGKKRELVAGISGDGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
289	3H03	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYALRWTTRYTYWGQGTLVTVSS
290	3H06	EVQLVESGGGLVQPGGSLTLSCAASGSSVSQLSMAWYRQAPGKKRELVAGISADGSTDYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRGTYWGQGTLVTVSS
291	3H07	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTSYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
292	3H09	EVQLVESGGGLVQPGGSLTLSCAASKSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRATYWGQGTLVTVSS
293	3H010	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTAYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
294	3H011	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWPTRYTYWGQGTLVTVSS

295	4A01	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISQDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
296	4A02	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISNDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWKTRYTYWGQGTLVTVSS
297	4A04	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISARGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
298	4A05	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSLAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWKTRRTYWGQGTLVTVSS
299	4A06	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
300	4A07	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS
301	4A08	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTNYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
302	4A010	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYKYWGQGTLVTVSS
303	4A011	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWKTRYTYWGQGTLVTVSS
304	4A09	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYIG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRVTYWGQGTLVTVSS
305	4B01	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRFTYWGQGTLVTVSS
306	4B02	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRFTYWGQGTLVTVSS
307	4B04	EVQLVESGGGLVQPGGSLTLSCAASGSSVLFLSMAWYRQAPGKKRELVAGVSSDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
308	4B05	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGHTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTHWGQGTLVTVSS
309	4B06	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTDYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
310	4B07	EVQLVESGGGLVQPGGSLTLSCAASGSSVGFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
311	4B08	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFMSMAWYRQAPGKKRELVAGISADGSTDYIA SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRSTYWGQGTLVTVSS
312	4B09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYIS SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRYTYWGQGTLVTVSS
313	4B011	EVQLVESGGGLVQPGGSLTLSCAASGSSVTFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRGTYWGQGTLVTVSS
314	4C01	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWKTRYTYWGQGTLVTVSS
315	4C02	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSTTYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRFTYWGQGTLVTVSS
316	4C03	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFMSMAWYRQAPGKKRELVAGISVDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
317	4C05	EVQLVESGGGLVQPGGSLTLSCAASGSSVSNLSMAWYRQAPGKKRELVAGISADGSTAYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
318	4C06	EVQLVESGGGLVQPGGSLTLSCAASNSSVSKLSMAWYRQAPGKKRELVAGISADGSTAYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
319	4C07	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSKDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
320	4C08	EVQLVESGGGLVQPGGSLTLSCVASGSQVSFLSMAWYRQAPGKKRELVAGISADGSTDYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
321	4C010	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFMSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
322	4C011	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
323	4D01	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
324	4D02	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISARGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYQWTTRYTYWGQGTLVTVSS
325	4D03	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISATGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS

326	4D04	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSIAWYRQAPGKKRELVAGISKDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRMTYWGQGTLVTVSS
327	4D05	EVQLVESGGGLVQPGGSLTLSCAASGSSSSFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
328	4D06	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISPDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS
329	4D08	EVQLVESGGGLVQPGGSLTLSCAASGSSVNFLSMAWYRQAPGKKRELVAGISADGSTHYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWLTRYTYWGQGTLVTVSS
330	4D09	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYIL SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYEWTTRYTYWGQGTLVTVSS
331	4D010	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISADGSTDYIH SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
332	4D011	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISVDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
333	4E01	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSVAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
334	4E02	EVQLVESGGGLVQPGGSLTLSCAASGSQVSFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
335	4E06	EVQLVESGGGLVQPGGSLTLSCAASGTSVSFLSMAWYRQAPGKKRELVAGISADGSTDYIR SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
336	4E07	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTMYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
337	4E08	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYKWTTRYTYWGQGTLVTVSS
338	4E09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSSAWYRQAPGKKRELVAGISADGSTLYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRSTYWGQGTLVTVSS
339	4E010	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
340	4E011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISATGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
341	4F02	EVQLVESGGGLVQPGGSLTLSCAASGSTVSFLSMAWYRQAPGKKRELVAGISHDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
342	4F03	EVQLVESGGGLVQPGGSLTLSCAASGSSVQFLSMAWYRQAPGKKRELVAGISYDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
343	4F04	EVQLVESGGGLVQPGGSLTLSCAASRSSVSFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWLTRYTYWGQGTLVTVSS
344	4F08	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSTAYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
345	4F09	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTDYIE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
346	4F010	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISIDGSTDYIK SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS
347	4F011	EVQLVESGGGLVQPGGSLTLSCAASGSKVSFLSMAWYRQAPGKKRELVAGISADGSKDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
348	4G01	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWPTRYTYWGQGTLVTVSS
349	4G02	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISRDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRHTYWGQGTLVTVSS
350	4G03	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYIH SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTRRYTYWGQGTLVTVSS
351	4G05	EVQLVESGGGLVQPGGSLTLSCAASGSSVSILSMAWYRQAPGKKRELVAGISADGSTIYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWITRYTYWGQGTLVTVSS
352	4G07	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSVAWYRQAPGKKRELVAGISANGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTNRYTYWGQGTLVTVSS
353	4G08	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISTDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYRYWGQGTLVTVSS
354	4G09	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISYDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRRTYWGQGTLVTVSS
355	4G010	EVQLVESGGGLVQPGGSLTLSCAASGHSVSFLSMAWYRQAPGKKRELVAGISADGSTDYIA SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
356	4G011	EVQLVESGGGLVQPGGSLTLSCAASGSSVRFLSMAWYRQAPGKKRELVAGISADGSTDYIG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS

357	4H01	EVQLVESGGGLVQPGGSLTLSCAASGSSVSFLSMAWYRQAPGKKRELVAGISANGSTDYYD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWRTRYTYWGQGTLVTVSS
358	4H03	EVQLVESGGGLVQPGGSLTLSCAASGSRVSFLSMAWYRQAPGKKRELVAGISADGSTSYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
359	4H04	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGVSADGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYEWTTRYTYWGQGTLVTVSS
360	4H05	EVQLVESGGGLVQPGGSLTLSCAASGSSVSRLSMAWYRQAPGKKRELVAGISARGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRSTYWGQGTLVTVSS
361	4H06	EVQLVESGGGLVQPGGSLTLSCAASGRSVSFLSMAWYRQAPGKKRELVAGISADGSTIYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRYTYWGQGTLVTVSS
362	4H07	EVQLVESGGGLVQPGGSLTLSCAASGRSVSFLSMAWYRQAPGKKRELVAGISANGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
363	4H08	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSMAWYRQAPGKKRELVAGISADGSTDYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWSTRYTYWGQGTLVTVSS
364	4H09	EVQLVESGGGLVQPGGSLTLSCAASGSSVSKLSMAWYRQAPGKKRELVAGISADGSTDYRD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTYRYTYWGQGTLVTVSS
365	4H011	EVQLVESGGGLVQPGGSLTLSCAASGSSVSRLSMAWYRQAPGKKRELVAGISVDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
366	4D09-M34L	EVQLVESGGGLVQPGGSLTLSCAASGSSVKFLSLAWYRQAPGKKRELVAGISADGSTDYIL SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYEWTTRYTYWGQGTLVTVSS
367	4H11-M34L	EVQLVESGGGLVQPGGSLTLSCAASGSSVSRLSLAWYRQAPGKKRELVAGISVDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTTRLTYWGQGTLVTVSS
368	41B11	EVQLVESGGGLVQPGGSLTLSCVASGTSSSINAMGWYRRAPGKQRELVAGISSDGSKVFNE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRPAAGSPMRYWGQGTLVTVSS
369	41C02	EVQLVESGGGLVQPGGSLTLSCVASGTTSSINAIGWYRRAPGKQRELVAGISSDGSEVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVDGSPLRYWGQGTLVTVSS
370	41D01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDDSNVYYE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSKRYWGQGTLVTVSS
371	41D02	EVQLVESGGGLVQPGGSLTLSCVASGQTYRVNAFGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFSAGSGTEMSYWGQGTLVTVSS
372	41D03	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMAWYRRAPGKQRELVAGISSDESTLYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFGSLSGSSTTYWGQGTLVTVSS
373	41D07	EVQLVESGGGLVQPGGSLTLSCVASGSASLTNATGWYRRAPGKQRELVAGISSDDSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFGSVSGSWTRYWGQGTLVTVSS
374	41E01	EVQLVESGGGLVQPGGSLTLSCVASGYPSLNNAMGWYRRAPGKQRELVAGISSDGSQVYGA SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRLVSGSSMSYWGQGTLVTVSS
375	41E02	EVQLVESGGGLVQPGGSLTLSCVASGSSSTINAIGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTGSGTSKSYWGQGTLVTVSS
376	41F07	EVQLVESGGGLVQPGGSLTLSCVASGSTSYINAMGWYRRAPGKQRELVAGISSDGSNMYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFSNMSGTTRRYWGQGTLVTVSS
377	41G01	EVQLVESGGGLVQPGGSLTLSCVASGSTSSVNALGWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVPGSAMGYWGQGTLVTVSS
378	42A03	EVQLVESGGGLVQPGGSLTLSCVASGSTSLSNAVGWYRRAPGKQRELVAGISSDGSKVSAE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRAESGSSMGYWGQGTLVTVSS
379	42A06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSTNAIGWYRRAPGKQRELVAGISSDGSKVYDD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTLYGSSRSYWGQGTLVTVSS
380	42A07	EVQLVESGGGLVQPGGSLTLSCVASGLTSTINAMGWYRRAPGKQRELVAGISSDGSKVYDD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFSPFSGSDTGYWGQGTLVTVSS
381	42A08	EVQLVESGGGLVQPGGSLTLSCVASGVSPSKNAIGWYRRAPGKQRELVAGISSDGSAVYVG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFSTFSGSSISYWGQGTLVTVSS
382	42A11	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAVGWYRRAPGKQRELVAGISSDGSYVYSE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTLAGSEMRYWGQGTLVTVSS
383	42B06	EVQLVESGGGLVQPGGSLTLSCVASGSTTMNNAMAWYRRAPGKQRELVAGISSDSSHVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSGVRYWGQGTLVTVSS
384	42B10	EVQLVESGGGLVQPGGSLTLSCVASGSTSKINAIGWYRRAPGKQRELVAGISSDSSIVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRPGAGHSNSYWGQGTLVTVSS
385	42C01	EVQLVESGGGLVQPGGSLTLSCVASGQTTALNAMGWYRRAPGKQRELVAGISSDGSEVNTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRASGTAMSYWGQGTLVTVSS
386	42C03	EVQLVESGGGLVQPGGSLTLSCVASGATSSINAIGWYRRAPGKQRELVAGISSDGSKLSSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFTSASGTDLSYWGQGTLVTVSS
387	42C07	EVQLVESGGGLVQPGGSLTLSCVASGSTSTINAMGWYRRAPGKQRELVAGISSDNSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRSANGSSKRYWGQGTLVTVSS

388	42C08	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAMGWYRRAPGKQRELVAGISSDGSRVYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFKTIAGAGMRYWGQGTLVTVSS
389	42C10	EVQLVESGGGLVQPGGSLTLSCVASGSTSLVNAMGWYRRAPGKQRELVAGISSDGSLVYAE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRYGSGSSLSYWGQGTLVTVSS
390	42C11	EVQLVESGGGLVQPGGSLTLSCVASGSTSLNNAIGWYRRAPGKQRELVAGISSDGSVVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVPGASMKYWGQGTLVTVSS
391	42D05	EVQLVESGGGLVQPGGSLTLSCVASGSTSPVNAMAWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVDGSAISYWGQGTLVTVSS
392	42D06	EVQLVESGGGLVQPGGSLTLSCVASGTTSSMNAIGWYRRAPGKQRELVAGISSDGSKLYDE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVKGSGGSYWGQGTLVTVSS
393	42D07	EVQLVESGGGLVQPGGSLTLSCVASGETSSINAMAWYRRAPGKQRELVAGISSDYSKLYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSRGYWGQGTLVTVSS
394	42D08	EVQLVESGGGLVQPGGSLTLSCVASGSTSTINAIGWYRRAPGKQRELVAGISSDSSKVYTE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRPGPGSQMAYWGQGTLVTVSS
395	42E01	EVQLVESGGGLVQPGGSLTLSCVASGSTYSMNAMGWYRRAPGKQRELVAGISSDGSQVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVAGSASGYWGQGTLVTVSS
396	42E02	EVQLVESGGGLVQPGGSLTLSCVASGSPSSINAYGWYRRAPGKQRELVAGISSDGSKVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGSSYSYWGQGTLVTVSS
397	42E05	EVQLVESGGGLVQPGGSLTLSCVASGSTSTINAIGWYRRAPGKQRELVAGISSDGSKVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFINLKGSSMAYWGQGTLVTVSS
398	42E06	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDGSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRMVTGSYGGYWGQGTLVTVSS
399	42E07	EVQLVESGGGLVQPGGSLTLSCVASGSISSINAMGWYRRAPGKQRELVAGISSDGSSVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFKSSYGLPMRYWGQGTLVTVSS
400	42F01	EVQLVESGGGLVQPGGSLTLSCVASGSTQVNNAMAWYRRAPGKQRELVAGISSDGSQVYYG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFKTVSGQSLRYWGQGTLVTVSS
401	42F08	EVQLVESGGGLVQPGGSLTLSCVASGSTASFNAMAWYRRAPGKQRELVAGISSDGSKVYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVTGRAARYWGQGTLVTVSS
402	42F10	EVQLVESGGGLVQPGGSLTLSCVASGSPLSINAIGWYRRAPGKQRELVAGISSDGSKVSAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFGPAIGASRTYWGQGTLVTVSS
403	42G05	EVQLVESGGGLVQPGGSLTLSCVASGSTTFINAIGWYRRAPGKQRELVAGISSDGSKVYED SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTVSGAPKSYWGQGTLVTVSS
404	42G07	EVQLVESGGGLVQPGGSLTLSCVASGSTSSINAIGWYRRAPGKQRELVAGISSDRSKVYAD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFHTVSGSSMSYWGQGTLVTVSS
405	42H05	EVQLVESGGGLVQPGGSLTLSCVASGETDTINAVGWYRRAPGKQRELVAGISSDGSKVYAE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRRLEGYSNRYWGQGTLVTVSS
406	42H08	EVQLVESGGGLVQPGGSLTLSCVASGSTSPINAIGWYRRAPGKQRELVAGISSDGSVVTTE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFRTGSGSSMGYWGQGTLVTVSS
407	42H11	EVQLVESGGGLVQPGGSLTLSCVASGSITSSNAMGWYRRAPGKQRELVAGISSDGSHVHQE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYYFTTVTGSSMSYWGQGTLVTVSS
408	51A01	EVQLVESGGGLVQPGGSLTLSCAASRYSVSNLSMAWYRQAPGKKRELVAGISADGSTVYVE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYYWTERRPYWGQGTLVTVSS
409	51A02	EVQLVESGGGLVQPGDSLTLSCAASMSTVSVLSMAWYRQAPGKKRELVAGISSDGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAIYYCYAYSWDDAHPYWGQGTLVTVSS
410	51A03	EVQLVESGGGLVQPGGSLTLSCAASDSYVSLLSMAWYRQAPGKKRELVAGISVDGSTHYVA SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWMTRLTYWGQGTLVTVSS
411	51A05	EVQLVESGGGLVQPGGSLTLSCAASDSAVSVLSIAWYRQAPGKKRELVAGISTDGSKHYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYDWADAQPYWGQGTLVTVSS
412	51B01	EVQLVESGGGLVQPGGSLTLSCAASHSSVTSLSLAWYRQAPGKKRELVAGISYDGSKYYAE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTDRLPYWGQGTLVTVSS
413	51B04	EVQLVESGGGLVQPGGSLTLSCAASDSVVKFLSMAWYRQAPGKKRELVAGISANGSRTYME SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWATRLPYWGQGTLVTVSS
414	51B11	EVQLVESGGGLVQPGGSLTLSCAASDPSVWNLSMAWYRQAPGKKRELVAGISPDGSTDYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYKWSNRLPYWGQGTLVTVSS
415	51C02	EVQLVESGGGLVQPGGSLTLSCAASGTSVMLLSLAWYRQAPGKKRELVAGISPNGSAVYTE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYGWKTRQPYWGQGTLVTVSS
416	51D01	EVQLVESGGGLVQPGGSLTLSCAASSSPVSNLSLAWYRQAPGKKRELVAGISPDGSTAYME SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWPNRRGYWGQGTLVTVSS
417	51D03	EVQLVESGGGLVQPGGSLTLSCAASWRSVLLLSVAWYRQAPGKKRELVAGISNDGSTDYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYDWTTRQRYWGQGTLVTVSS
418	51E02	EVQLVESGGGLVQPGGSLTLSCAASSSSVQYLSMAWYRQAPGKKRELVAGISTDGSAVYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYNWSYAQPYWGQGTLVTVSS

419	51E03	EVQLVESGGGLVQPGGSLTLSCAASGTSVSLLSLAWYRQAPGKKRELVAGISTGGSTHYIE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYNWTDSLQYWGQGTLVTVSS
420	51E05	EVQLVESGGGLVQPGGSLTLSCAASLSSVSNLSIAWYRQAPGKKRELVAGISTDGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTSLPYWGQGTLVTVSS
421	51F01	EVQLVESGGGLVQPGGSLTLSCAASMYSVSFLSMAWYRQAPGKKRELVAGISNEGSTYYMD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYKWRSRSTYWGQGTLVTVSS
422	51F02	EVQLVESGGGLVQPGGSLTLSCAASKSSVSHLSLAWYRQAPGKKRELVAGISADGSHVYTN SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSQTTRDPYWGQGTLVTVSS
423	51F03	EVQLVESGGGLVQPGGSLTLSCAASYTSVLDLSIAWYRQAPGKKRELVAGISDDGSRYYTD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTARDTYWGQGTLVTVSS
424	51F04	EVQLVESGGGLVQPGGSLTLSCAASMSDVSFLSMAWYRQAPGKKRELVAGISAEGSTLYME SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWTSRLSYWGQGTLVTVSS
425	51G02	EVQLVESGGGLVQPGGSLTLSCAASESSVSFLSSAWYRQAPGKKRELVAGISTDGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRSRYWGQGTLVTVSS
426	51G04	EVQLVESGGGLVQPGGSLTLSCAASGDSVSLLSMAWYRQAPGKKRELVAGISANGSTSYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYNWTSRYRYWGQGTLVTVSS
427	51G10	EVQLVESGGGLVQPGGSLTLSCAASGSDVWYLSLAWYRQAPGKKRELVAGISDDGSRHYIE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWKTRFPYWGQGTLVTVSS
428	51H04	EVQLVESGGGLVQPGGSLTLSCAASKSAVAFLSIAWYRQAPGKKRELVAGISPDGSTVYIE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRYPYWGQGTLVTVSS
429	51H05	EVQLVESGGGLVQPGGSLTLSCAASFSAVAYLSMAWYRQAPGKKRELVAGISDDGSTVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYEWTNALPYWGQGTLVTVSS
430	52B01	EVQLVESGGGLVQPGGSLTLSCAASVYSVYDLSTAWYRQAPGKKRELVAGISDDGSTVYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWITRSPYWGQGTLVTVSS
431	52C04	EVQLVESGGGLVQPGGSLTLSCAASGDSVSFLSMAWYRQAPGKKRELVAGISDEGSTVYIG SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRRQYWGQGTLVTVSS
432	52D04	EVQLVESGGGLVQPGGSLTLSCAASSSSVSLLSLAWYRQAPGKKRELVAGISDDGSIVYMD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWITRSPYWGQGTLVTVSS
433	53A04	EVQLVESGGGLVQPGGSLTLSCAASADSVSFLSIAWYRQAPGKKRELVAGISDDGSKHYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWEESRQYWGQGTLVTVSS
434	53A05	EVQLVESGGGLVQPGGSLTLSCAASASSVTLLSIAWYRQAPGKKRELVAGISTDGSTDYLH SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYTWTTRLPYWGQGTLVTVTS
435	53A09	EVQLVESGGGLVQPGGSLTLSCAASADSVSFLSIAWYRQAPGKKRELVAGISDDGSKHYFD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWEESRQYWGQGTLVTVSS
436	53B05	EVQLVESGGGLVQPGGSLTLSCAASGTSVWLLSMAWYRQAPGKKRELVAGISYDGSTVYVE SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRQPYWGQGTLVTVSS
437	53B06	EVQLVESGGGLVQPGGSLTLSCAASGSSVSILSIAWYRQAPGKKRELVAGISDDGSTVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYVWGTRLPYWGQGTLVTVSS
438	53C03	EVQLVESGGGLVQPGGSLTLSCAASGTAVSNLSIAWYRQAPGKKRELVAGISDDGSTVYVD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYEWTNALPYWGQGTLVTVSS
439	53C04	EVQLVESGGGLVQPGGSLTLSCAASGSAVSMLSLAWYRQAPGKKRELVAGISDDGSQVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYRWEDALTYWGQGTLVTVSS
440	53H03	EVQLVESGGGLVQPGGSLTLSCAASGMTVFFLSMAWYRQAPGKKRELVAGISVDGSTVYSD SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTRYPYWGQGTLVTVSS
441	53H04	EVQLVESGGGLVQPGGSLTLSCAASQYSVTFLSVAWYRQAPGKKRELVAGISDDGSNVYID SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWIDSLRYWGQGTLVTVSS
442	54B05	EVQLVESGGGLVQPGGSLTLSCAASGETVSFLSLAWYRQAPGKKRELVAGISTDGSTVYFV SVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWTTPRAYWGQGTLVTVSS

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446	DL3	ESIFSINVMA
447	DL80	GSSFSITSMA
448	DL18	SSIFSISSMS
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450	DL17	GSTLNIKIMA
451	DL46	GSTLNIKIMA

452	DL15	GSTFNIKTMA
453	DL26	GSTFNIKLMA
454	DL83	GSTFNFKIMA
455	DL5	GFMFSSYSMS
456	DL22	GFMFSSYSMS
457	DL85	GFTFSSHSMS
458	DL69	GSSFSHNTMG
459	DL27	GGRFSYATMG
460	DL51	GSRFSYATMG
461	DL54	GSTFTSNVMG
462	DL11	GSSVSFLSMA
463	DL19	GSSVSFLSMA
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476	DL84	GFTLDYYAIG
477	DL2	GSTSSINAMG
478	DL43	GSTSSINAMG
479	DL92	GITSSVYSMG
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494	DL61	GTIFTASTMG
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498	DH12	GSIFRGAAMY
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695	3C06	GTSVSFLSIA
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719	3F010	YSSVSRLSMA
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724	3G06	GSSVKFLSMA
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727	3G09	GSSVSVLSMA
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731	3H03	GSSVRFLSMA
732	3H06	GSSVSQLSMA
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736	3H011	GSSVKFLSMA
737	4A01	GSSVRFLSMA
738	4A02	GSSVRFLSMA
739	4A04	GSRVSFLSMA

740	4A05	GSSVSFLSLA
741	4A06	GSSVRFLSMA
742	4A07	GSKVSFLSMA
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745	4A011	GSKVSFLSMA
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776	4E02	GSQVSFLSMA
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788	4F010	GSSVSFLSMA
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812	41D01	GSTSSINAMA
813	41D02	GQTYRVNAFG
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818	41F07	GSTSYINAMG
819	41G01	GSTSSVNALG
820	42A03	GSTSLSNAVG
821	42A06	GSTSSTNAIG
822	42A07	GLTSTINAMG
823	42A08	GVSPSKNAIG
824	42A11	GSTSSINAVG
825	42B06	GSTTMNNAMA
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831	42C10	GSTSLVNAMG
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833	42D05	GSTSPVNAMA
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841	42E07	GSISSINAMG
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869	51G10	GSDVWYLSLA
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871	51H05	FSAVAYLSMA
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873	52C04	GDSVSFLSMA
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877	53A09	ADSVSFLSIA
878	53B05	GTSVWLLSMA
879	53B06	GSSVSILSIA
880	53C03	GTAVSNLSIA
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888	DL3	RITSGGSTNYADSVKG
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890	DL18	AITTFDYTNYADSVKG
891	DL94	AITSFGSTNYADSVKG
892	DL17	TLTSGGNTNYADSVKG
893	DL46	TLTSGGNTNYADSVKG
894	DL15	TLTSGGNTNYADSVKG
895	DL26	TLTSGGNTNYADSVKG
896	DL83	SLTSEGLTNYRDSVKG
897	DL5	AITTWGSTNYADSVKG
898	DL22	AITSYGSTNYADSVKG
899	DL85	AITTYGSTNYIDSVKG
900	DL69	RITTFGTTNYADSVKG
901	DL27	RITSSGFSTNYADSVKG
902	DL51	RITSSGFSTNYADSVKG
903	DL54	NMHSGGSTNYADSVKG
904	DL11	GISVDGSTNYADSVKG
905	DL19	GISVDGSTNYADSVKG
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908	DL67	GISVDGSTNYADSVKG
909	DL56	GISTDGSTNYVDSVKG
910	DL13	GISTDGTTNYVDSVKD
911	DL77	GISTDGTTNYVDSVKD
912	DL79	GISTDGTTNYVDSVKD
913	DL20	GISTDGSTNYADSVKG
914	DL41	GISTDGSTNYADSVKG
915	DL59	GISTDGSTNYADSVKG
916	DL16	GISSDGSTNYVDSVKG
917	DL6	GISADGSTDYIDSVKG
918	DL84	GISSDGSTHYVDSVKG
919	DL2	GISSDGSKNYADSVKG
920	DL43	GISSDGSKVYADSVKG
921	DL92	GSSSDGSTHYVDSVRG
922	DL10	IIRSGGSSNYADTVKG
923	DL82	LITSGGSSNYADTVKG
924	DL23	IITSGGSSNYADTVKG
925	DL42	TIFDGSYTNYADSVKG
926	DL45	SITTFGSTNYADPVKG
927	DL58	TITRDGTRNYADSLKG
928	DL70	TISRGGTRTYADSVKG

929	DL89	LIGSAGSTKYADSVKG
930	DL38	RITSGGITKYADSVKG
931	DL52	RITSGGITKYADSVKG
932	DL64	RITSGGITKYADSVKG
933	DL33	RITSGGITKYADSVKG
934	DL12	AITTSGNTSYADSVKG
935	DL29	VITRGGATNYADSVKG
936	DL61	SIAGDGRTNYAESTEG
937	DH1	VITSFSSTNYADSVKG
938	DH10	IIRSGGSSNYADTVKG
939	DH11	GISVDGSTNYADSVKG
940	DH12	AITTSGNTSYADSVKG
941	DH15	TLTSGGNTNYADSVKG
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961	DH67	GISVDGSTNYADSVKG
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964	DH80	AITSFGSTNYADSVKD
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967	DH84	GISSDGSTHYVDSVKG
968	DH89	LIGSAGSTKYADSVKG
969	DH92	GSSSDGSTHYVDSVRG
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972	1A03	GISSDGSKVYADSVKG
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974	1A05	GISSDGSKVYADSVKG
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976	1A07	GISSDGSKVYADSVKG

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1468	1F07	FRTVSGSSMRY
1469	1F08	FRNVSGSSMRY
1470	1F09	FRTVTGSSMRY
1471	1F010	FRTVSGSSMRY
1472	1F011	FRTVKGSSMRY
1473	1F012	FRTNSGSSMRY
1474	1G01	FRTVSGASMRY
1475	1G04	FRTVNLSSMRY
1476	1G05	FRTVTGSSMRY
1477	1G06	FRKVSGSSARY
1478	1G07	FRTYSGSSMRY
1479	1G09	FRTVSKSSMRY
1480	1G011	FKTVSGSSMRY
1481	1H01	FRTRSGSSMRY
1482	1H02	FRTSSGSSMRY
1483	1H06	FRFLSGSSMRY
1484	1H07	FRTVSGSSMRY
1485	1H08	FRLVSGSSMRY
1486	1H010	FRTVSGSSMRF
1487	1H011	FRTQSGSSMRY
1488	1H012	FRTVSGSSMPY
1489	2A01	FRTLSGSSMRY
1490	2A03	FRTVSGSAMRY
1491	2A04	FRTTSGSSMRY
1492	2A05	FRTVSGTSMRY
1493	2A06	FRTRSGSSMRY
1494	2A08	FRTSSGSSMRY
1495	2A09	FRTVSGSSMSY
1496	2A011	FRPVSGSSMRY
1497	2B01	FRHVSGSSMRY
1498	2B02	FRTKSGSSMRY
1499	2B03	FTTVSGSSMRY

1500	2B05	FHTVSGSSMRY
1501	2B07	FRTVRGSSMRY
1502	2B010	FRTVLGSSMRY
1503	2B011	FRTVSGSSMRS
1504	2B012	FRTVRGSSMRY
1505	2C01	FRYVSGSSMRY
1506	2C02	FRTVYGSSMRY
1507	2C04	FRTVLGSSMRY
1508	2C06	YRTVSGSSMRY
1509	2C07	FRSVSGSSMRY
1510	2C08	FRRVSGSSMRY
1511	2C09	FRTVSGTSMRY
1512	2C010	FRTVAGSSMRY
1513	2D02	FRIVSGSSMRY
1514	2D03	FRTVSGVSMRY
1515	2D04	FRTVQGSSMRY
1516	2D05	FRTASGSSMRY
1517	2D06	FRTVSGSSSRY
1518	2D07	FRTVQGSSMRY
1519	2D09	FRTVRGSSMRY
1520	2D010	FRTKSGSSMRY
1521	2D011	FRTVWGSSMRY
1522	2D012	FRTRSGSSMRY
1523	2E01	FHTVCGTSMGY
1524	2E02	FRTVSGSSQRY
1525	2E05	FRTVSGSSMSY
1526	2E06	FRTVRGSSMRY
1527	2E08	FRTQSGSSMRY
1528	2E09	FRTLSGSSMRY
1529	2E010	FHTVSGSSMRY
1530	2E011	FRRVSGSSMRY
1531	2F01	FRLVSGSSMRY
1532	2F02	FRTVSGSYMRY
1533	2F03	FRTVGGSSMRY
1534	2F06	FRTHSGSSMRY
1535	2F07	FRTVSTSSMRY
1536	2F08	FRTVLGTSMRY
1537	2F09	FRTVSGSSMRY
1538	2F11	FRTVSGSSMGY
1539	2G03	FRTVSGSSMRA
1540	2G04	FRILSGSSMRY
1541	2G07	FRTVQGSSMRY
1542	2G08	FRTVSGQSMGY
1543	2G09	FRTVSGSSARY
1544	2G011	FRYVSGSSMRY
1545	2H010	FRTVSGSSMRY
1546	2H011	FRRVSGSSMRY
1547	2H02	FHTVSGSSMRY

1548	2H03	FRQVSGSSMRY
1549	2H04	FRTVSGSYMRY
1550	2H06	FRTASGSSMRY
1551	2H07	FRTVSGHSMRY
1552	2H08	FRTVSGSSSRY
1553	2E05-M106Y	FRTVSGSSYSY
1554	2E05-M106Q	FRTVSGSSQSY
1555	3A01	YRWTRRYTY
1556	3A02	YRWRTRYTY
1557	3A03	YRWTTRRTY
1558	3A04	YRWTTRYIY
1559	3A05	YRWRTRYTY
1560	3A06	YRWTRRYTY
1561	3A08	YRWRTRYTY
1562	3A09	YRWTTRYIY
1563	3A010	YRWTTRRTY
1564	3A011	YRWRTRYTY
1565	3B01	YRWTTRYTY
1566	3B02	YRWRTRYTY
1567	3B04	YHWTTRYTY
1568	3B05	YRWTTRRTY
1569	3B06	YRWTTRYTY
1570	3B07	YRWTTRYTY
1571	3B09	YRWTTRYAY
1572	3B010	YRWVTRYTY
1573	3B011	YRWVTRYTY
1574	3C01	YRWSTRYTY
1575	3C02	YRWRTRYTY
1576	3C03	YRWTTRGTY
1577	3C04	YRWDTRYTY
1578	3C05	YRWTTRRTY
1579	3C06	YRWRTRYTY
1580	3C08	YRWTGRYTY
1581	3C09	YRWRTRYTY
1582	3C011	YRWRTRYTY
1583	3D01	YRWITRYTY
1584	3D02	YRWITRYTY
1585	3D03	YRWRTRYTY
1586	3D05	YRWTRRYTY
1587	3D07	YSWTTRYTY
1588	3D08	YRWTNRYTY
1589	3D09	YRWTTRYRY
1590	3D010	YRWTTRYTY
1591	3D011	YRWTTRYKY
1592	3E01	YRWHTRYTY
1593	3E02	YRWTRRYTY
1594	3E03	YRWMTRYTY

1595	3E04	YRWTTRYRY
1596	3E09	YRWSTRYTY
1597	3E011	YRWTTRYTF
1598	3F03	YRWRTRYTY
1599	3F05	YRWTTRRTY
1600	3F06	YRWATRYTY
1601	3F08	YRWHTRYTY
1602	3F09	YRWGTRYTY
1603	3F010	YRWTTRNTY
1604	3F011	YRWRTRYTY
1605	3G01	YRWTTRYAY
1606	3G02	YRWRTRYTY
1607	3G04	YRWTTRRTY
1608	3G06	YRWTTRRTY
1609	3G07	YRWTSRYTY
1610	3G08	YRWTTRVTY
1611	3G09	YRWTTRTTY
1612	3G010	YRWRTRYTY
1613	3G011	YRWATRYTY
1614	3H01	YRWTTRRTY
1615	3H03	LRWTTRYTY
1616	3H06	YRWTTRGTY
1617	3H07	YRWRTRYTY
1618	3H09	YRWTTRATY
1619	3H010	YRWTTRRTY
1620	3H011	YRWPTRYTY
1621	4A01	YRWRTRYTY
1622	4A02	YRWKTRYTY
1623	4A04	YRWSTRYTY
1624	4A05	YRWKTRRTY
1625	4A06	YRWTTRRTY
1626	4A07	YRWTTRYRY
1627	4A08	YRWRTRYTY
1628	4A010	YRWTTRYKY
1629	4A011	YRWKTRYTY
1630	4A09	YRWTTRVTY
1631	4B01	YRWTTRFTY
1632	4B02	YRWTTRFTY
1633	4B04	YRWRTRYTY
1634	4B05	YRWTTRYTH
1635	4B06	YRWTRRYTY
1636	4B07	YRWTTRYTY
1637	4B08	YRWTTRSTY
1638	4B09	YSWTTRYTY
1639	4B011	YRWTTRGTY
1640	4C01	YRWKTRYTY
1641	4C02	YRWTTRFTY
1642	4C03	YRWRTRYTY

1643	4C05	YRWTTRRTY
1644	4C06	YRWSTRYTY
1645	4C07	YRWTTRLTY
1646	4C08	YRWTRRYTY
1647	4C010	YRWTTRLTY
1648	4C011	YRWTRRYTY
1649	4D01	YRWTTRRTY
1650	4D02	YQWTTRYTY
1651	4D03	YRWTRRYTY
1652	4D04	YRWTTRMTY
1653	4D05	YRWTTRRTY
1654	4D06	YRWTTRYRY
1655	4D08	YRWLTRYTY
1656	4D09	YEWTTRYTY
1657	4D010	YRWRTRYTY
1658	4D011	YRWRTRYTY
1659	4E01	YRWRTRYTY
1660	4E02	YRWSTRYTY
1661	4E06	YRWTTRLTY
1662	4E07	YRWTTRLTY
1663	4E08	YKWTTRYTY
1664	4E09	YRWTTRSTY
1665	4E010	YRWRTRYTY
1666	4E011	YRWSTRYTY
1667	4F02	YRWTTRYTY
1668	4F03	YRWRTRYTY
1669	4F04	YRWLTRYTY
1670	4F08	YRWRTRYTY
1671	4F09	YRWTTRYTY
1672	4F010	YRWTTRYRY
1673	4F011	YRWTTRYTY
1674	4G01	YRWPTRYTY
1675	4G02	YRWTTRHTY
1676	4G03	YRWTRRYTY
1677	4G05	YRWHTRYTY
1678	4G07	YRWTNRYTY
1679	4G08	YRWTTRYRY
1680	4G09	YRWTTRRTY
1681	4G010	YRWSTRYTY
1682	4G011	YRWSTRYTY
1683	4H01	YRWRTRYTY
1684	4H03	YRWTTRYTY
1685	4H04	YEWTTRYTY
1686	4H05	YRWTTRSTY
1687	4H06	YRWTTRYTY
1688	4H07	YRWSTRYTY
1689	4H08	YRWSTRYTY
1690	4H09	YRWTYRYTY

1691	4H011	YRWTTRLTY
1692	4D09-M34L	YEWTTRYTY
1693	4H11-M34L	YRWTTRLTY
1694	41B11	FRPAAGSPMRY
1695	41C02	FRTVDGSPLRY
1696	41D01	FRTVSGSSKRY
1697	41D02	FSAGSGTEMSY
1698	41D03	FGSLSGSSTTY
1699	41D07	FGSVSGSWTRY
1700	41E01	FRLVSGSSMSY
1701	41E02	FRTGSGTSKSY
1702	41F07	FSNMSGTTRRY
1703	41G01	FRTVPGSAMGY
1704	42A03	FRAESGSSMGY
1705	42A06	FRTLYGSSRSY
1706	42A07	FSPFSGSDTGY
1707	42A08	FSTFSGSSISY
1708	42A11	FRTLAGSEMRY
1709	42B06	FRTVSGSGVRY
1710	42B10	FRPGAGHSNSY
1711	42C01	FRRASGTAMSY
1712	42C03	FTSASGTDLSY
1713	42C07	FRSANGSSKRY
1714	42C08	FKTIAGAGMRY
1715	42C10	FRYGSGSSLSY
1716	42C11	FRTVPGASMKY
1717	42D05	FRTVDGSAISY
1718	42D06	FRTVKGSGGSY
1719	42D07	FRTVSGSSRGY
1720	42D08	FRPGPGSQMAY
1721	42E01	FRTVAGSASGY
1722	42E02	FRTVSGSSYSY
1723	42E05	FINLKGSSMAY
1724	42E06	FRMVTGSYGGY
1725	42E07	FKSSYGLPMRY
1726	42F01	FKTVSGQSLRY
1727	42F08	FRTVTGRAARY
1728	42F10	FGPAIGASRTY
1729	42G05	FRTVSGAPKSY
1730	42G07	FHTVSGSSMSY
1731	42H05	FRRLEGYSNRY
1732	42H08	FRTGSGSSMGY
1733	42H11	FTTVTGSSMSY
1734	51A01	YYWTERRPY
1735	51A02	YSWDDAHPY
1736	51A03	YRWMTRLTY
1737	51A05	YDWADAQPY

1738	51B01	YSWTDRLPY
1739	51B04	YRWATRLPY
1740	51B11	YKWSNRLPY
1741	51C02	YGWKTRQPY
1742	51D01	YRWPNRRGY
1743	51D03	YDWTTRQRY
1744	51E02	YNWSYAQPY
1745	51E03	YNWTDSLQY
1746	51E05	YSWTTSLPY
1747	51F01	YKWRSRSTY
1748	51F02	YSQTTRDPY
1749	51F03	YRWTARDTY
1750	51F04	YRWTSRLSY
1751	51G02	YSWTTRSRY
1752	51G04	YNWTSRYRY
1753	51G10	YSWKTRFPY
1754	51H04	YSWTTRYPY
1755	51H05	YEWTNALPY
1756	52B01	YSWITRSPY
1757	52C04	YSWTTRRQY
1758	52D04	YSWITRSPY
1759	53A04	YRWEESRQY
1760	53A05	YTWTTRLPY
1761	53A09	YRWEESRQY
1762	53B05	YSWTTRQPY
1763	53B06	YVWGTRLPY
1764	53C03	YEWTNALPY
1765	53C04	YRWEDALTY
1766	53H03	YSWTTRYPY
1767	53H04	YSWIDSLRY
1768	54B05	YSWTTPRAY

SEQ ID NO:	**Description**	**AA Sequence**
1769	Anti-HSA sdAb clone 6C	EVQLVESGGGLVQPGNSLRLSCAASGFTFSRFGMSWVRQAPGKGLEWVSS ISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSRSSQGTLVTVSS
1770	Anti-HSA sdAb clone 7A	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGADTLYADSLKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSKSSQGTLVTVSS
1771	Anti-HSA sdAb clone 7G	EVQLVESGGGLVQPGNSLRLSCAASGFTYSSFGMSWVRQAPGKGLEWVSS ISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSKSSQGTLVTVSS

1772	Anti-HSA sdAb clone 8H	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGTDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSRSSQGTLVTVSS
1773	Anti-HSA sdAb clone 9A	EVQLVESGGGLVQPGNSLRLSCAASGFTFSRFGMSWVRQAPGKGLEWVSS ISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSKSSQGTLVTVSS
1774	Anti-HSA sdAb clone 10G	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGRDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSVSSQGTLVTVSS
1775	wt anti-HSA	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLEWVSS ISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSRSSQGTLVTVSS
1776	Anti-HSA sdAb clone 6CE	EVQLVESGGGLVQPGNSLRLSCAASGFTFSRFGMSWVRQAPGKGLEWVSS ISGSGSDTLYAESVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSRSSQGTLVTVSS
1777	Anti-HSA sdAb clone 8HE	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGTDTLYAESVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSRSSQGTLVTVSS
1778	Anti-HSA sdAb clone 10GE	EVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSS ISGSGRDTLYAESVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGG SLSVSSQGTLVTVSS
1779	wt anti-HSA CDR1	GFTFSSFGMS
1780	wt anti-HSA CDR2	SISGSGSDTLYADSVK
1781	wt anti-HSACDR3	GGSLSR
1782	CDR1 variant 1	GFTFSRFGMS
1783	CDR1 variant 2	GFTFSKFGMS
1784	CDR1 variant 3	GFTYSSFGMS
1785	CDR2 variant 1	SISGSGADTLYADSLK
1786	CDR2 variant 2	SISGSGTDTLYADSVK
1787	CDR2 variant 3	SISGSGRDTLYADSVK
1788	CDR2 variant 4	SISGSGSDTLYAESVK
1789	CDR2 variant 5	SISGSGTDTLYAESVK
1790	CDR2 variant 6	SISGSGRDTLYAESVK
1791	CDR3 variant 1	GGSLSK
1792	CDR3 variant 2	GGSLSV

SEQ ID NO:	Description	AA Sequence
1793	Anti-CD3, clone 2B2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVAR IRSKYNNYATYYADQVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HANFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCASSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCTLWYSNRWVFGGGTKLTVL
1794	Anti-CD3, clone 9F2	EVQLVESGGGLVQPGGSLKLSCΛΛSGFEFNKYΛMNWVRQΛPGKGLEWVΛR IRSKYNKYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSFGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYDNRWVFGGGTKLTVL
1795	Anti-CD3, clone 5A2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSHISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGYVTSGNYPNWVQQKPGQAPRGLIGGTSFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWIFGGGTKLTVL
1796	Anti-CD3, clone 6A2	EVQLVESGGGLVQPGGSLKLSCAASGFMFNKYAMNWVRQAPGKGLEWVAR IRSKSNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSYISYWATWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSFGAVTSGNYPNWVQQKPGQAPRGLIGGTKLLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNSWVFGGGTKLTVL
1797	Anti-CD3, clone 2D2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYKDSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSPISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVVSGNYPNWVQQKPGQAPRGLIGGTEFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1798	Anti-CD3, clone 3F2	EVQLVESGGGLVQPGGSLKLSCAASGFTYNKYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADEVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSPISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL

		TVSPGGTVTLTCGSSKGAVTSGNYPNWVQQKPGQAPRGLIGGTKELAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCTLWYSNRWVFGGGTKLTVL
1799	Anti-CD3, clone 1A2	EVQLVESGGGLVQPGGSLKLSCAASGNTFNKYAMNWVRQAPGKGLEWVAR IRSKYNNYETYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HTNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTYFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1800	Anti-CD3, clone 1C2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNNYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADAVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSQISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTDGNYPNWVQQKPGQAPRGLIGGIKFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1801	Anti-CD3, clone 2E4	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAVNWVRQAPGKGLEWVAR IRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGESTGAVTSGNYPNWVQQKPGQAPRGLIGGTKILAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1802	Anti-CD3, clone 10E4	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYPMNWVRQAPGKGLEWVAR IRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKNEDTAVYYCVR HGNFNNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTKGNYPNWVQQKPGQAPRGLIGGTKMLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVFGGGTKLTVL
1897	Anti-CD3, clone 2H2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADEVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSPISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVVSGNYPNWVQQKPGQAPRGLIGGTEFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1898	Anti-CD3, clone 2A4	EVQLVESGGGLVQPGGSLKLSCAASGNTFNKYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGDSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL

		TVSPGGTVTLTCGSSTGAVTHGNYPNWVQQKPGQAPRGLIGGTKVLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1803	Anti-CD3, clone 10B2	EVQLVESGGGLVQPGGSLKLSCAASGFTFNNYAMNWVRQAPGKGLEWVAR IRSGYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSYTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFNAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYANRWVFGGGTKLTVL
1804	Anti-CD3, clone 1G4	EVQLVESGGGLVQPGGSLKLSCAASGFEFNKYAMNWVRQAPGKGLEWVAR IRSKYNNYETYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSLISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSSGAVTSGNYPNWVQQKPGQAPRGLIGGTKFGAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1805	wt anti-CD3	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL
1806	Anti-CD3, clone 2G5	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYALNWVRQAPGKGLEWVAR IRSKYNNYATEYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSPISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTNFLAPGT PERFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWAFGGGTKLTVL
1807	Anti-CD3, clone 8A5	EVQLVESGGGLVQPGGSLKLSCAASGFTFNEYAMNWVRQAPGKGLEWVAR IRSKYNNYATYYADDVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVR HGNFGNSGISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTVGNYPNWVQQKPGQAPRGLIGGTEFLAPGT PARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVL

Linkers

SEQ ID NO:	Description	AA Sequence
1808	Linker	GGGGSGGGS
1809	Linker	(GS)n
1810	Linker	(GGS)n

1811	Linker	(GGGS)n
1812	Linker	(GGSG)n
1813	Linker	(GGSGG)n
1814	Linker	(GGGGS)n
1815	Linker	(GGGGG)n
1816	Linker	$(GGG)_n$
1817	Linker	(GGGGSGGGGSGGGGSGGGGS)
1818	Linker	GGGGSGGGGSGGGGS
1819	6X Histidine	HHHHHH

CD3 Binding Domain CDR Sequences

SEQ ID NO:	CD3 Binding Domain CDR	Sequence
1820	HC CDR1 variant 1	GNTFNKYAMN
1821	HC CDR1 variant 2	GFEFNKYAMN
1822	HC CDR1 variant 3	GFMFNKYAMN
1823	HC CDR1 variant 4	GFTYNKYAMN
1824	HC CDR1 variant 5	GFTFNNYAMN
1825	HC CDR1 variant 6	GFTFNGYAMN
1826	HC CDR1 variant 7	GFTFNTYAMN
1827	HC CDR1 variant 8	GFTFNEYAMN
1828	HC CDR1 variant 9	GFTFNKYPMN
1829	HC CDR1 variant 10	GFTFNKYAVN
1830	HC CDR1 variant 11	GFTFNKYAIN
1831	HC CDR1 variant 12	GFTFNKYALN

1832	HC CDR2 variant 1	RIRSGYNNYATYYADSVK
1833	HC CDR2 variant 2	RIRSKSNNYATYYADSVK
1834	HC CDR2 variant 3	RIRSKYNKYATYYADSVK
1835	HC CDR2 variant 4	RIRSKYNNYETYYADSVK
1836	HC CDR2 variant 5	RIRSKYNNYATEYADSVK
1837	HC CDR2 variant 6	RIRSKYNNYATYYKDSVK
1838	HC CDR2 variant 7	RIRSKYNNYATYYADEVK
1839	HC CDR2 variant 8	RIRSKYNNYATYYADAVK
1840	HC CDR2 variant 9	RIRSKYNNYATYYADQVK
1841	HC CDR2 variant 10	RIRSKYNNYATYYADDVK
1842	HC CDR3 variant 1	HANFGNSYISYWAY
1843	HC CDR3 variant 2	HTNFGNSYISYWAY
1844	HC CDR3 variant 3	HGNFNNSYISYWAY
1845	HC CDR3 variant 4	HGNFGDSYISYWAY
1846	HC CDR3 variant 5	HGNFGNSHISYWAY
1847	HC CDR3 variant 6	HGNFGNSPISYWAY
1848	HC CDR3 variant 7	HGNFGNSQISYWAY
1849	HC CDR3 variant 8	HGNFGNSLISYWAY
1850	HC CDR3 variant 9	HGNFGNSGISYWAY
1851	HC CDR3 variant 10	HGNFGNSYISYWAT
1852	LC CDR1 variant 1	ASSTGAVTSGNYPN
1853	LC CDR1 variant 2	GESTGAVTSGNYPN
1854	LC CDR1 variant 3	GSYTGAVTSGNYPN
1855	LC CDR1 variant 4	GSSFGAVTSGNYPN
1856	LC CDR1 variant 5	GSSKGAVTSGNYPN
1857	LC CDR1 variant 6	GSSSGAVTSGNYPN
1858	LC CDR1 variant 7	GSSTGYVTSGNYPN

1859	LC CDR1 variant 8	GSSTGAVVSGNYPN
1860	LC CDR1 variant 9	GSSTGAVTDGNYPN
1861	LC CDR1 variant 10	GSSTGAVTKGNYPN
1862	LC CDR1 variant 11	GSSTGAVTHGNYPN
1863	LC CDR1 variant 12	GSSTGAVTVGNYPN
1864	LC CDR1 variant 13	GSSTGAVTSGYYPN
1865	LC CDR2 variant 1	GIKFLAP
1866	LC CDR2 variant 2	GTEFLAP
1867	LC CDR2 variant 3	GTYFLAP
1868	LC CDR2 variant 4	GTSFLAP
1869	LC CDR2 variant 5	GTNFLAP
1870	LC CDR2 variant 6	GTKLLAP
1871	LC CDR2 variant 7	GTKELAP
1872	LC CDR2 variant 8	GTKILAP
1873	LC CDR2 variant 9	GTKMLAP
1874	LC CDR2 variant 10	GTKVLAP
1875	LC CDR2 variant 11	GTKFNAP
1876	LC CDR2 variant 12	GTKFGAP
1877	LC CDR2 variant 13	GTKFLVP
1878	LC CDR3 variant 1	TLWYSNRWV
1879	LC CDR3 variant 2	ALWYSNRWV
1880	LC CDR3 variant 3	VLWYDNRWV
1881	LC CDR3 variant 4	VLWYANRWV
1882	LC CDR3 variant 5	VLWYSNSWV
1883	LC CDR3 variant 6	VLWYSNRWI
1884	LC CDR3 variant 7	VLWYSNRWA
1890	Exemplary anti-DLL3	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWVRQAPGKGLEWVARIRSKYNNYA TYYADQVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQG

	trispecific protein (anti-CD3:anti-ALB:anti-DLL3 configuration)(CAT)	TLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCASSTGAVTSGNYPNW VQQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCTLWYSN RWVFGGGTKLTVLGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWV RQAPGKGLEWVSSISGSGRDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYC TIGGSLSVSSQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLTLSCAASSSSVSL LSLAWYRQAPGKKRELVAGISDDGSIVYMDSVKGRFTISRDNAKNSVYLQMNSLRAEDT AVYYCYAYSWITRSPYWGQGTLVTVSSHHHHHH
1891	Exemplary anti-DLL3 trispecific protein (anti-DLL3:anti-ALB:anti-CD3 configuration)(TAC)	EVQLVESGGGLVQPGGSLTLSCAASSSSVSLLSLAWYRQAPGKKRELVAGISDDGSIVY MDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAYSWITRSPYWGQGTLVTVSSG GGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFSKFGMSWVRQAPGKGLEWVSSI SGSGRDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSSQGTL VTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWVRQAPGKGL EWVARIRSKYNNYATYYADQVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANF GNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCA SSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPGTPARFSGSLLGGKAALTLSGVQP EDEAEYYCTLWYSNRWVFGGGTKLTVLHHHHHH

DLL3 Protein UniProtKB Accession Q9NYJ7 (SEQ ID NO: 1885)

>sp|Q9NYJ7|DLL3_HUMAN Delta-like protein 3 OS=Homo sapiens OX=9606 GN=DLL3 PE=1 SV=1
MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFF
RVCLKPGLSEEAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTF
SFIIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEP
PAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCL
EGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTC
PRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQ
PCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALG
FGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAP
PGLRPGDPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHAL
PDALNNLRTQEGSGDGPSSSVDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRA
GQRQHLLFPYPSSILSVK

51X5 (SEQ ID NO: 1886)

EVQLVESGGGLVQPGGSLTLSCAASLSSVSVLSIAWYRQAPGKKRELVAGISTDGSTVYIDSVKGRFTISRDNAKNS
VYLQMNSLRAEDTAVYYCYAYSWTTSLPYWGQGTLVTVSS

51X5 CDR1 (SEQ ID NO: 1887)

LSSVSVLSIA

51X5 CDR2 (SEQ ID NO: 1888)

GISTDGSTVYIDSVKG

51X5 CDR3 (SEQ ID NO: 1889)

YSWTTSLPY

>NP_058637.1 delta-like protein 3 isoform 1 precursor [Homo sapiens](SEQ ID No. 1892)
MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSE
EAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAW
SLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPL
EDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDG
NPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNC

EKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALG
FGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQR
YLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS
VDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLFPYPSSILSVK

DLL3 Protein Sequence (SEQ ID NO: 1893)

RSPCSARLPCRLFFRVCLKPGLSEEAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFI
IETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRC
GPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGP
CDGNPCANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRV
DRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERAD
PCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYL

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating cancer, the method comprising administration of an effective amount of a Delta Like Ligand 3 (DLL3) targeting trispecific protein to a subject, wherein said protein comprises

(a) a first domain (A) which specifically binds to human CD3;

(b) a second domain (B) which is a half-life extension domain; and

(c) a third domain (C) which specifically binds to DLL3,

wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 100 mg.

2. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 14 mg.

3. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 5 mg.

4. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 2 mg.

5. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1 μg to about 1 mg.

6. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 15 μg to about 3600 μg.

7. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 15 μg.

8. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 45 μg.

9. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 135 μg.

10. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 405 μg.

11. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 1215 μg.

12. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 3600 μg.

13. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 5 mg.

14. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 7 mg.

15. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 10 mg.

16. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 12 mg.

17. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 14 mg.

18. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 20 mg.

19. The method of claim 1, wherein the DLL3 targeting trispecific protein is administered at a dosage of about 50 mg.

20. The method of any one of claims 1-19, wherein the DLL3 targeting trispecific protein is administered once a week.

21. The method of any one of claims 1-19, wherein the DLL3 targeting trispecific protein is administered twice per week.

22. The method of any one of claims 1-19, wherein the DLL3 targeting trispecific protein is administered every other week.

23. The method of any one of claims 1-19, wherein the DLL3 targeting trispecific protein is administered every three weeks.

24. The method of any one of claims 1-23, wherein the DLL3 targeting trispecific protein is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally.

25. A method of treating cancer, the method comprising administration of an effective amount of a DLL3 targeting trispecific protein to a subject, wherein said protein comprises

(a) a first domain (A) which specifically binds to human CD3;

(b) a second domain (B) which is a half-life extension domain; and

(c) a third domain (C) which specifically binds to DLL3,

wherein the domains are linked in the order H_2N-(A)-(B)-(C)-COOH, or by linkers L1 and L2, and wherein the DLL3 targeting trispecific protein is administered according to a schedule comprising the following steps:

(i) administration of a first dose of the DLL3 targeting trispecific protein, and

(ii) administration of a second dose of the DLL3 targeting trispecific protein, wherein the second dose is higher than the first dose.

26. The method of claim 25, wherein the first dose is about 1 mg to about 50 mg.

27. The method of claim 25, wherein the first dose is about 1 mg to about 20 mg.

28. The method of claim 25, wherein the first dose is about 1 mg to about 10 mg.

29. The method of claim 25, wherein the first dose is about 1 mg to about 5 mg.

30. The method of claim 25, wherein the first dose is about 1 mg to about 3 mg.

31. The method of claim 25, wherein the first dose is about 2000 μg.

32. The method of claim 25, wherein the first dose is about 3600 μg.

33. The method of any one of claims 25-32, wherein the first dose is administered for about 1 week to about 36 weeks.

34. The method of any one of claims 25-32, wherein the first dose is administered for about 1 week to about 27 weeks.

35. The method of any one of claims 25-32, wherein the first dose is administered for about 1 week to about 18 weeks.

36. The method of any one of claims 25-32, wherein the first dose is administered for about 1 week to about 9 weeks.

37. The method of any one of claims 25-36, wherein the first dose is administered once a day.

38. The method of any one of claims 25-36, wherein the first dose is administered twice a day.

39. The method of any one of claims 25-36, wherein the first dose is administered three times a day.

40. The method of any one of claims 25-36, wherein the first dose is administered five times a day.

41. The method of any one of claims 25-36, wherein the first dose is administered once a week.

42. The method of any one of claims 25-36, wherein the first dose is administered twice per week.

43. The method of any one of claims 25-36, wherein the first dose is administered every other week.

44. The method of any one of claims 25-36, wherein the first dose is administered every three weeks.

45. The method of any one of claims 25-44, wherein the first dose is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally.

46. The method of claim 25, wherein the second dose is about 1 mg to about 100 mg.

47. The method of claim 25, wherein the second dose is about 1 mg to about 50 mg.

48. The method of claim 25, wherein the second dose is about 50 mg to about 100 mg.

49. The method of claim 25, wherein the second dose is about 7.2 mg.

50. The method of claim 25, wherein the second dose is about 12 mg.

51. The method of claim 25, wherein the second dose is about 24 mg.

52. The method of any one of claims 25-51, wherein the second dose is administered for about 1 week to about 36 weeks.

53. The method of any one of claims 25-51, wherein the second dose is administered for about 1 week to about 27 weeks.

54. The method of any one of claims 25-51, wherein the second dose is administered for about 1 week to about 18 weeks.

55. The method of any one of claims 25-51, wherein the second dose is administered for about 1 week to about 9 weeks.

56. The method of any one of claims 25-55, wherein the second dose is administered once a day.

57. The method of any one of claims 25-55, wherein the second dose is administered twice a day.

58. The method of any one of claims 25-55, wherein the second dose is administered three times a day.

59. The method of any one of claims 25-55, wherein the second dose is administered five times a day.

60. The method of any one of claims 25-55, wherein the second dose is administered once a week.

61. The method of any one of claims 25-55, wherein the second dose is administered twice per week.

62. The method of any one of claims 25-55, wherein the second dose is administered every other week.

63. The method of any one of claims 25-55, wherein the second dose is administered every three weeks.

64. The method of any one of claims 25-63, wherein the second dose is maintained to the end of the schedule after the administration of the first dose.

65. The method of any one of claims 25-64, wherein the second dose is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally.

66. The method of any one of claims 1-65, wherein the DLL3 targeting trispecific protein has an elimination half-time of at least 12 hours, at least 20 hours, at least 25 hours, at least 30 hours, at least 35 hours, at least 40 hours, at least 45 hours, at least 50 hours, or at least 100 hours.

67. The method of any one of claims 1-66, wherein the third domain comprises a VHH domain.

68. The method of claim 67, wherein the VHH domain is human, humanized, affinity matured, or a combination thereof.

69. The method of any one of claims 1-68, wherein the third domain comprises one or more sequences selected from the group consisting of SEQ ID NO: 1-442.

70. The method of any one of claims 1-69, wherein the first domain comprises a variable light chain and variable heavy chain each of which is capable of specifically binding to human CD3.

71. The method of claim 70, wherein the first domain is humanized or human.

72. The method of any one of claims 1-71, wherein the second domain binds human serum albumin.

73. The method of claim 72, wherein the second domain comprises a scFv, a variable heavy domain (VH), a variable light domain (VL), a peptide, a ligand, or a small molecule.

74. The method of any one of claims 1-73, wherein linkers L1 and L2 are each independently selected from $(GS)_n$ (SEQ ID NO: 1809), $(GGS)_n$ (SEQ ID NO: 1810), $(GGGS)_n$ (SEQ ID NO: 1811), $(GGSG)_n$ (SEQ ID NO: 1812), $(GGSGG)_n$ (SEQ ID NO: 1813), $(GGGGS)_n$ (SEQ ID NO: 1814), or GGGGSGGGS (SEQ ID NO: 1808), wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

75. The method of any one of claims 1-73, wherein linkers L1 and L2 are each independently $(GGGGS)_4$ (SEQ ID NO: 1817), $(GGGGS)_3$ (SEQ ID NO: 1818) or GGGGSGGGS (SEQ ID NO: 1808).

76. The method of any one of claims 1-75, wherein the domains are linked in the order H_2N-(C)-L1-(B)-L2-(A)-COOH.

77. The method of any one of claims 1-76, wherein the DLL3 targeting trispecific protein is less than about 80 kDa.

78. The method of any one of claims 1-76, wherein the DLL3 targeting trispecific protein is about 50 to about 75 kDa.

79. The method of any one of claims 1-76, wherein the DLL3 targeting trispecific protein is less than about 60 kDa.

80. The method of any one of claims 1-79, wherein the DLL3 targeting trispecific protein comprises a sequence selected from the group consisting of SEQ ID NO: 1890-1891.

81. The method of any one of claims 1-79, wherein the DLL3 targeting trispecific protein comprises a sequence as set forth in SEQ ID NO: 1890.

82. The method of any one of claims 1-81, wherein the cancer is a tumorous disease, an autoimmune disease or an infection disease associated with DLL3.

83. The method of any one of claims 1-81, wherein the cancer is a neuroendocrine cancer, a prostate cancer, a lung cancer, a stomach cancer, a squamous cell carcinoma, a pancreatic cancer, a cholangiocarcinoma, a triple negative breast cancer or an ovarian cancer.

84. The method of any one of claims 1-81, wherein the cancer is a small cell lung cancer.

85. The method of any one of claims 1-81, wherein the cancer is a neuroendocrine prostate cancer.

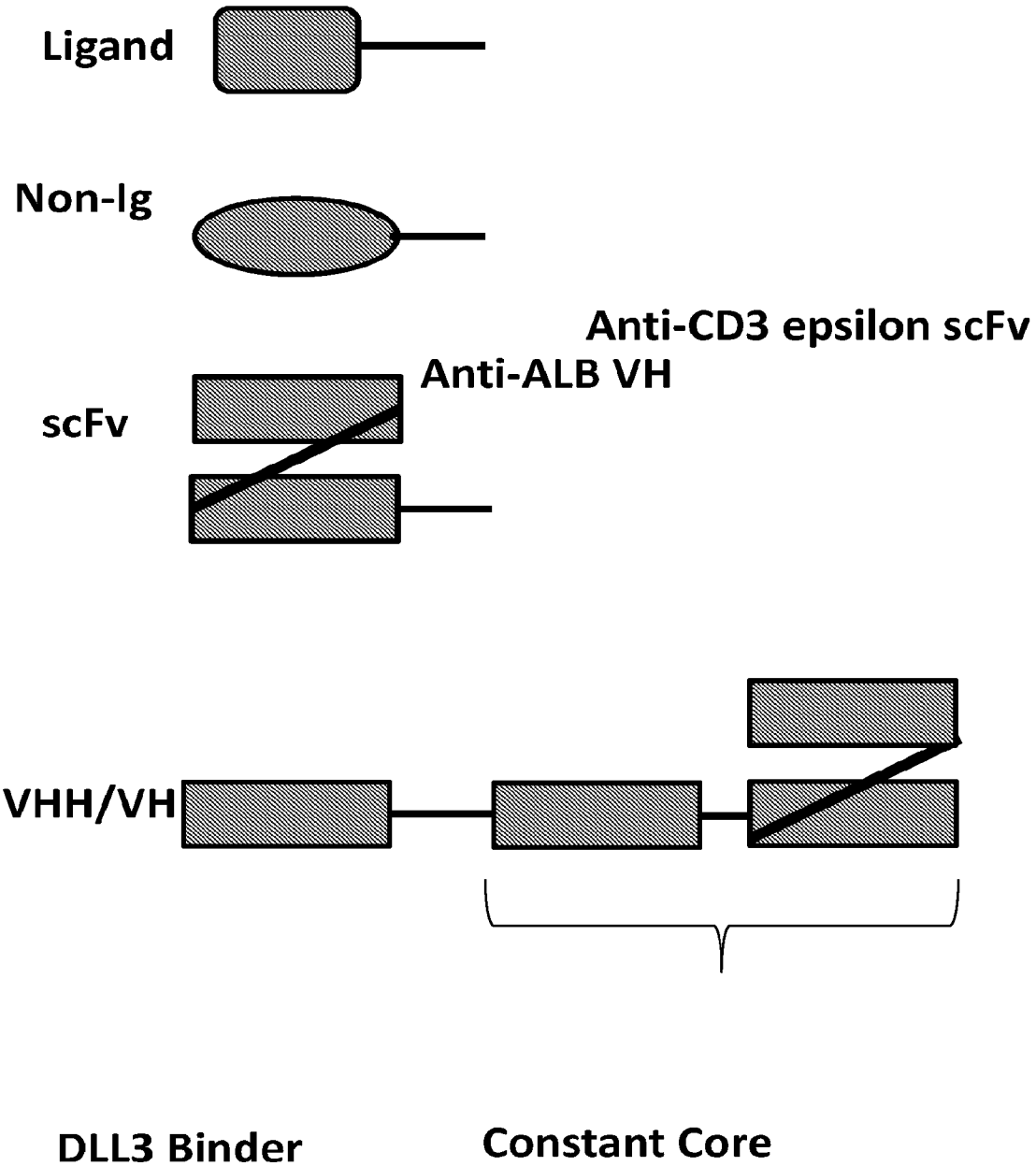
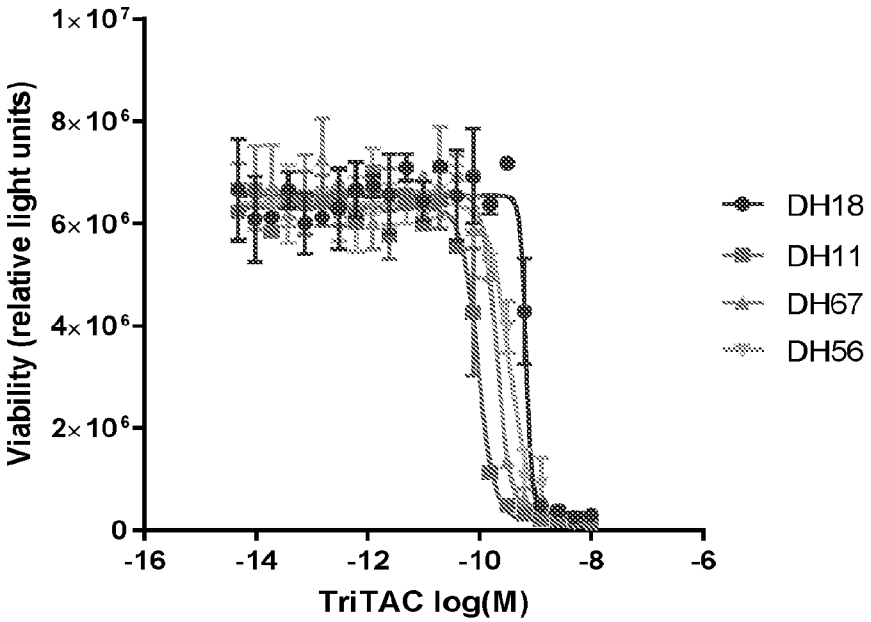

Ligand
Non-Ig
Anti-CD3 epsilon scFv
Anti-ALB VH
scFv
VHH/VH
DLL3 Binder
Constant Core

FIG. 1

FIG. 2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8×10^6
6×10^6
4×10^6
2×10^6
0
Viability (relative light units)
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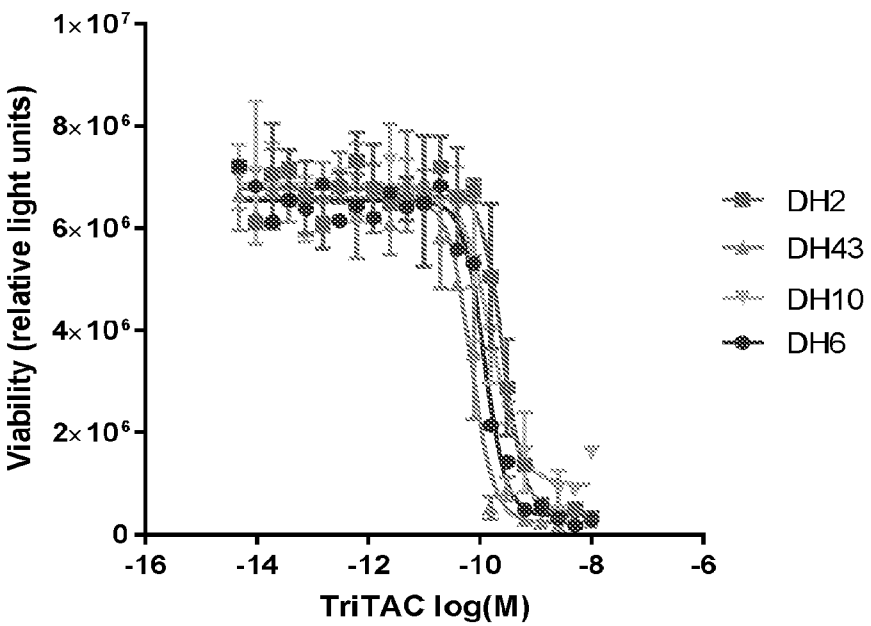
-14
-12
-10
-8
-6
TriTAC log(M)
DH18
DH11
DH67
DH56

FIG. 3


1×10^7
8×10^6
6×10^6
4×10^6
2×10^6
0
Viability (relative light units)
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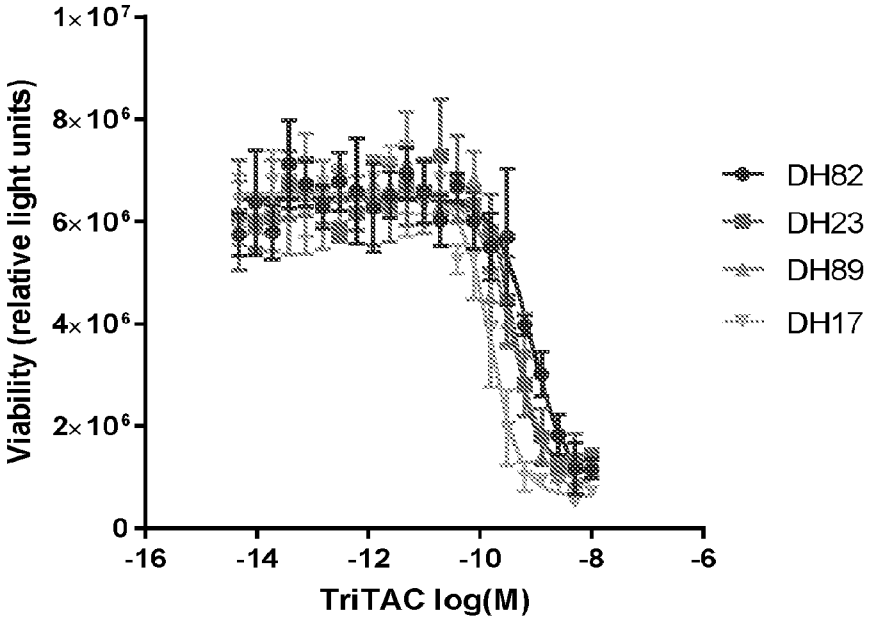
-14
-12
-10
-8
-6
TriTAC log(M)
DH2
DH43
DH10
DH6

FIG. 4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6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
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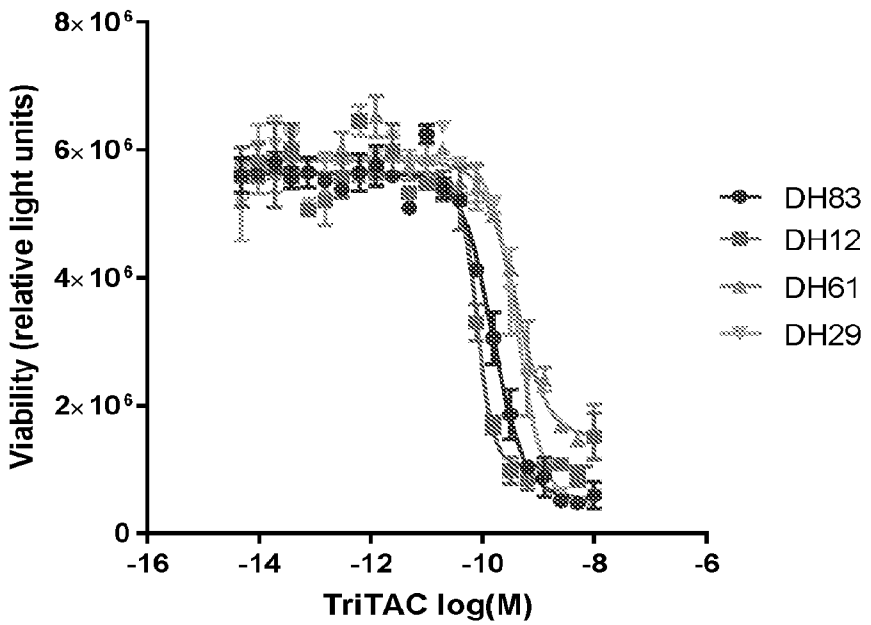
-14
-12
-10
-8
-6
TriTAC log(M)
DH82
DH23
DH89
DH17

FIG. 5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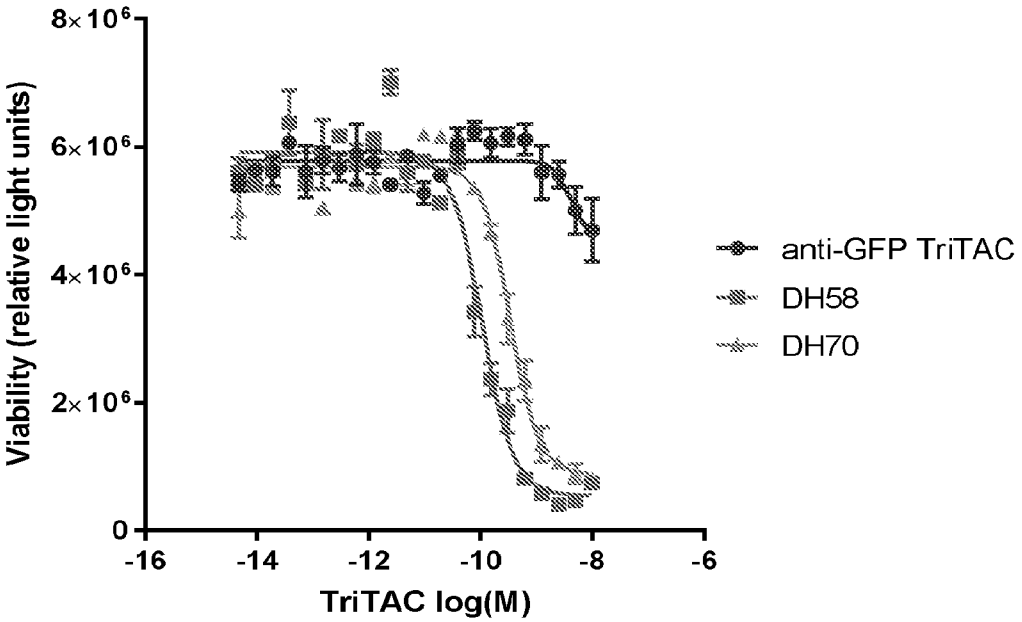
6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
-16
-14
-12
-10
-8
-6
TriTAC log(M)
DH83
DH12
DH61
DH29

FIG. 6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6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
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-14
-12
-10
-8
-6
TriTAC log(M)
anti-GFP TriTAC
DH58
DH70

FIG. 7

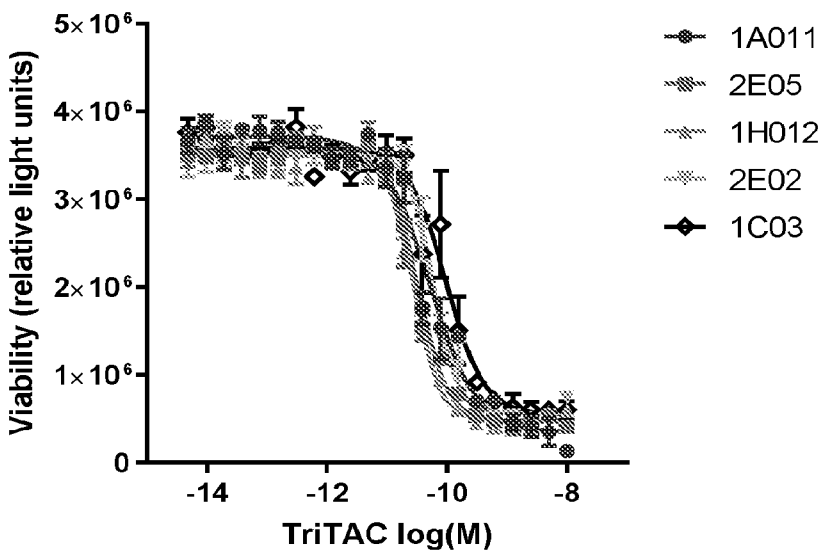

5×10⁶
4×10⁶
3×10⁶
2×10⁶
1×10⁶
0
Viability (relative light units)
-14
-12
-10
-8
TriTAC log(M)
1A011
2E05
1H012
2E02
1C03

FIG. 8

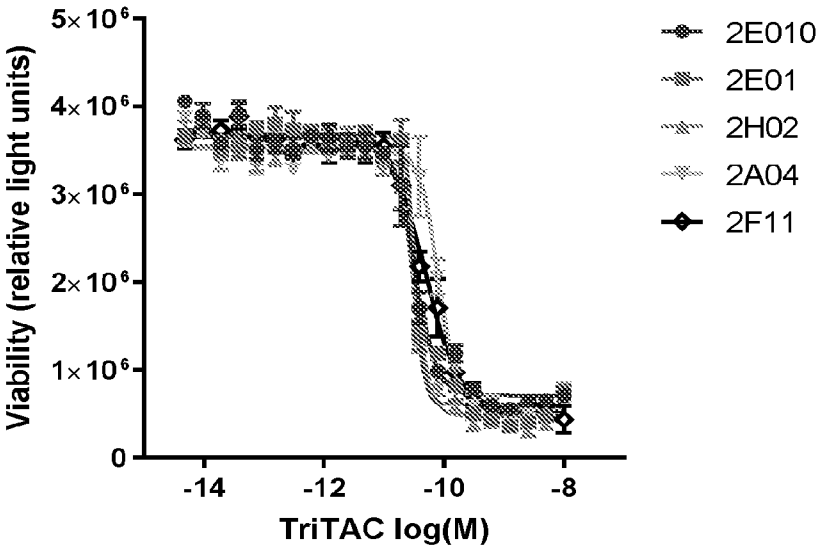

Viability (relative light units)
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
-14
-12
-10
-8
TriTAC log(M)
2E010
2E01
2H02
2A04
2F11

FIG. 9

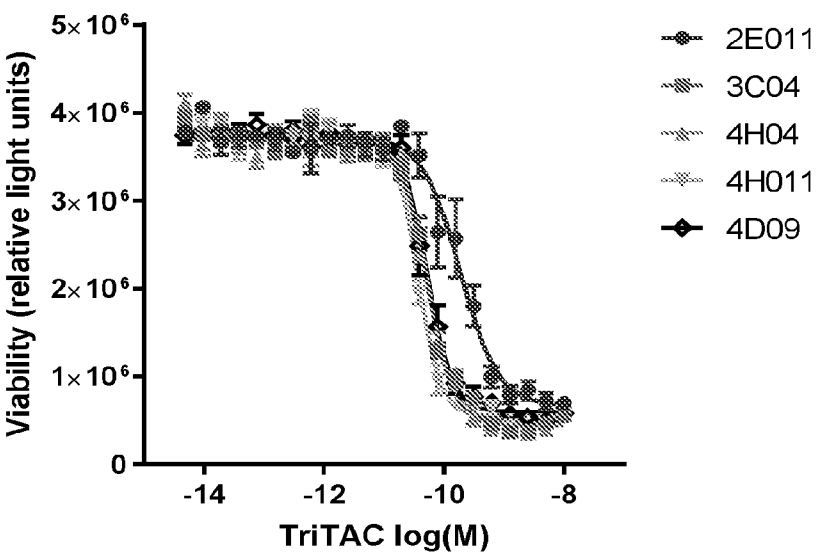

Viability (relative light units)
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
-14
-12
-10
-8
TriTAC log(M)
2E011
3C04
4H04
4H011
4D09

FIG. 10

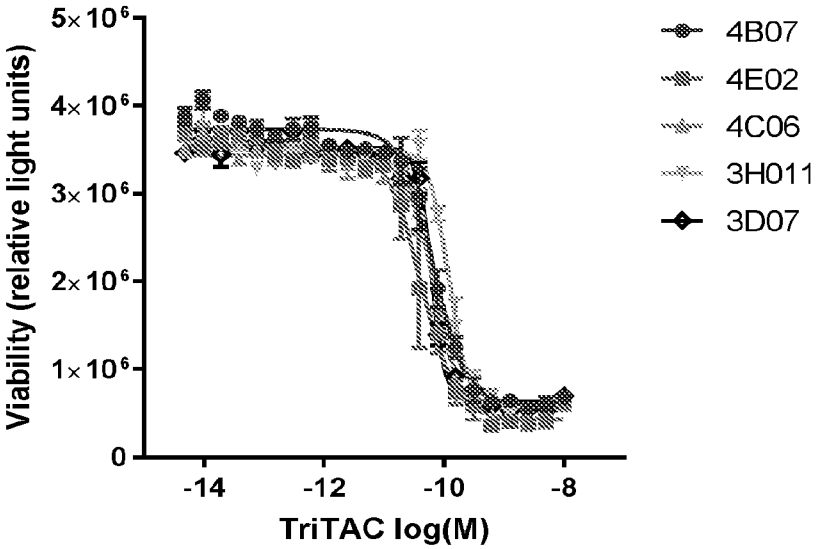

Viability (relative light units)
5×10⁶
4×10⁶
3×10⁶
2×10⁶
1×10⁶
0
-14
-12
-10
-8
TriTAC log(M)
4B07
4E02
4C06
3H011
3D07

FIG. 11

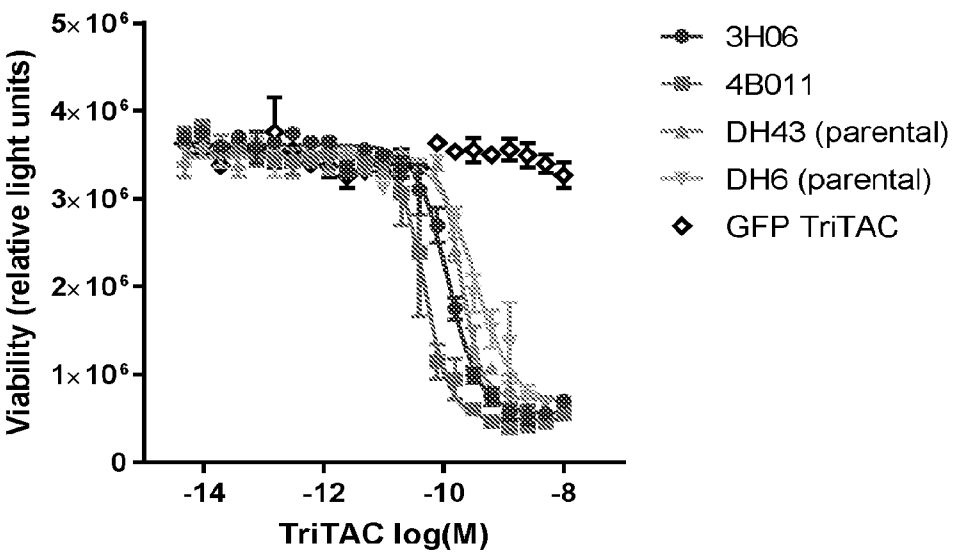

Viability (relative light units)
5×10⁶
4×10⁶
3×10⁶
2×10⁶
1×10⁶
0
-14
-12
-10
-8
TriTAC log(M)
3H06
4B011
DH43 (parental)
DH6 (parental)
GFP TriTAC

FIG. 12

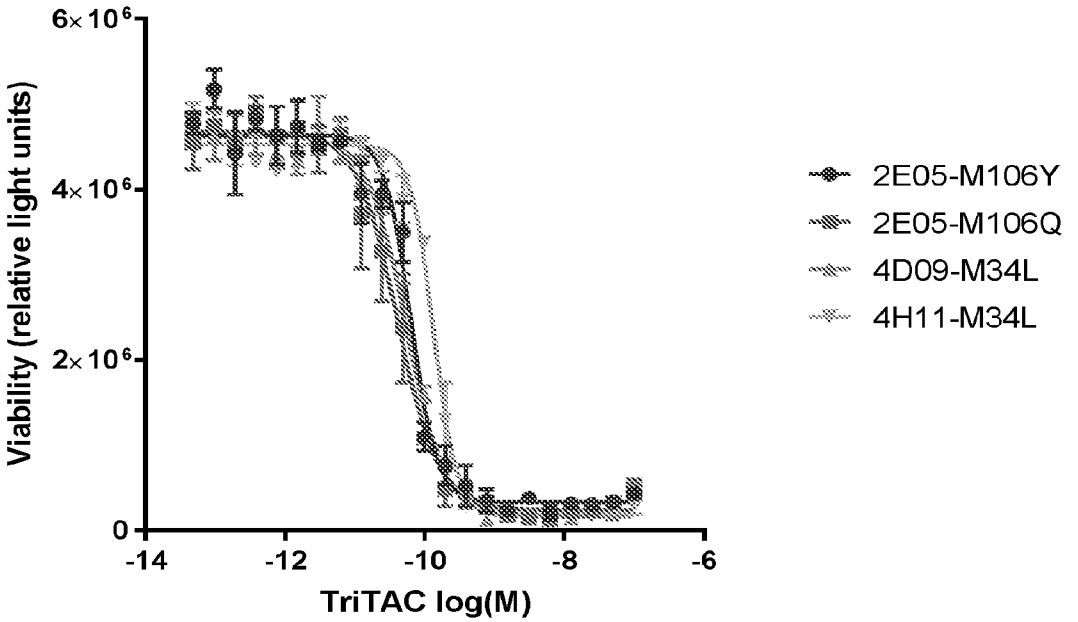

6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
-14
-12
-10
-8
-6
TriTAC log(M)
2E05-M106Y
2E05-M106Q
4D09-M34L
4H11-M34L

FIG. 13

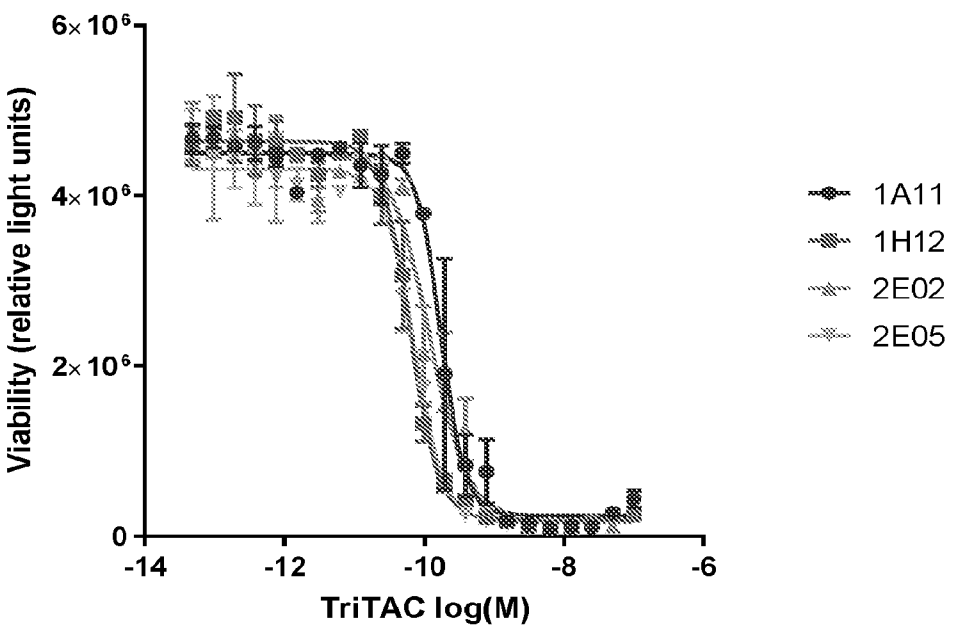

6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
-14
-12
-10
-8
-6
TriTAC log(M)
1A11
1H12
2E02
2E05

FIG. 14

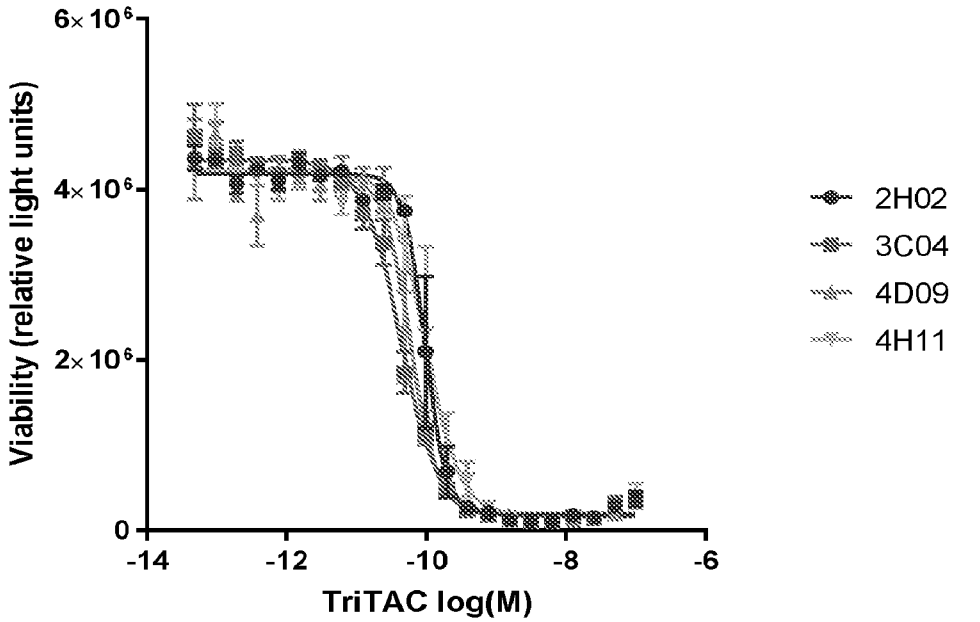

6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
-14
-12
-10
-8
-6
TriTAC log(M)
2H02
3C04
4D09
4H11

FIG. 15

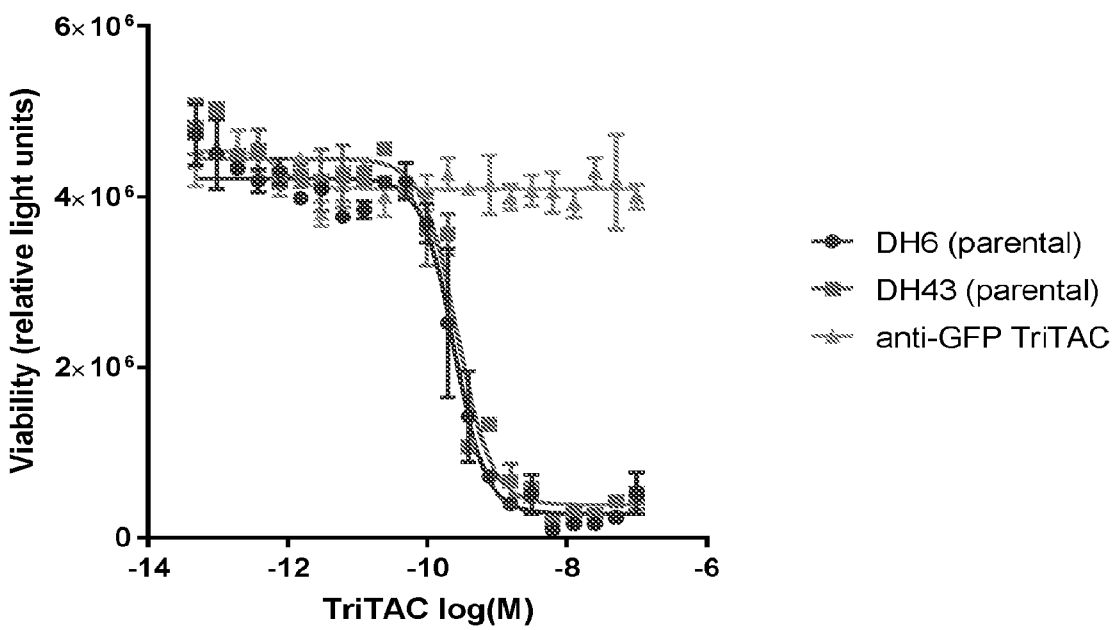

6×10⁶
4×10⁶
2×10⁶
0
Viability (relative light units)
-14
-12
-10
-8
-6
TriTAC log(M)
DH6 (parental)
DH43 (parental)
anti-GFP TriTAC

FIG. 16

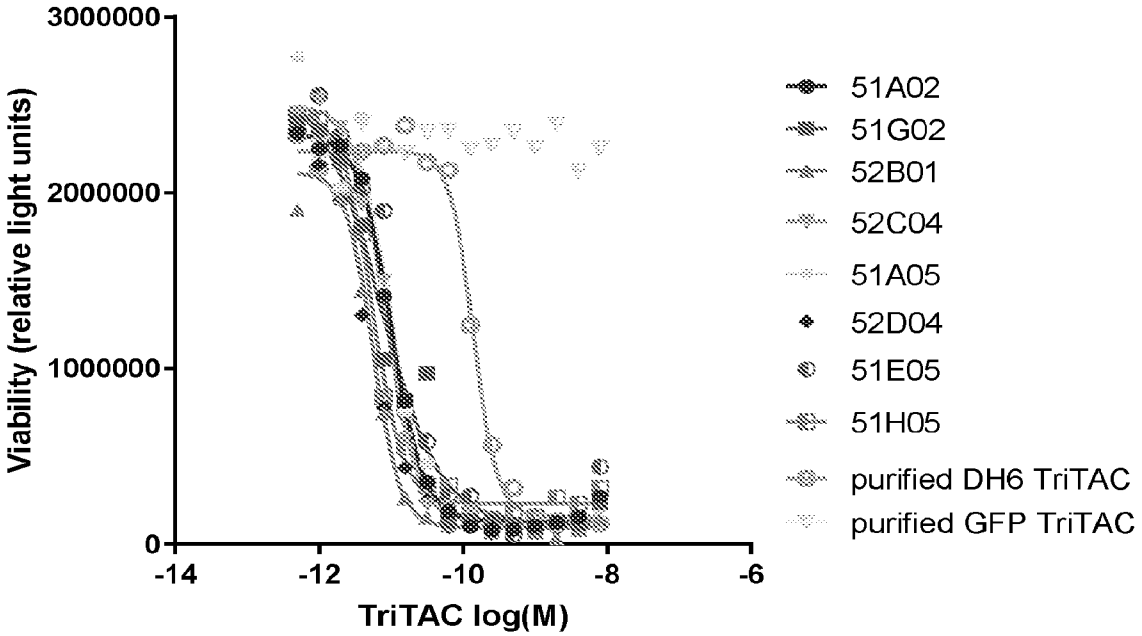

3000000
2000000
1000000
0
Viability (relative light units)
-14
-12
-10
-8
-6
TriTAC log(M)
51A02
51G02
52B01
52C04
51A05
52D04
51E05
51H05
purified DH6 TriTAC
purified GFP TriTAC

FIG. 17

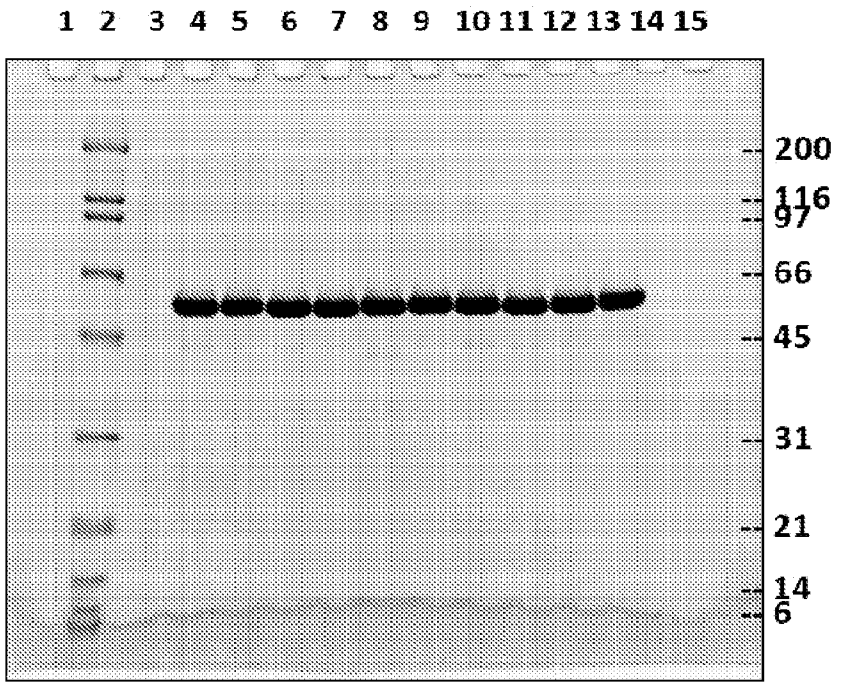

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
200
116
97
66
45
31
21
14
6

FIG. 18

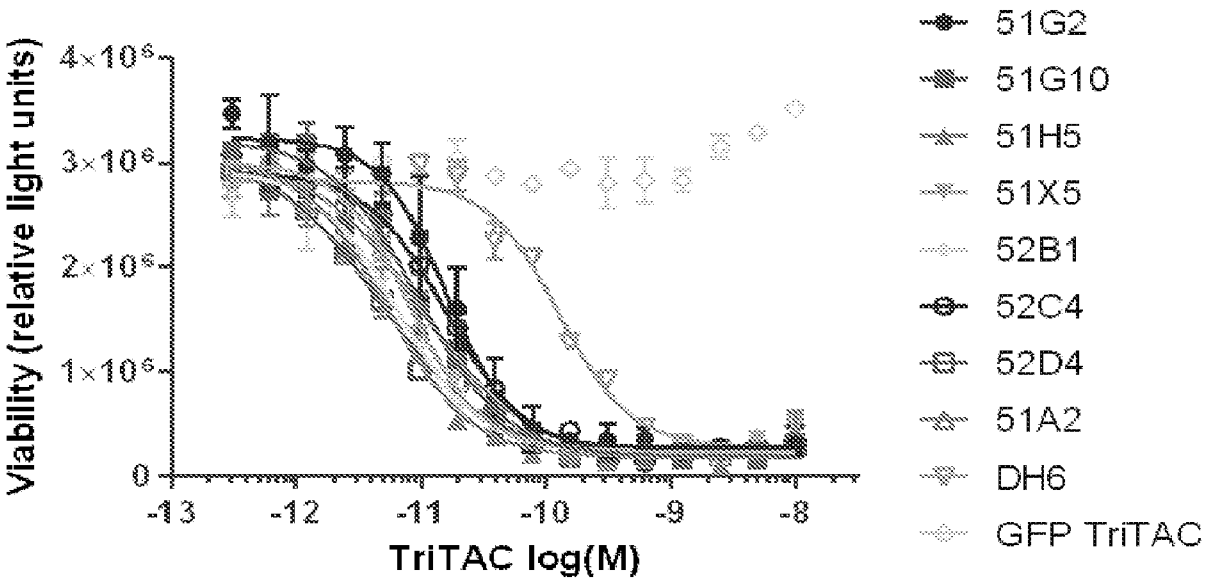

Viability (relative light units)
4×10^6
3×10^6
2×10^6
1×10^6
0
-13
-12
-11
-10
-9
-8
TriTAC log(M)
51G2
51G10
51H5
51X5
52B1
52C4
52D4
51A2
DH6
GFP TriTAC

FIG. 19

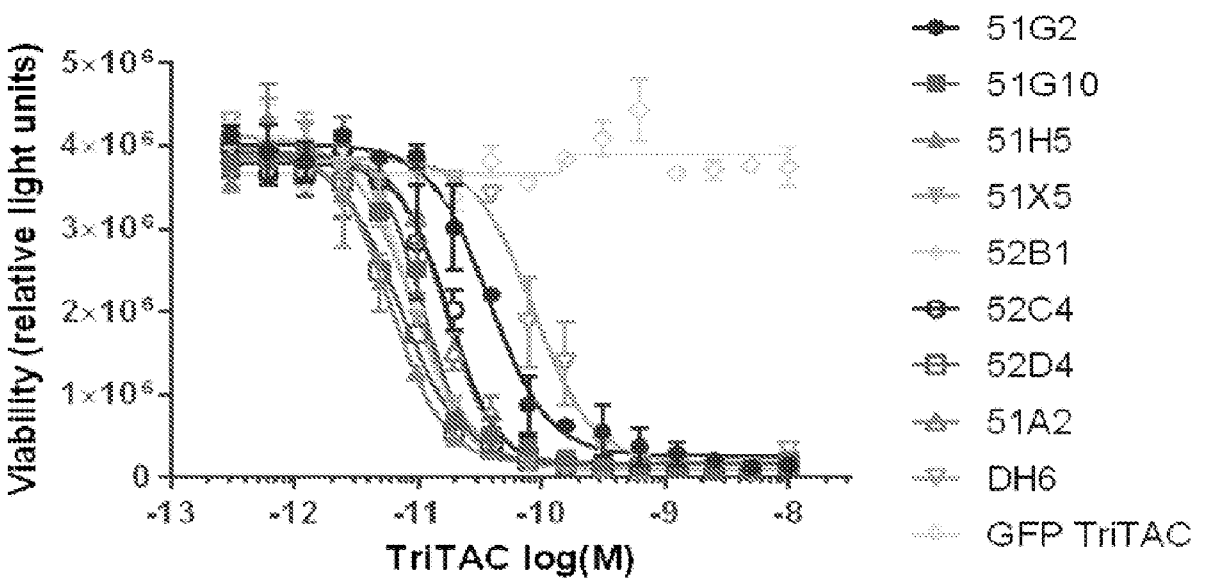

Viability (relative light units)
5×10^6
4×10^6
3×10^6
2×10^6
1×10^6
0
-13
-12
-11
-10
-9
-8
TriTAC log(M)
51G2
51G10
51H5
51X5
52B1
52C4
52D4
51A2
DH6
GFP TriTAC

FIG. 20

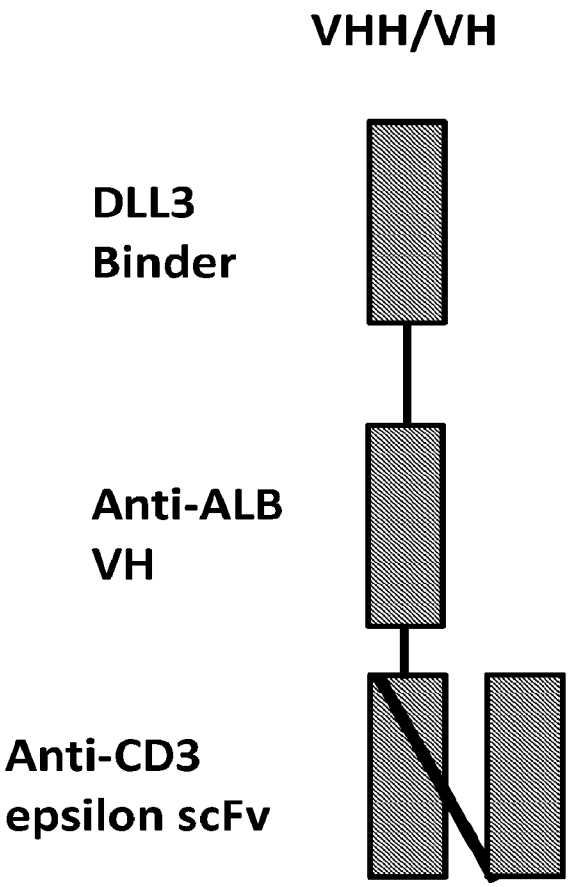


FIG. 21

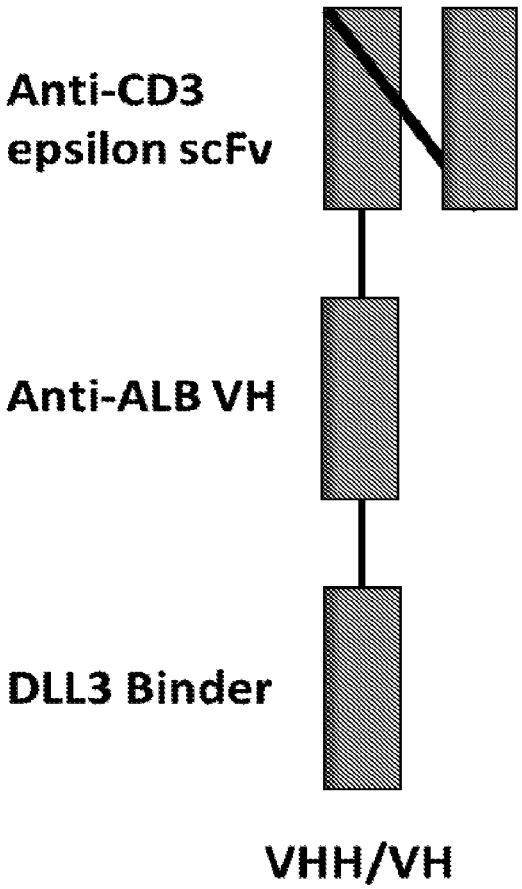


FIG. 22

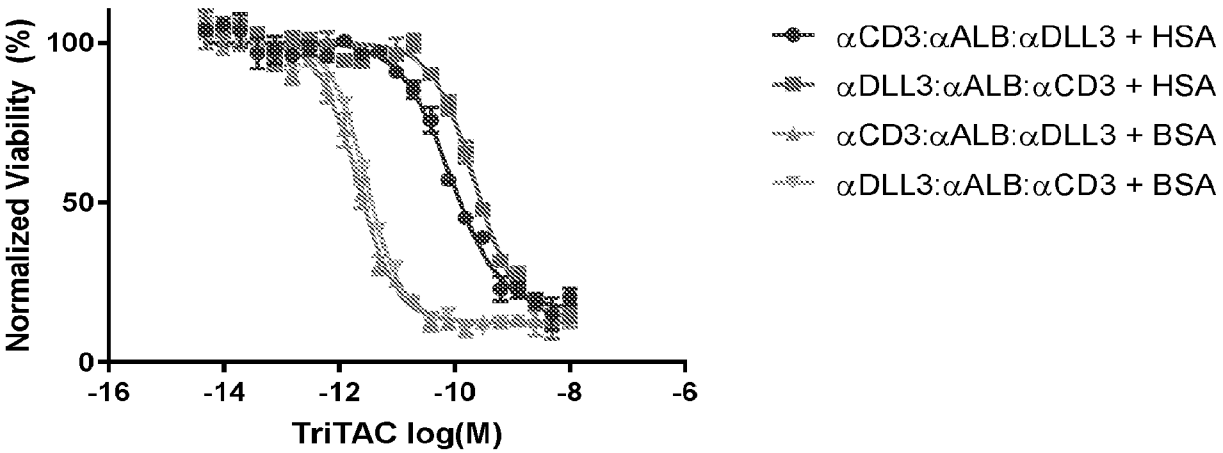

Normalized Viability (%)
100
50
0
-16
-14
-12
-10
-8
-6
TriTAC log(M)
αCD3:αALB:αDLL3 + HSA
αDLL3:αALB:αCD3 + HSA
αCD3:αALB:αDLL3 + BSA
αDLL3:αALB:αCD3 + BSA

FIG. 23

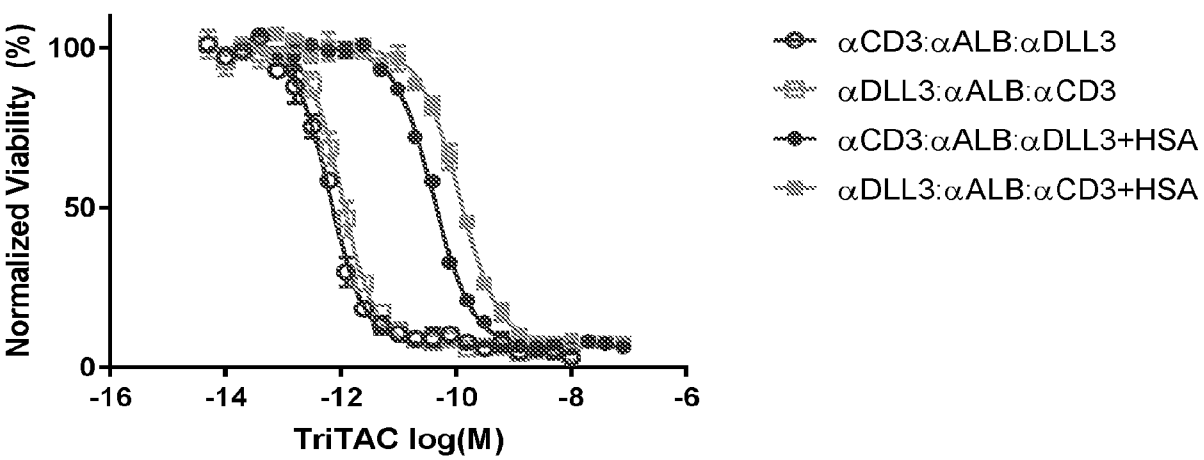

Normalized Viability (%)
100
50
0
-16
-14
-12
-10
-8
-6
TriTAC log(M)
αCD3:αALB:αDLL3
αDLL3:αALB:αCD3
αCD3:αALB:αDLL3+HSA
αDLL3:αALB:αCD3+HSA

FIG. 24

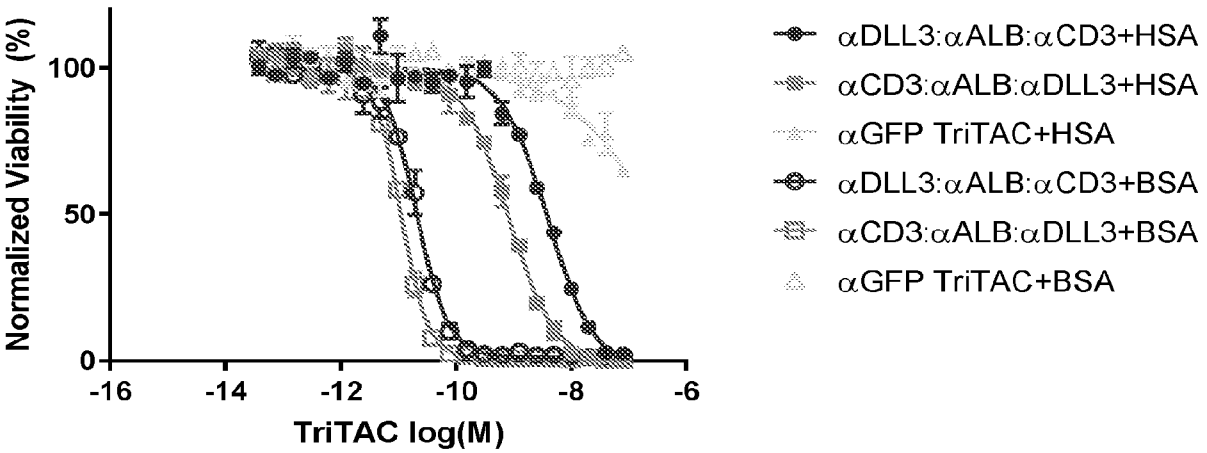

Normalized Viability (%)
100
50
0
-16
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3:αALB:αCD3+HSA
αCD3:αALB:αDLL3+HSA
αGFP TriTAC+HSA
αDLL3:αALB:αCD3+BSA
αCD3:αALB:αDLL3+BSA
αGFP TriTAC+BSA

FIG. 25

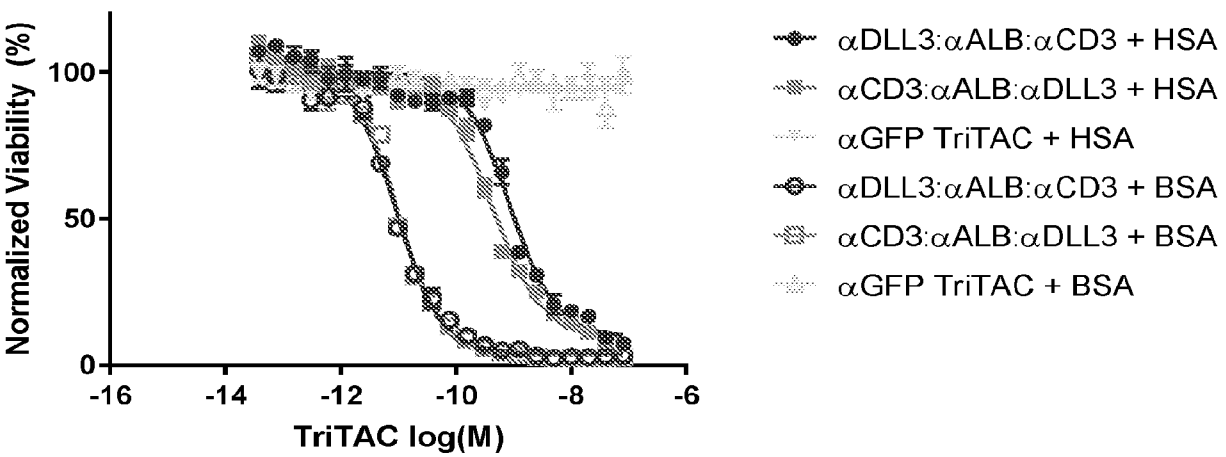

Normalized Viability (%)
100
50
0
-16
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3:αALB:αCD3 + HSA
αCD3:αALB:αDLL3 + HSA
αGFP TriTAC + HSA
αDLL3:αALB:αCD3 + BSA
αCD3:αALB:αDLL3 + BSA
αGFP TriTAC + BSA

FIG. 26

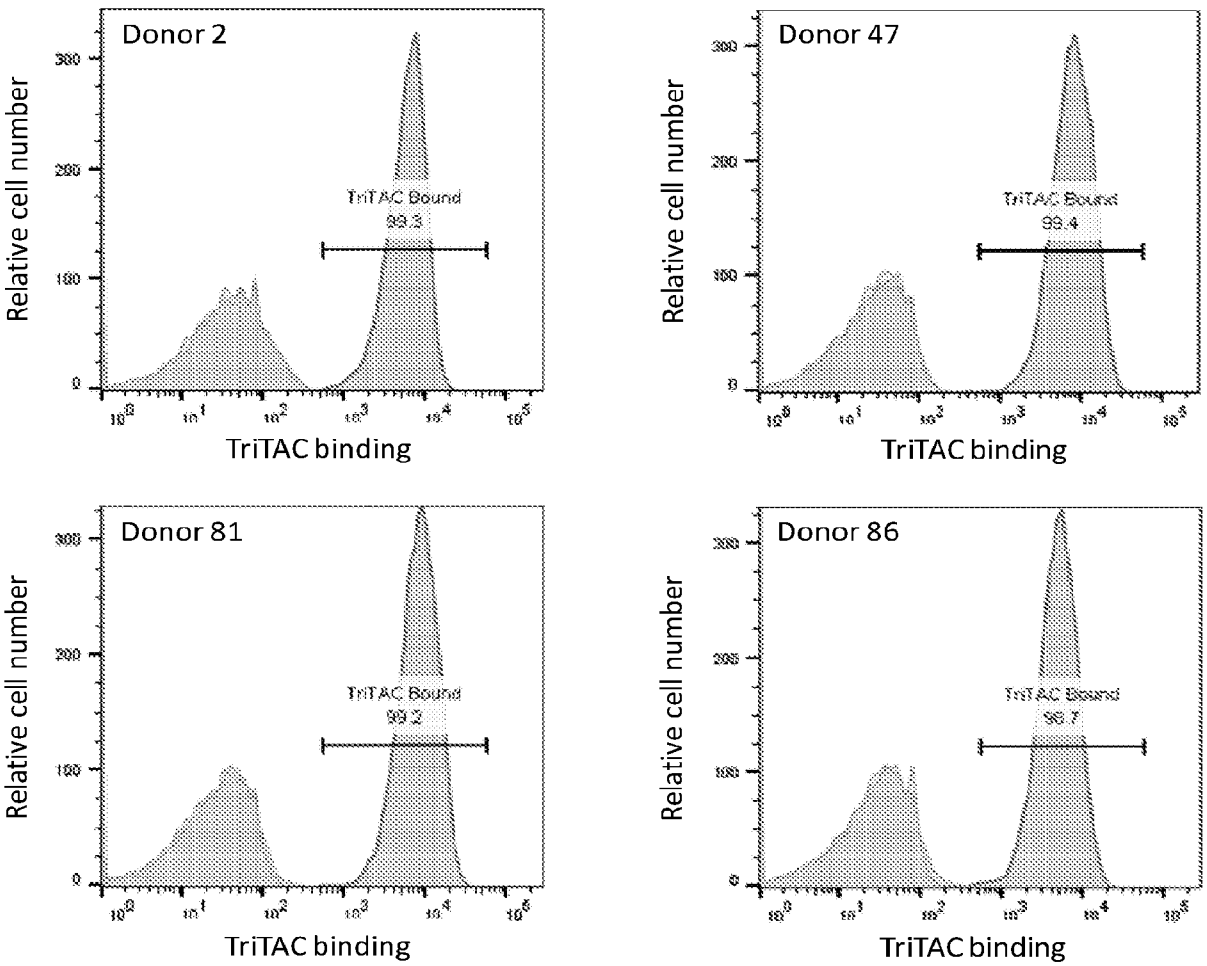

Donor 2
TriTAC Bound
99.3
Relative cell number
TriTAC binding
Donor 47
TriTAC Bound
99.4
Relative cell number
TriTAC binding
Donor 81
TriTAC Bound
99.2
Relative cell number
TriTAC binding
Donor 86
TriTAC Bound
98.7
Relative cell number
TriTAC binding

FIG. 27

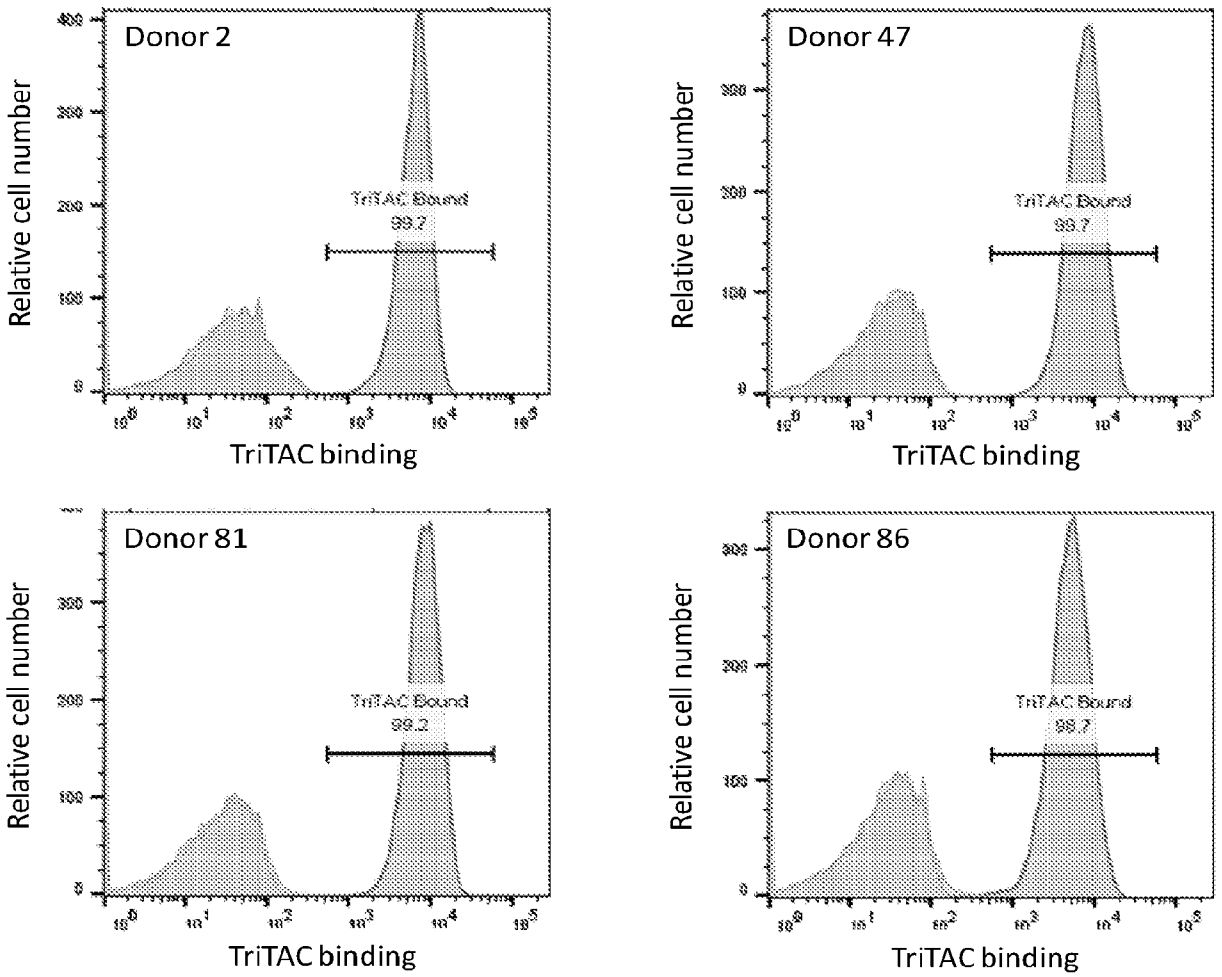

Donor 2
Donor 47
Donor 81
Donor 86
Relative cell number
TriTAC binding
TriTAC Bound
99.2
99.7

FIG. 28

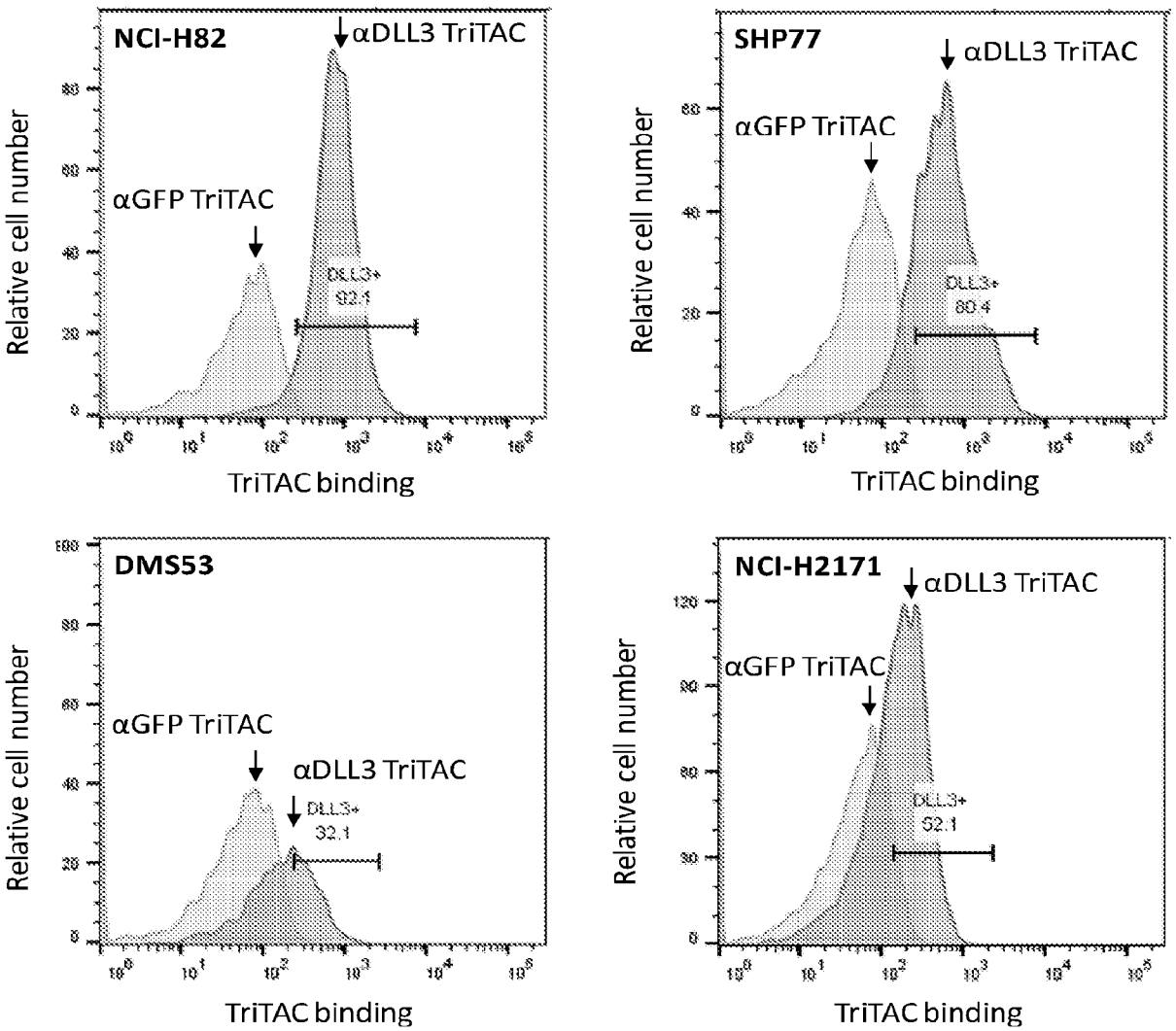

NCI-H82
αDLL3 TriTAC
αGFP TriTAC
DLL3+
92.1
Relative cell number
TriTAC binding
SHP77
αDLL3 TriTAC
αGFP TriTAC
DLL3+
80.4
Relative cell number
TriTAC binding
DMS53
αGFP TriTAC
αDLL3 TriTAC
DLL3+
32.1
Relative cell number
TriTAC binding
NCI-H2171
αDLL3 TriTAC
αGFP TriTAC
DLL3+
52.1
Relative cell number
TriTAC binding

FIG. 29

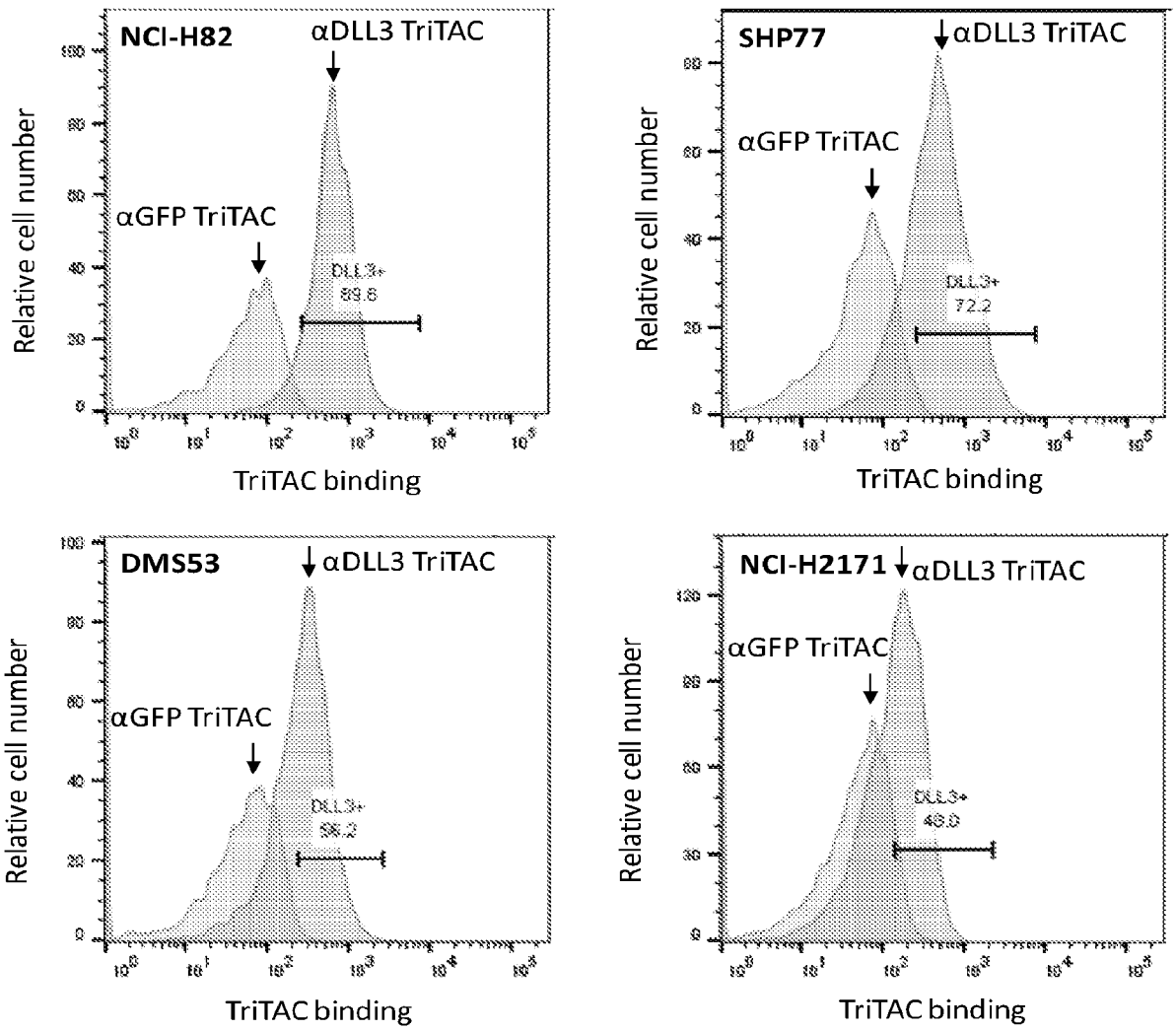

NCI-H82
αDLL3 TriTAC
αGFP TriTAC
DLL3+
89.6
Relative cell number
TriTAC binding
SHP77
αDLL3 TriTAC
αGFP TriTAC
DLL3+
72.2
Relative cell number
TriTAC binding
DMS53
αDLL3 TriTAC
αGFP TriTAC
DLL3+
58.2
Relative cell number
TriTAC binding
NCI-H2171
αDLL3 TriTAC
αGFP TriTAC
DLL3+
48.0
Relative cell number
TriTAC binding

FIG. 30

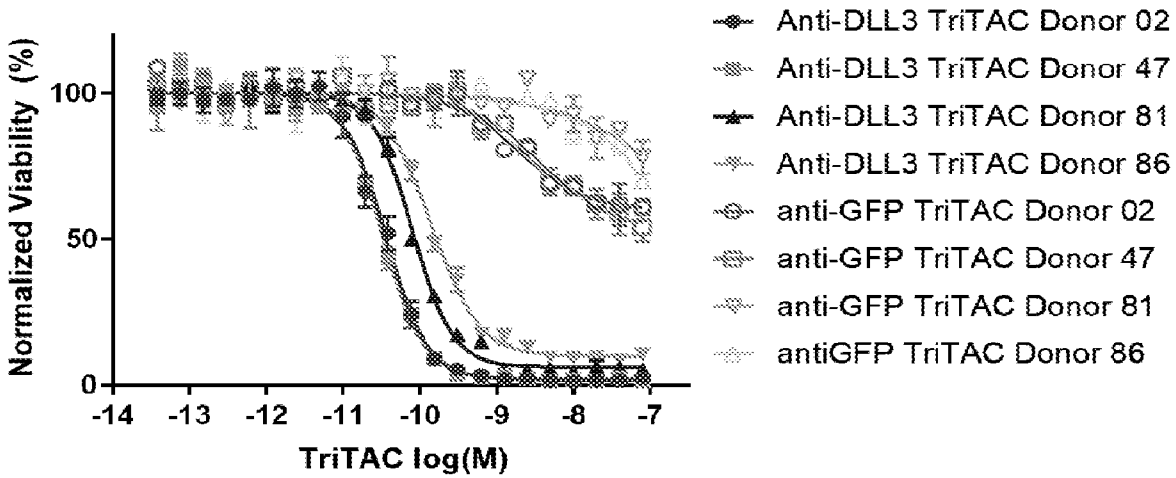

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
antiGFP TriTAC Donor 86

FIG. 31

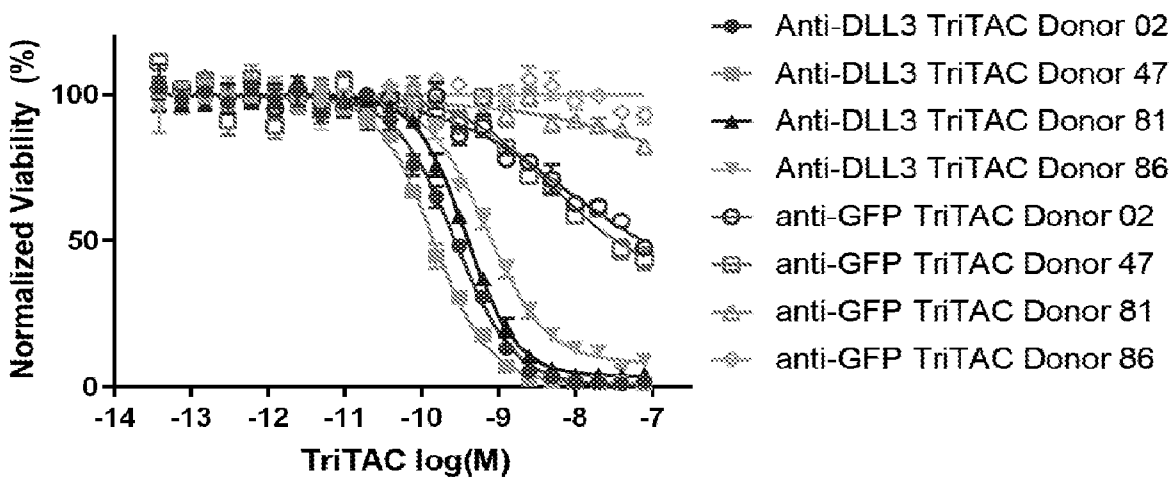

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 32

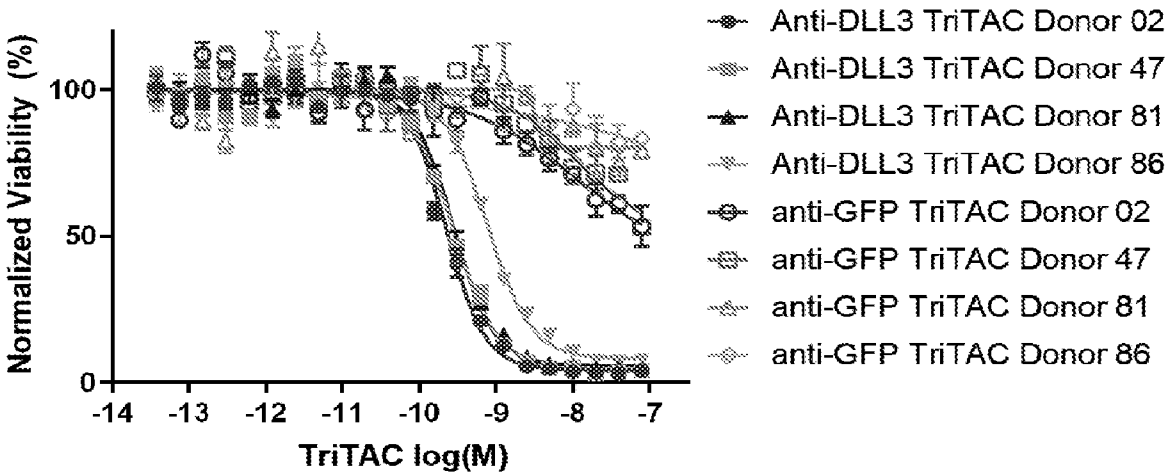

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 33

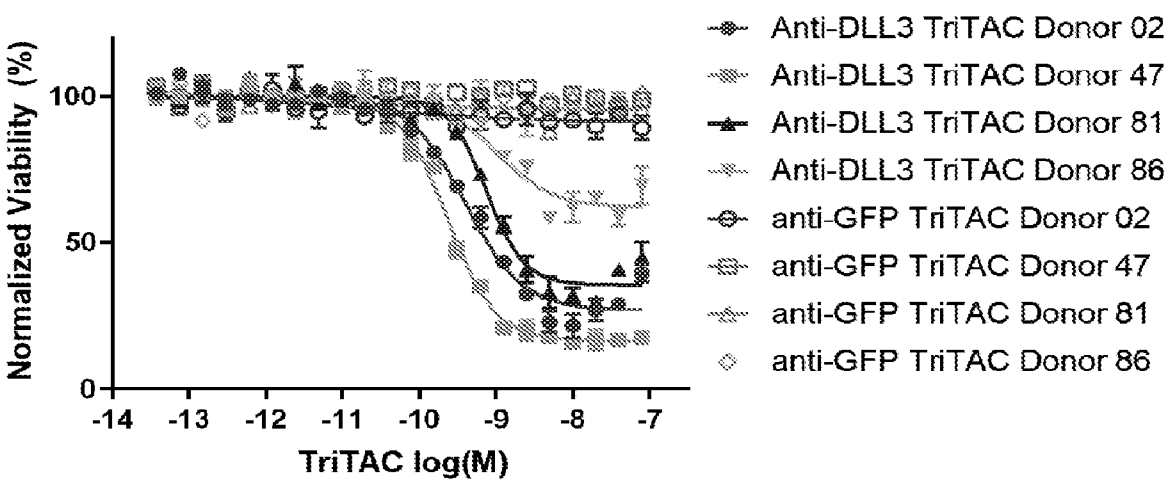

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 34

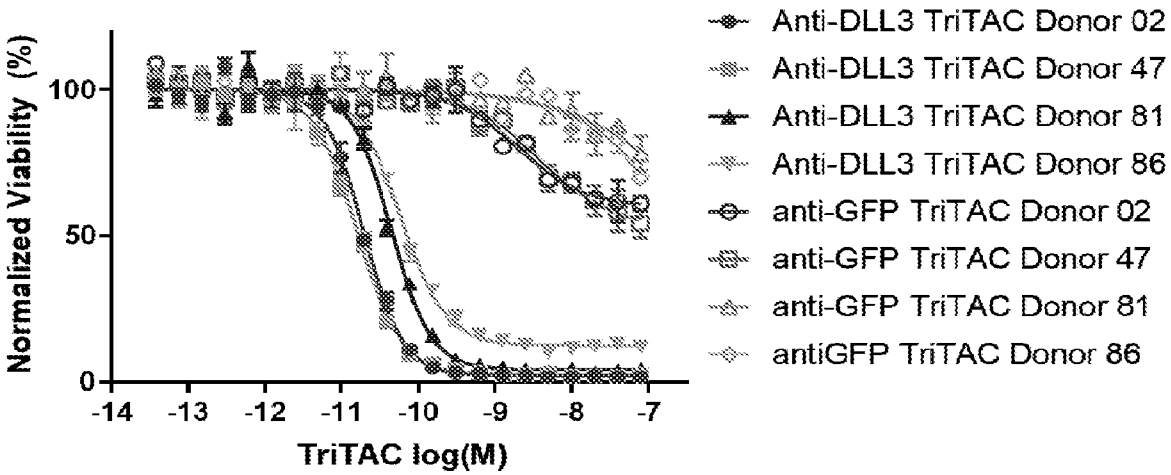

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
antiGFP TriTAC Donor 86

FIG. 35

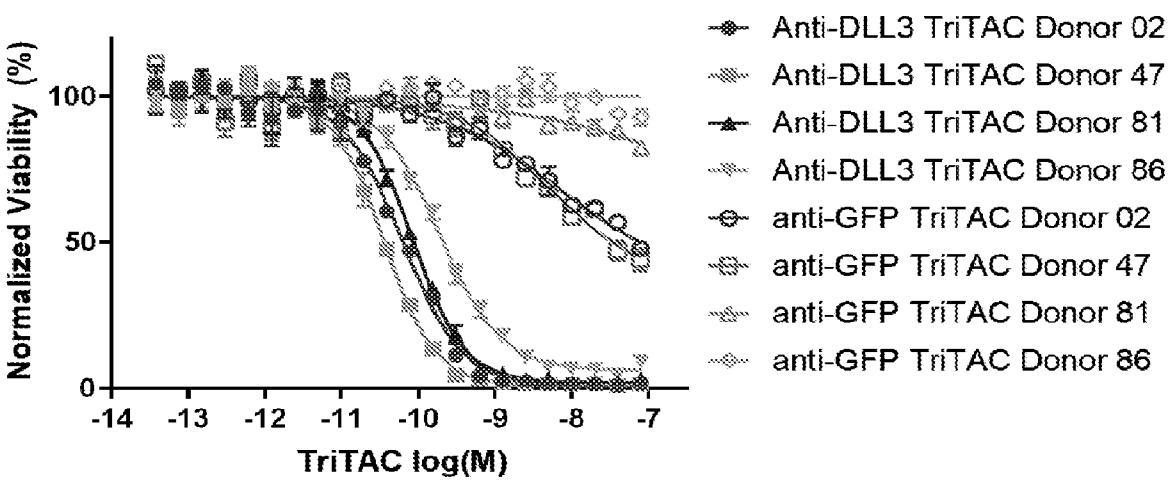

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 36

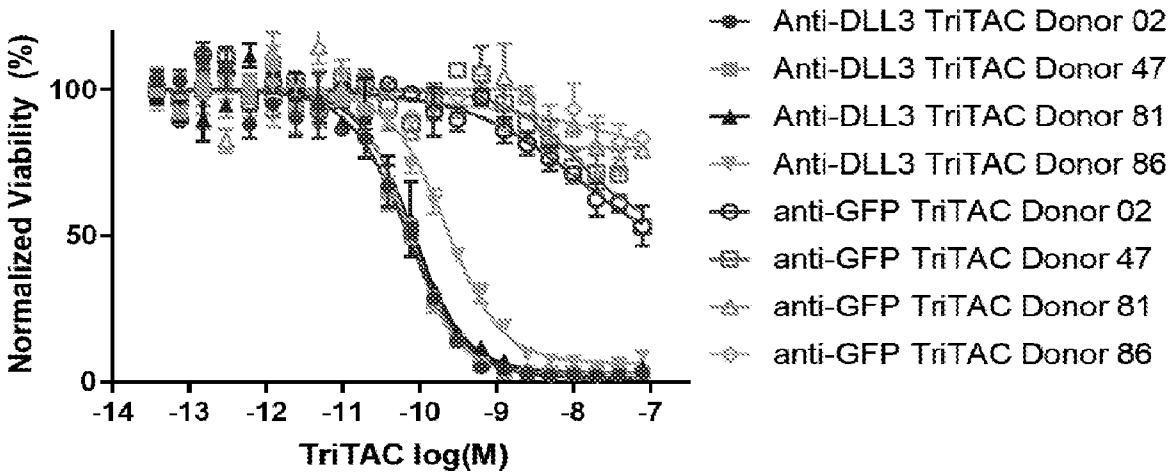

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 37

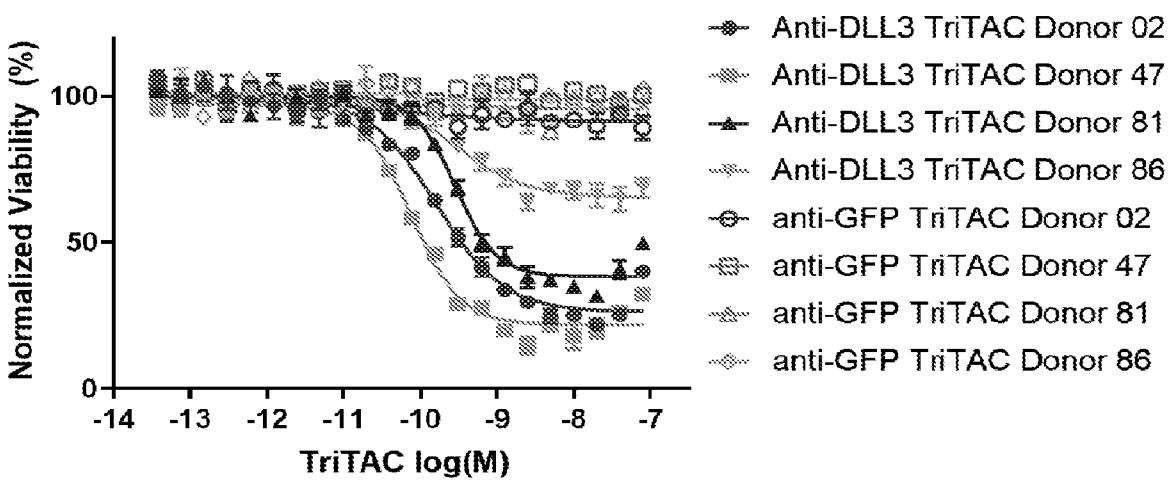

Normalized Viability (%)
100
50
0
-14
-13
-12
-11
-10
-9
-8
-7
TriTAC log(M)
Anti-DLL3 TriTAC Donor 02
Anti-DLL3 TriTAC Donor 47
Anti-DLL3 TriTAC Donor 81
Anti-DLL3 TriTAC Donor 86
anti-GFP TriTAC Donor 02
anti-GFP TriTAC Donor 47
anti-GFP TriTAC Donor 81
anti-GFP TriTAC Donor 86

FIG. 38

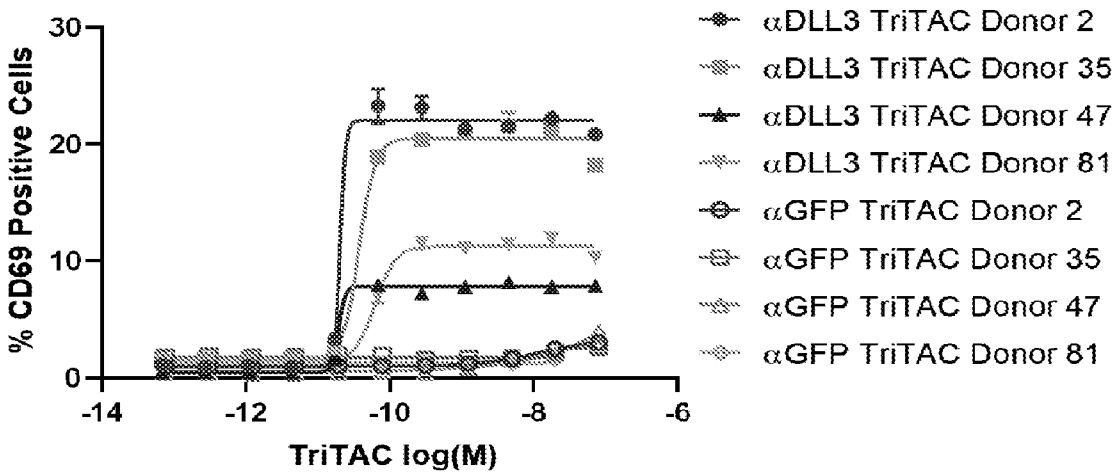

% CD69 Positive Cells
30
20
10
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 39

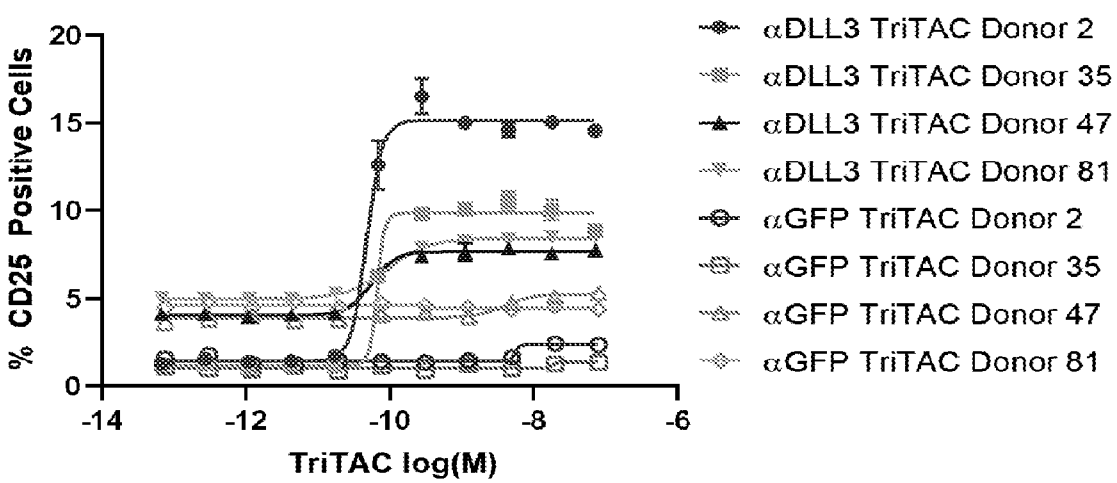

% CD25 Positive Cells
20
15
10
5
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 40

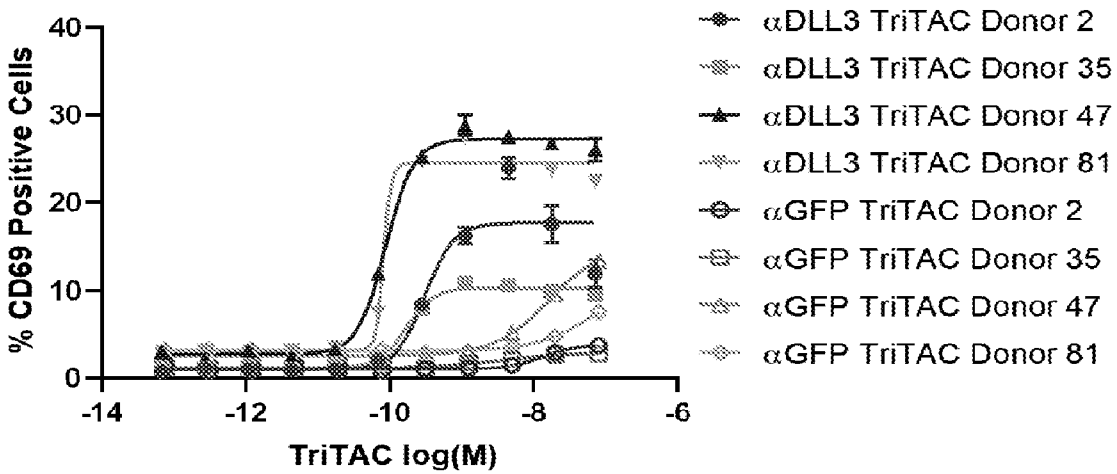

% CD69 Positive Cells
40
30
20
10
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 41

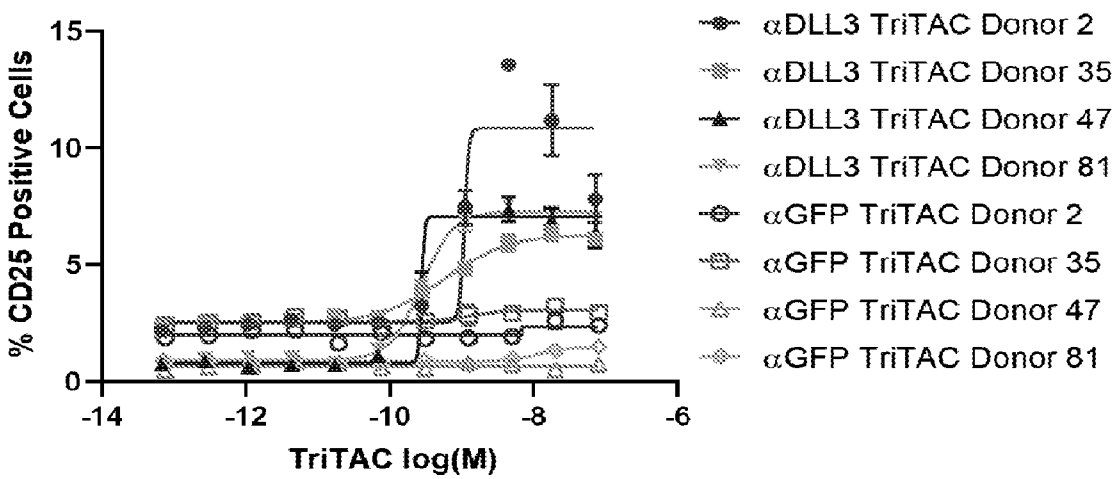

% CD25 Positive Cells
15
10
5
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 42

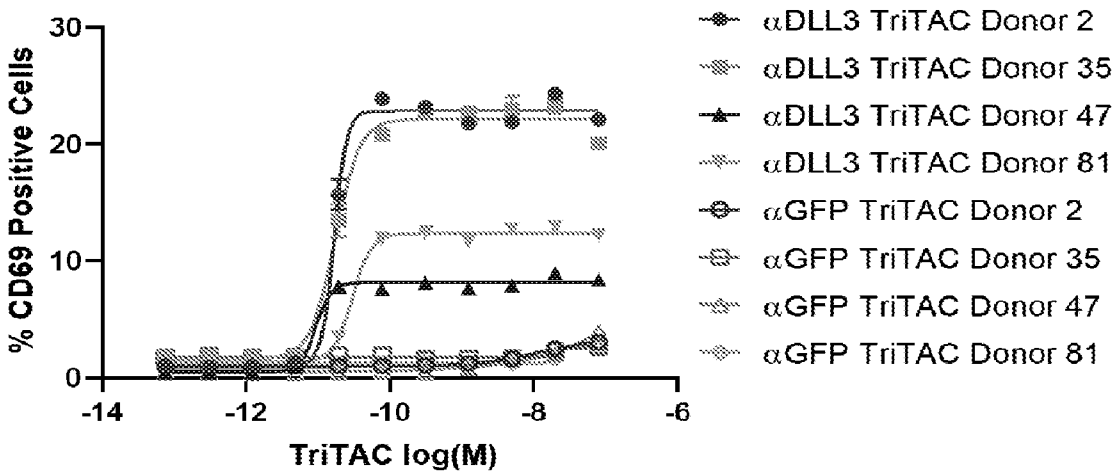

% CD69 Positive Cells
30
20
10
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 43

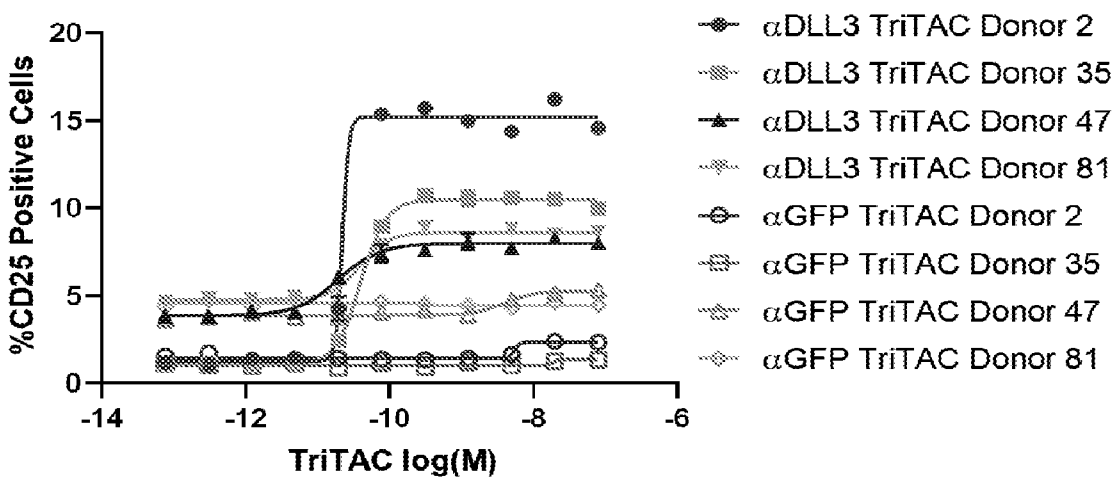

%CD25 Positive Cells
20
15
10
5
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 44

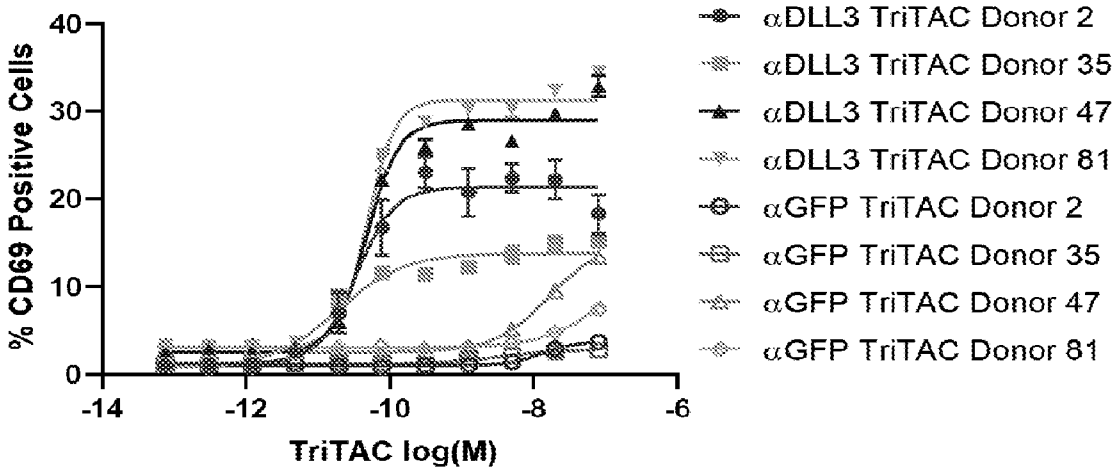

% CD69 Positive Cells
40
30
20
10
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 45

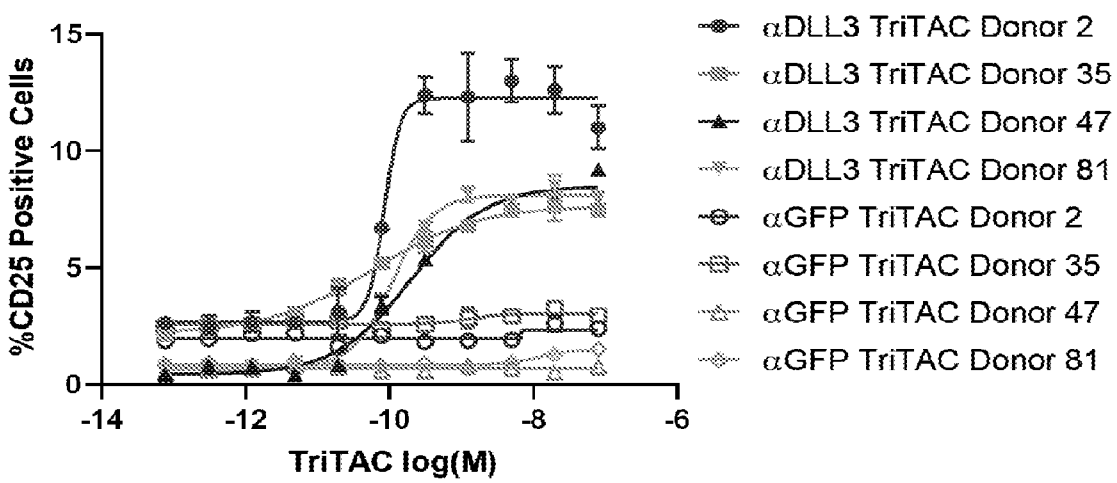

%CD25 Positive Cells
15
10
5
0
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC Donor 2
αDLL3 TriTAC Donor 35
αDLL3 TriTAC Donor 47
αDLL3 TriTAC Donor 81
αGFP TriTAC Donor 2
αGFP TriTAC Donor 35
αGFP TriTAC Donor 47
αGFP TriTAC Donor 81

FIG. 46

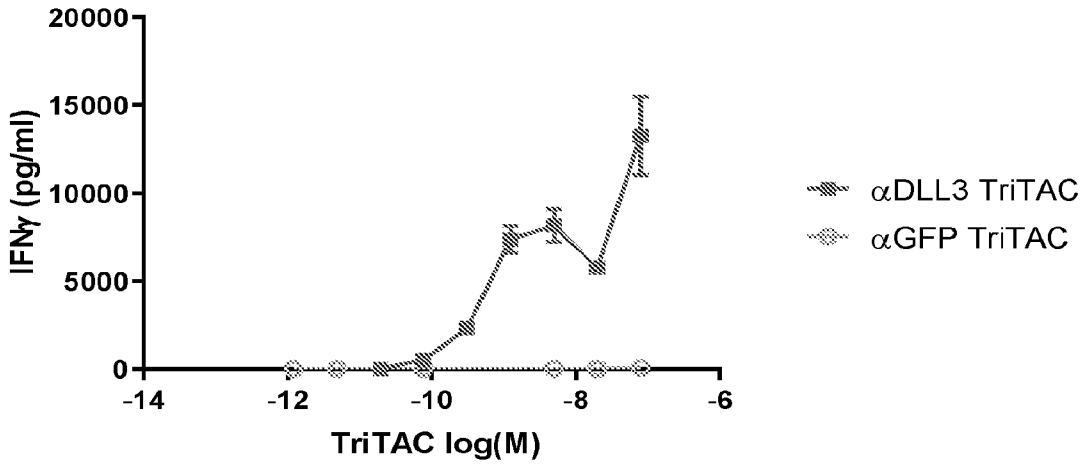

20000
15000
10000
5000
0
IFNγ (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 47

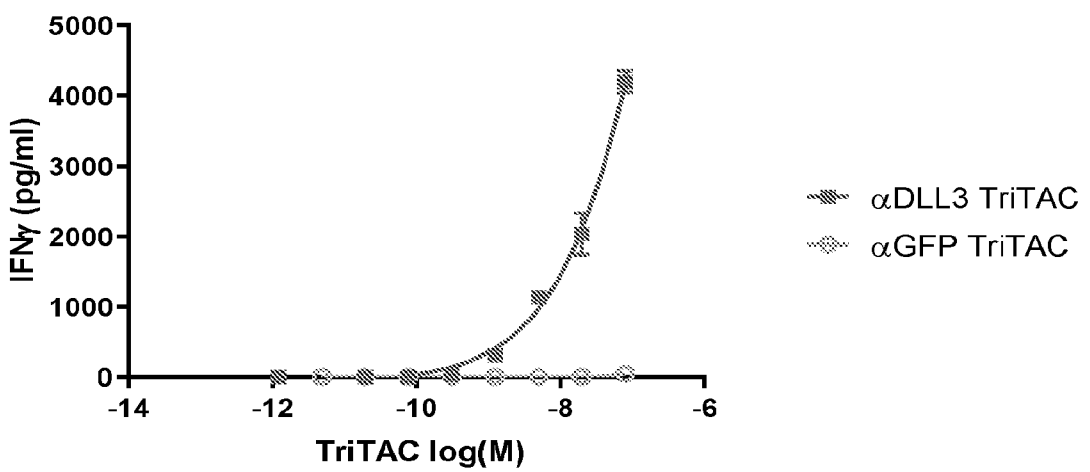

5000
4000
3000
2000
1000
0
IFNγ (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 48

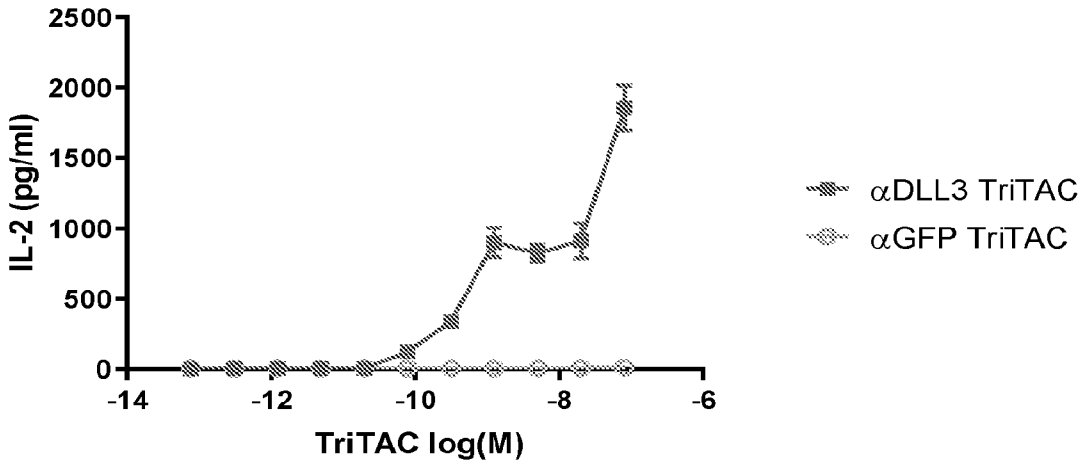

2500
2000
1500
1000
500
0
IL-2 (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 49

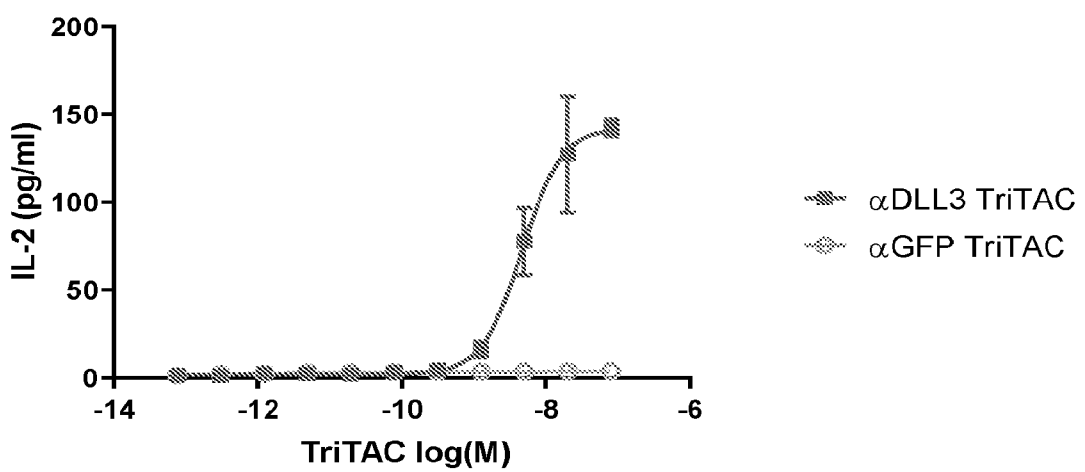

200
150
100
50
0
IL-2 (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 50

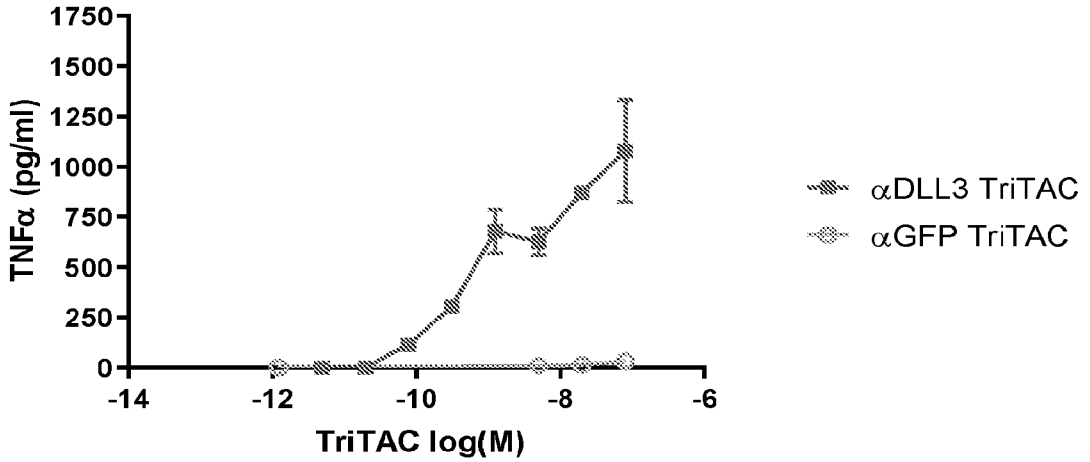

1750
1500
1250
1000
750
500
250
0
TNFα (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 51

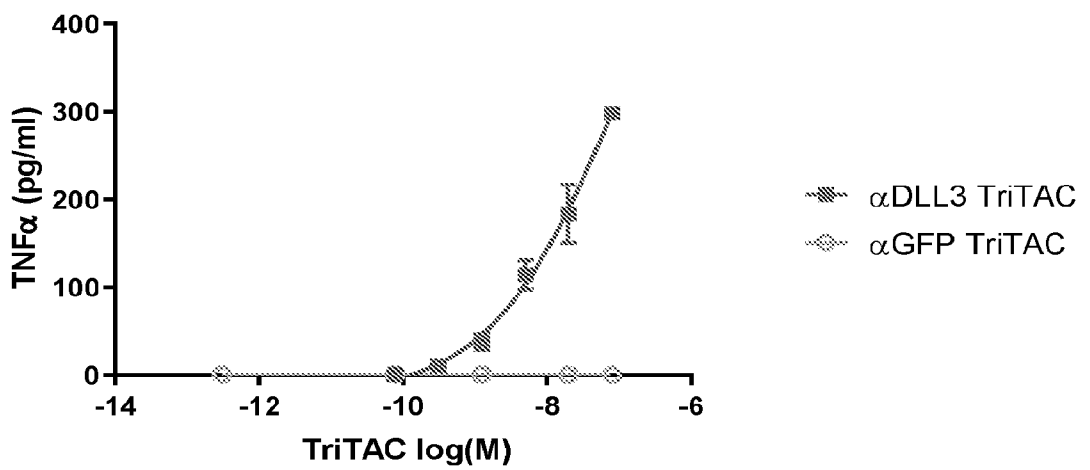

400
300
200
100
0
TNFα (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 52

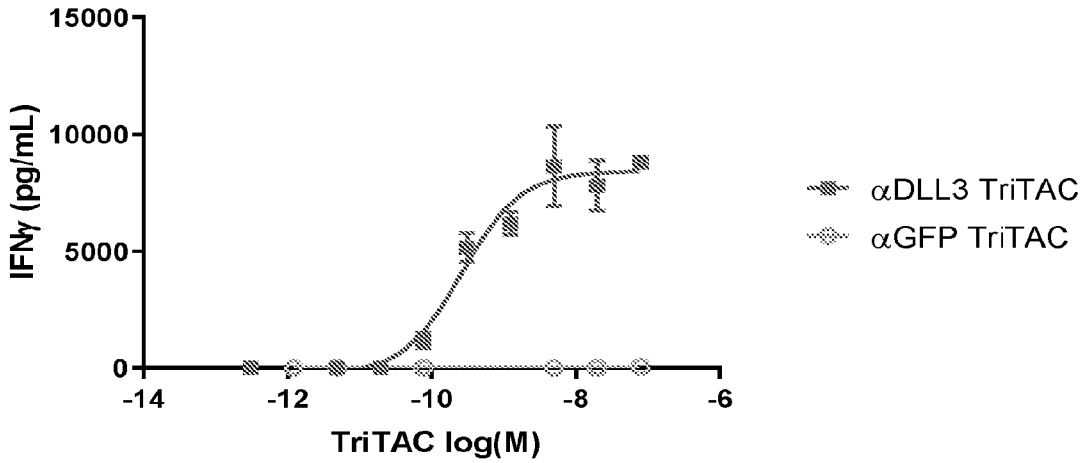

15000
10000
5000
0
IFNγ (pg/mL)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 53

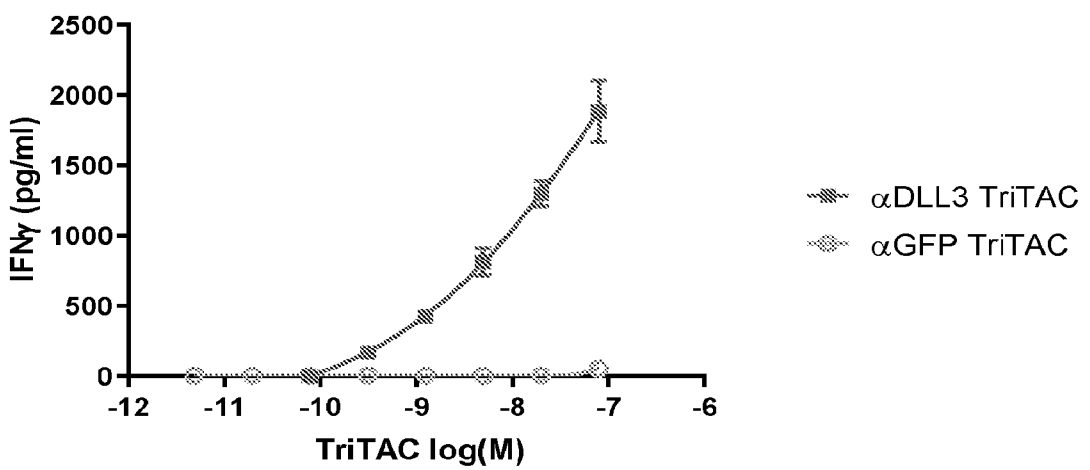

2500
2000
1500
1000
500
0
IFNγ (pg/ml)
-12
-11
-10
-9
-8
-7
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 54

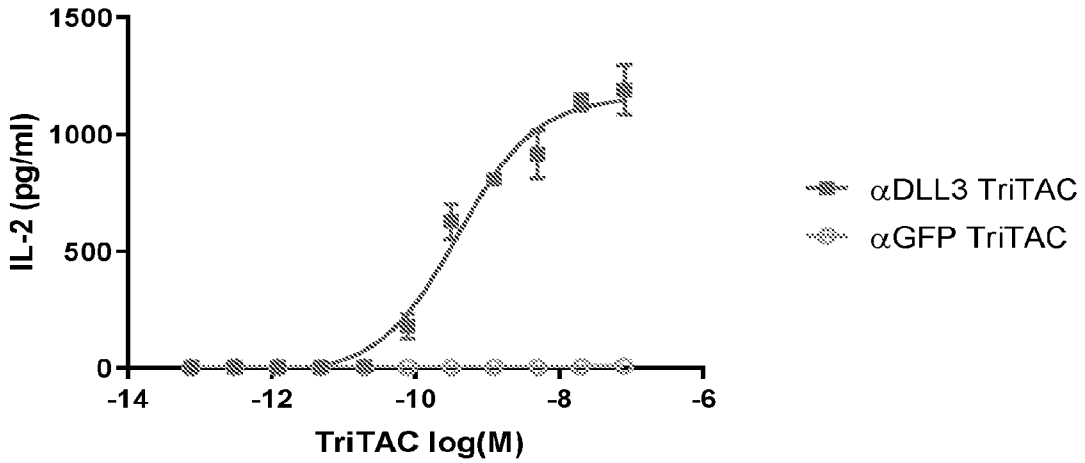

1500
1000
500
0
IL-2 (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 55

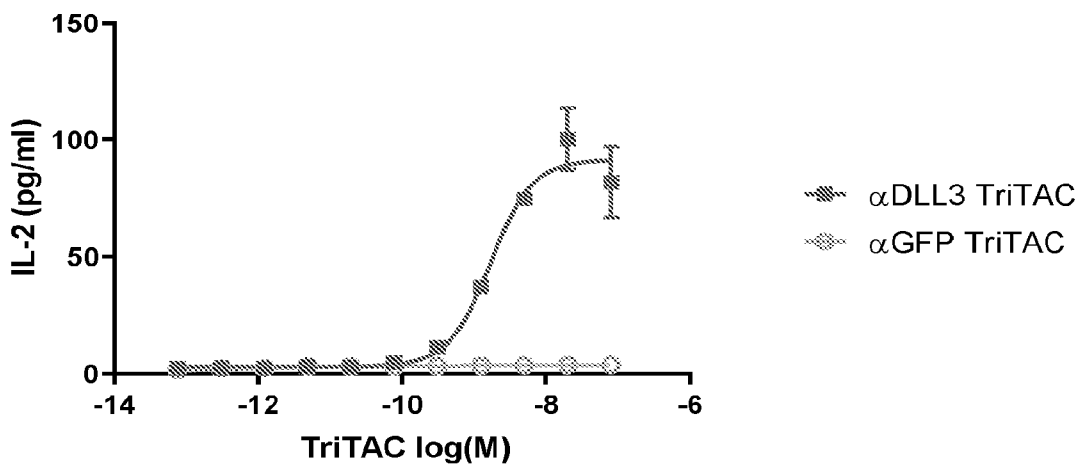

150
100
50
0
IL-2 (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 56

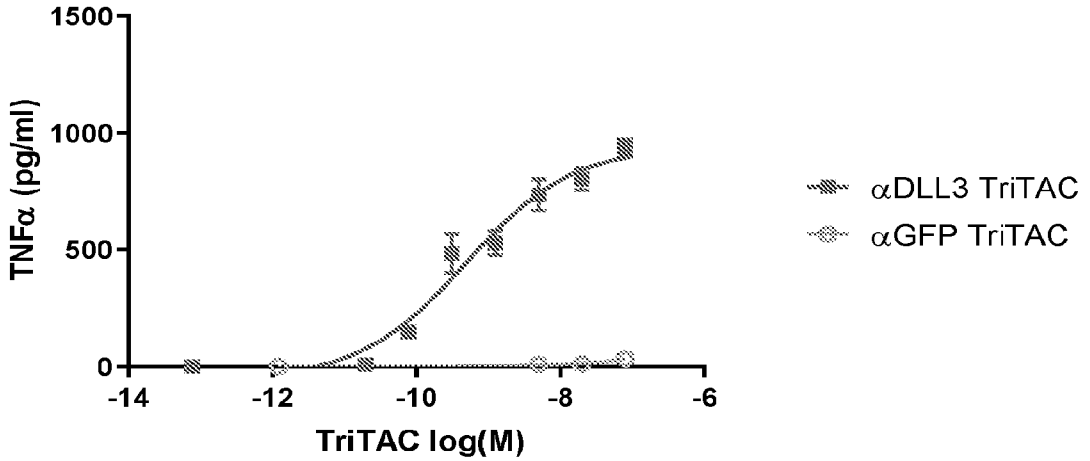

1500
1000
500
0
TNFα (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 57

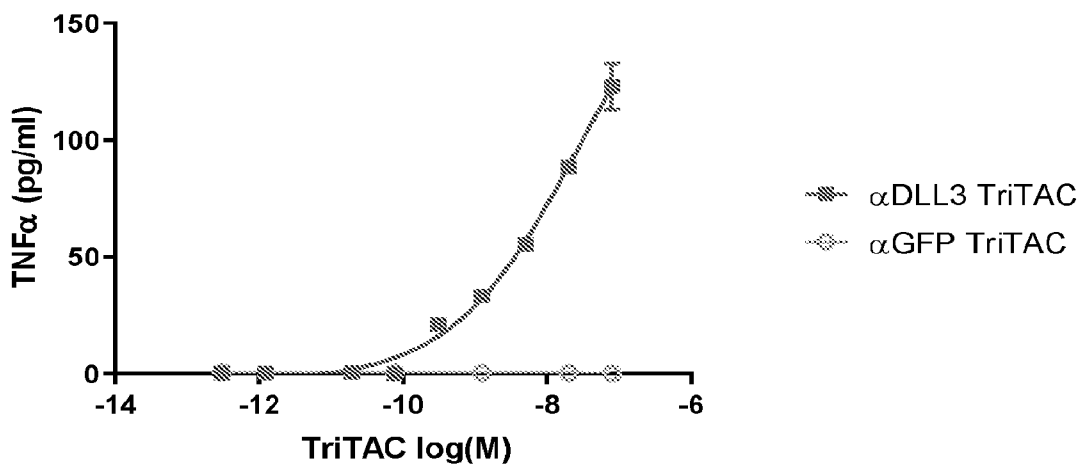

150
100
50
0
TNFα (pg/ml)
-14
-12
-10
-8
-6
TriTAC log(M)
αDLL3 TriTAC
αGFP TriTAC

FIG. 58

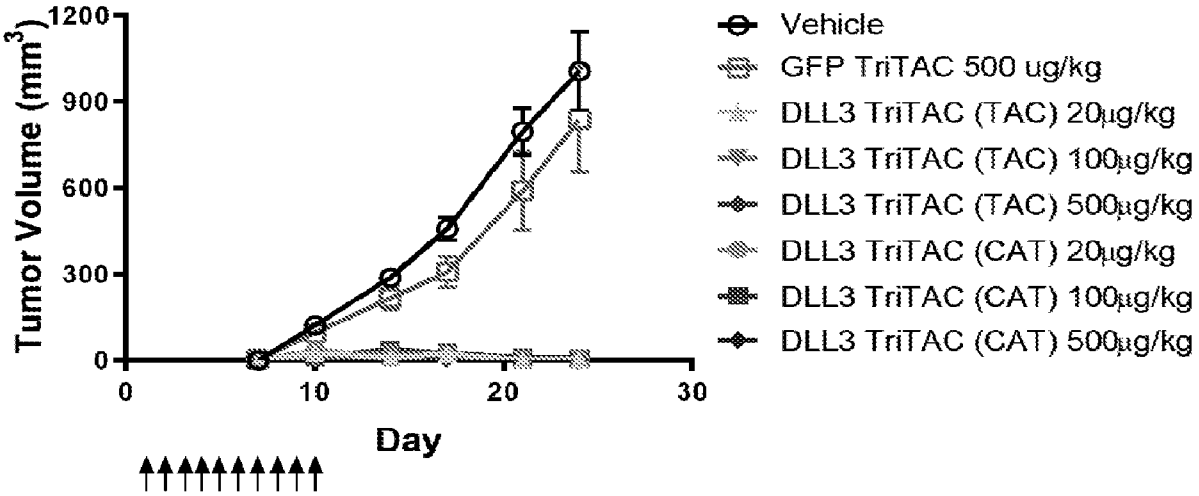

Tumor Volume (mm3)
1200
900
600
300
0
0
10
20
30
Day
Vehicle
GFP TriTAC 500 ug/kg
DLL3 TriTAC (TAC) 20µg/kg
DLL3 TriTAC (TAC) 100µg/kg
DLL3 TriTAC (TAC) 500µg/kg
DLL3 TriTAC (CAT) 20µg/kg
DLL3 TriTAC (CAT) 100µg/kg
DLL3 TriTAC (CAT) 500µg/kg

FIG. 59

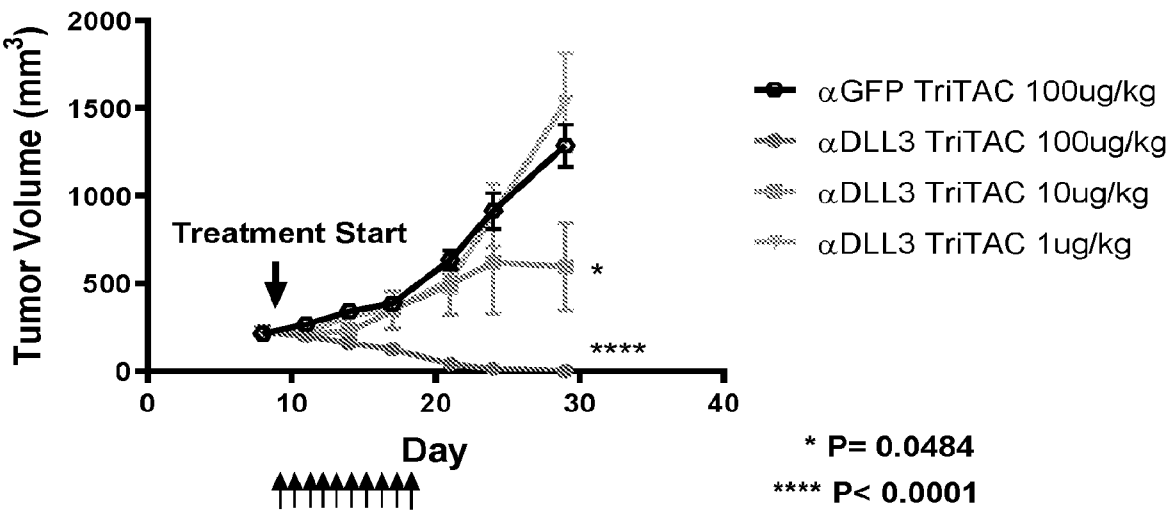

Tumor Volume (mm3)
2000
1500
1000
500
0
Treatment Start
*
****
0
10
20
30
40
Day
αGFP TriTAC 100ug/kg
αDLL3 TriTAC 100ug/kg
αDLL3 TriTAC 10ug/kg
αDLL3 TriTAC 1ug/kg
* P= 0.0484
**** P< 0.0001

FIG. 60

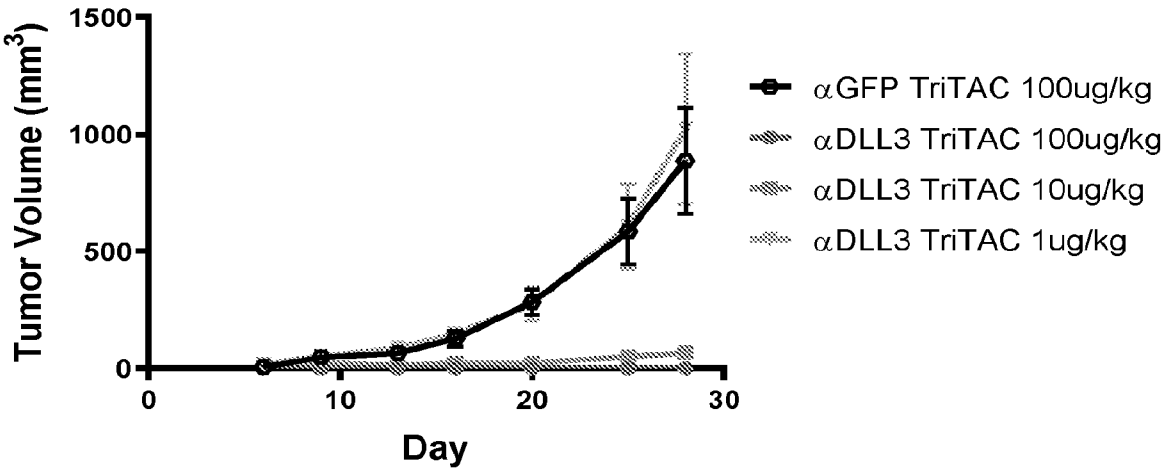

Tumor Volume (mm3)
1500
1000
500
0
0
10
20
30
Day
αGFP TriTAC 100ug/kg
αDLL3 TriTAC 100ug/kg
αDLL3 TriTAC 10ug/kg
αDLL3 TriTAC 1ug/kg

FIG. 61

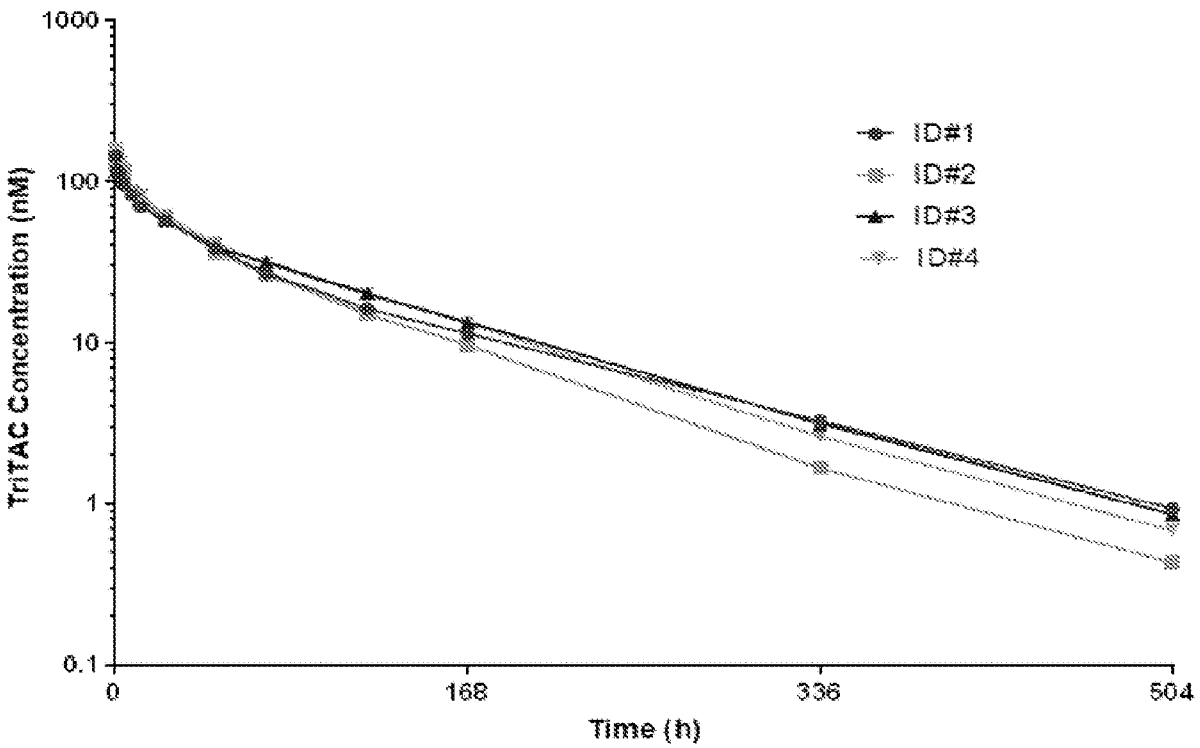

TriTAC Concentration (nM)
1000
100
10
1
0.1
0
168
336
504
Time (h)
ID#1
ID#2
ID#3
ID#4

FIG. 62

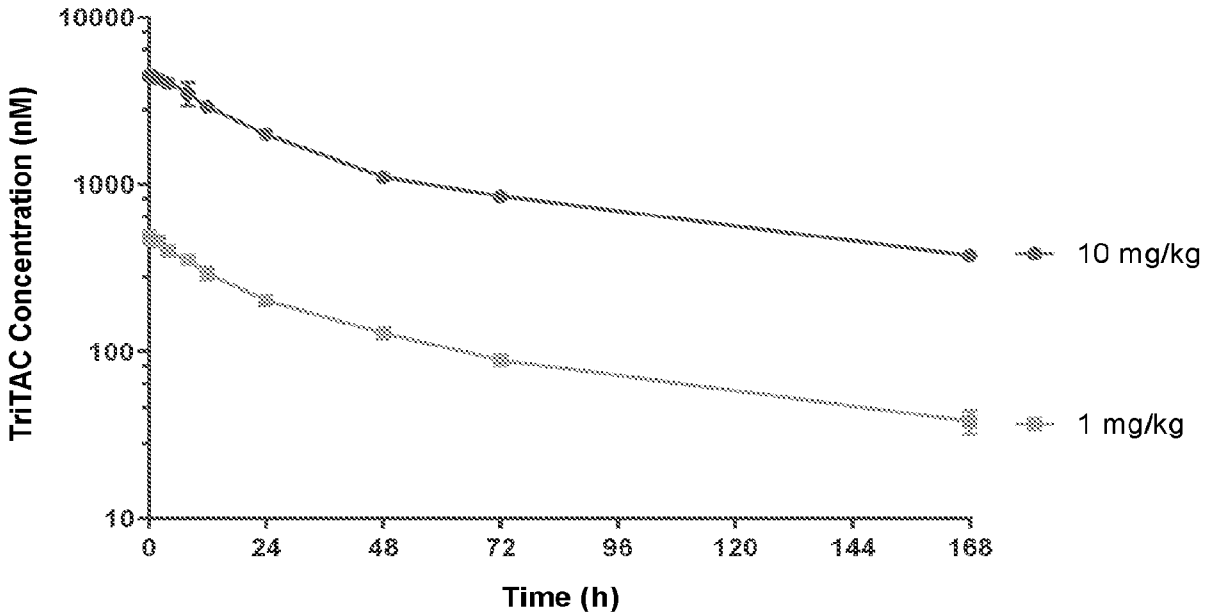

10000
1000
100
10
TriTAC Concentration (nM)
0
24
48
72
96
120
144
168
Time (h)
10 mg/kg
1 mg/kg

FIG. 63

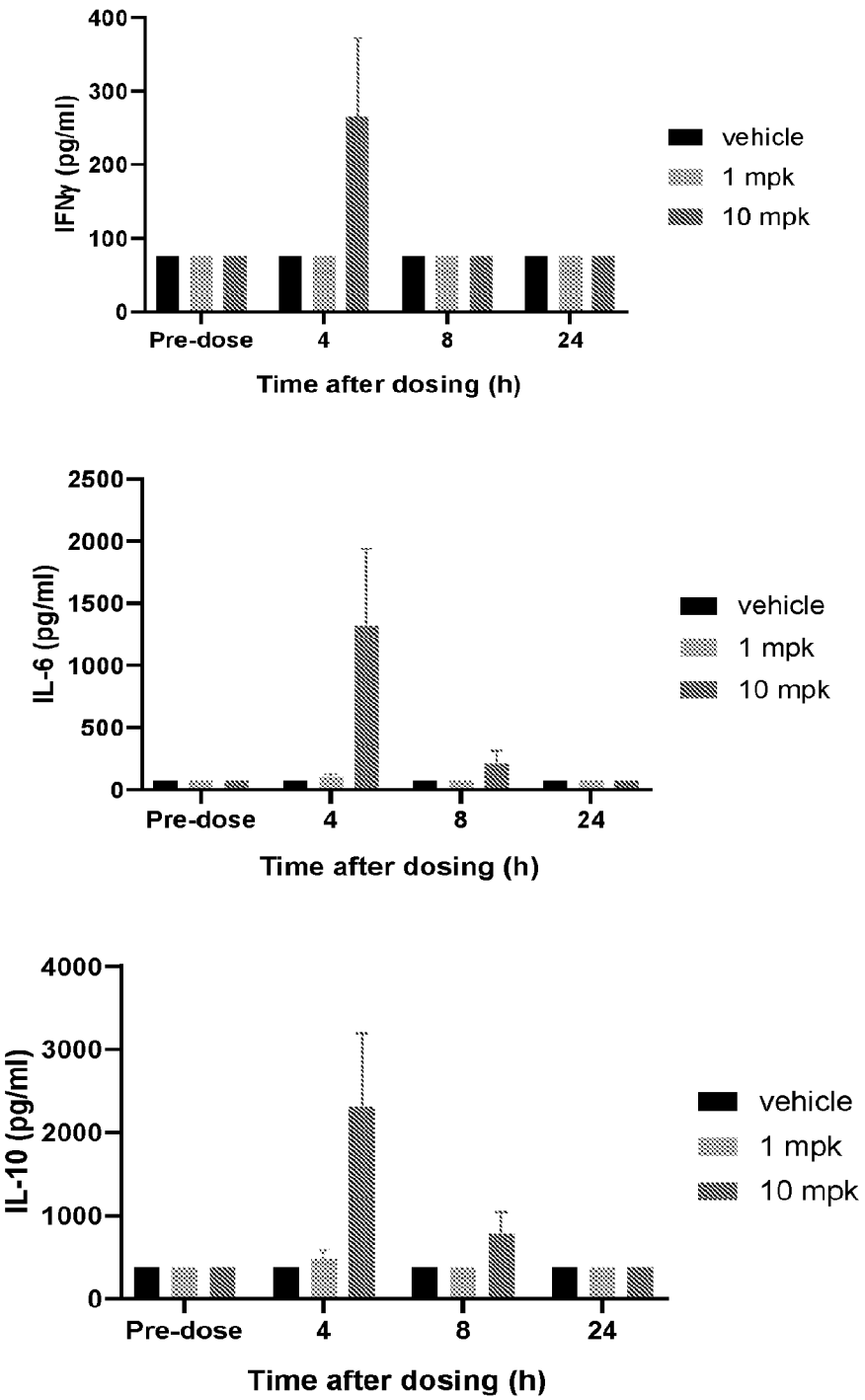

IFNγ (pg/ml)
400
300
200
100
0
Pre-dose
4
8
24
Time after dosing (h)
vehicle
1 mpk
10 mpk
IL-6 (pg/ml)
2500
2000
1500
1000
500
0
Pre-dose
4
8
24
Time after dosing (h)
vehicle
1 mpk
10 mpk
IL-10 (pg/ml)
4000
3000
2000
1000
0
Pre-dose
4
8
24
Time after dosing (h)
vehicle
1 mpk
10 mpk

FIG. 64

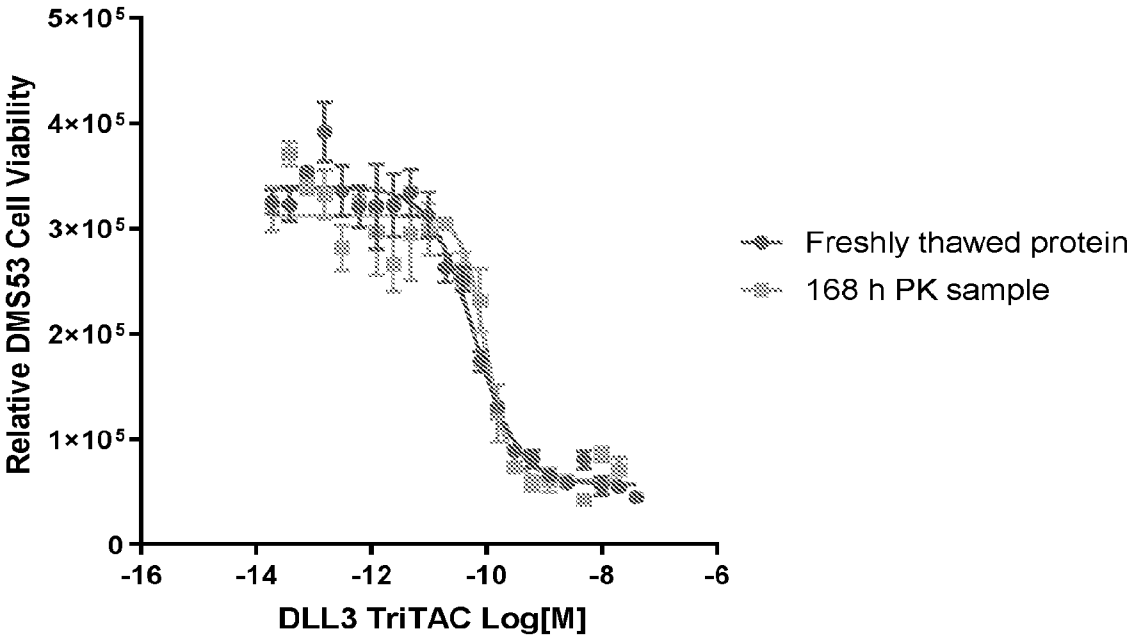

5×10^5
4×10^5
3×10^5
2×10^5
1×10^5
0
Relative DMS53 Cell Viability
-16
-14
-12
-10
-8
-6
DLL3 TriTAC Log[M]
Freshly thawed protein
168 h PK sample

FIG. 65

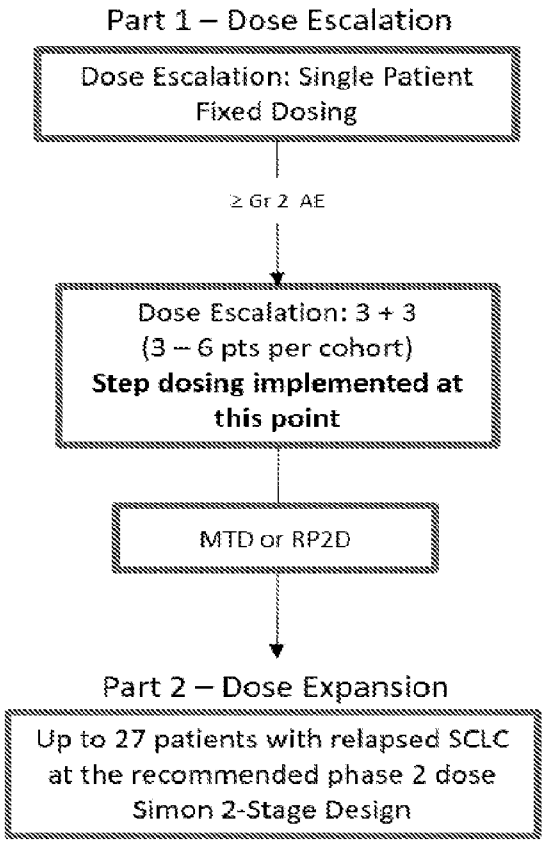

Part 1 – Dose Escalation
Dose Escalation: Single Patient Fixed Dosing
≥ Gr 2 AE
Dose Escalation: 3 + 3 (3 – 6 pts per cohort) Step dosing implemented at this point
MTD or RP2D
Part 2 – Dose Expansion
Up to 27 patients with relapsed SCLC at the recommended phase 2 dose Simon 2-Stage Design

FIG. 66

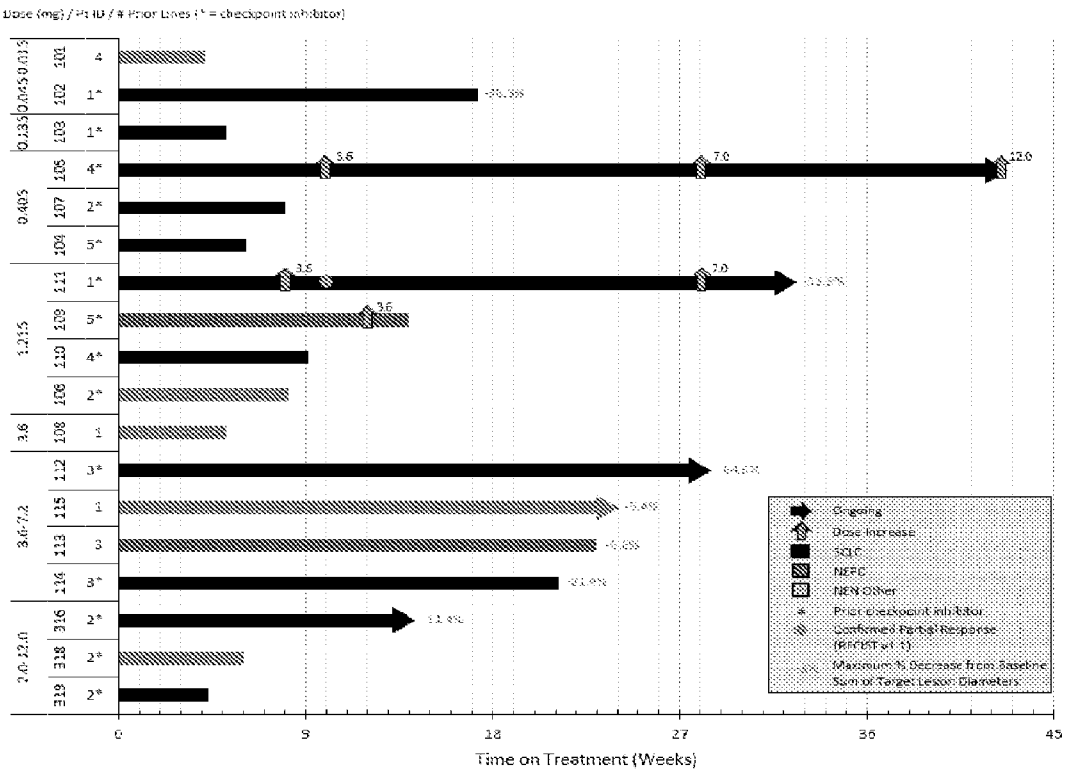

Dose (mg) / Pt ID / # Prior Lines (* = checkpoint inhibitor)
0.015
0.045
0.135
0.405
1.215
3.6
3.6-7.2
7.2-12.0
101
102
103
105
107
104
111
109
110
106
108
112
115
113
114
116
118
119
4
1*
1*
4*
2*
5*
1*
5*
4*
2*
1
3*
1
3
3*
2*
2*
3.6
7.0
12.0
3.6
7.0
3.6
0
9
18
27
36
45
Time on Treatment (Weeks)
Ongoing
Dose Increase
SDC
NEPC
NEN Other
Prior checkpoint inhibitor
Confirmed Partial Response (RECIST v1.1)
Maximum % Decrease from Baseline Sum of Target Lesion Diameters

FIG. 67

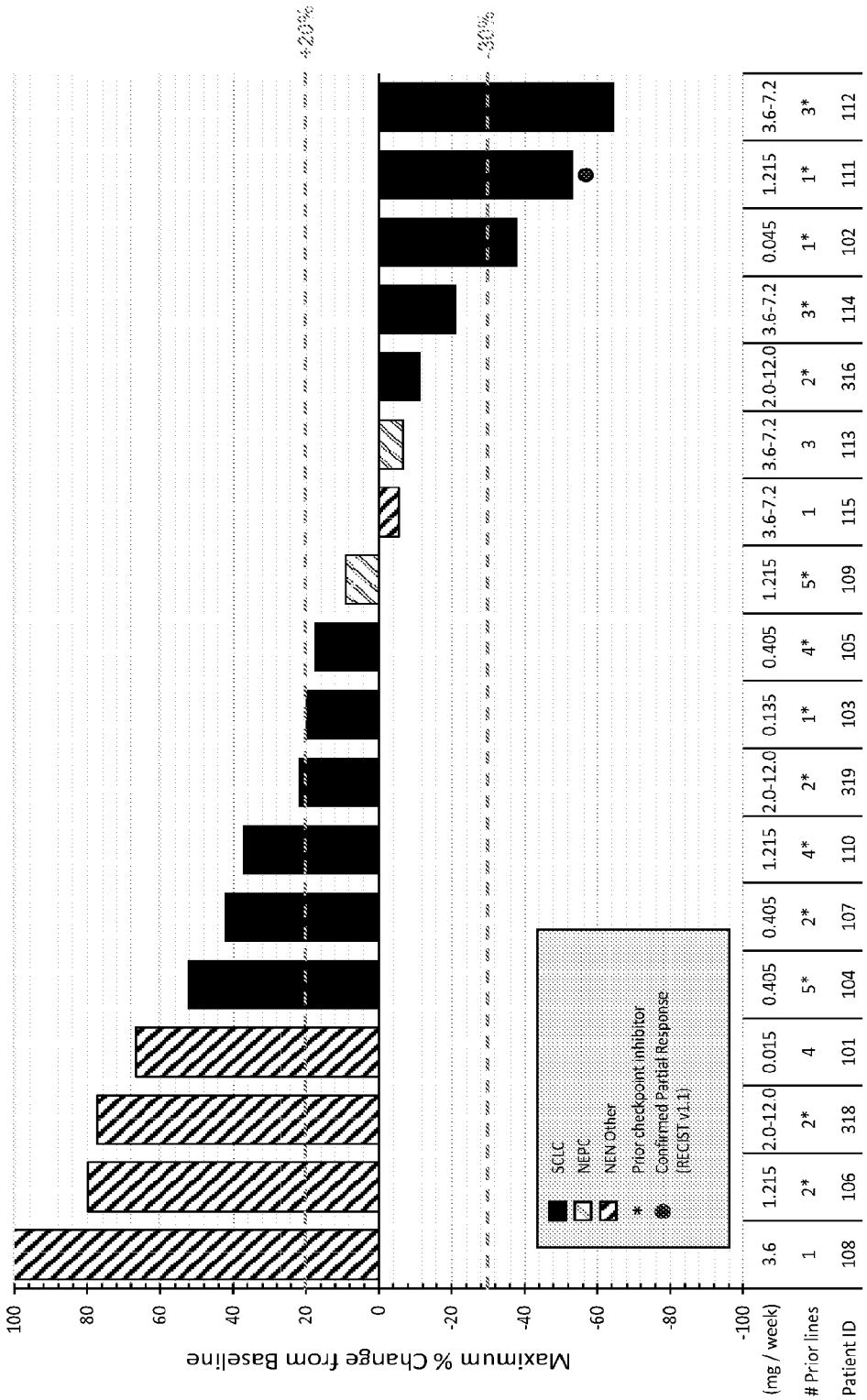

Maximum % Change from Baseline
100
80
60
40
20
0
-20
-40
-60
-80
-100
-42%
-30%
SCLC
NEPC
NEN Other
Prior checkpoint inhibitor
Confirmed Partial Response (RECIST v1.1)
Dose (mg / week) 3.6 1.215 2.0-12.0 0.015 0.405 0.405 1.215 2.0-12.0 0.135 0.405 1.215 3.6-7.2 3.6-7.2 2.0-12.0 3.6-7.2 0.045 1.215 3.6-7.2
Prior lines 1 2* 2* 4 5* 2* 4* 2* 1* 4* 5* 1 3 2* 3* 1* 1* 3*
Patient ID 108 106 318 101 104 107 110 319 103 105 109 115 113 316 114 102 111 112

FIG. 68

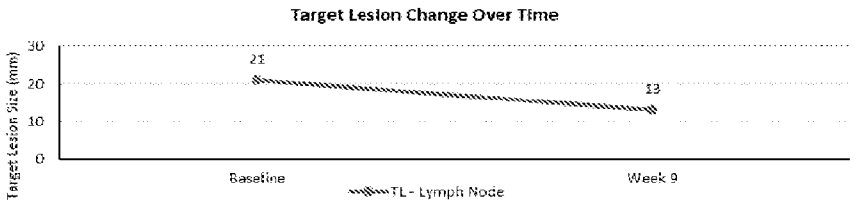

Target Lesion Change Over Time
Target Lesion Size (mm)
30
20
10
0
21
13
Baseline
Week 9
TL - Lymph Node

FIG. 69

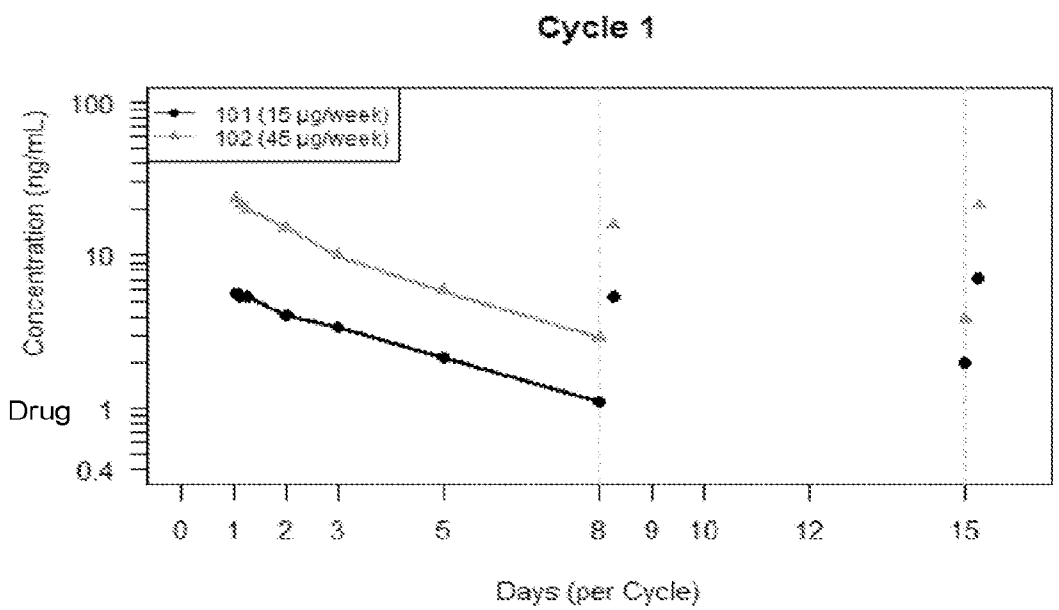

Cycle 1
Concentration (ng/mL)
Drug
100
10
1
0.4
101 (15 µg/week)
102 (45 µg/week)
0
1
2
3
5
8
9
10
12
15
Days (per Cycle)

FIG.70A

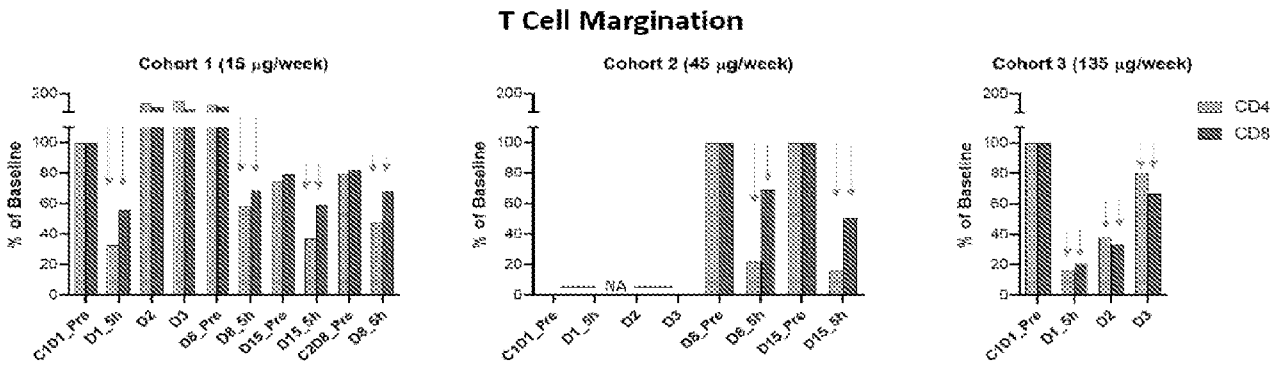


FIG. 70B

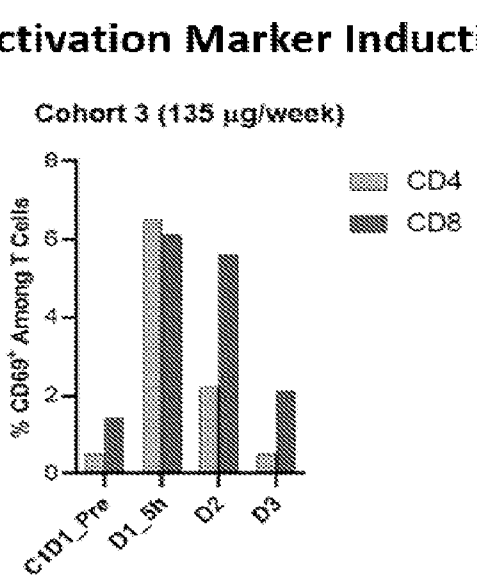


FIG. 71A

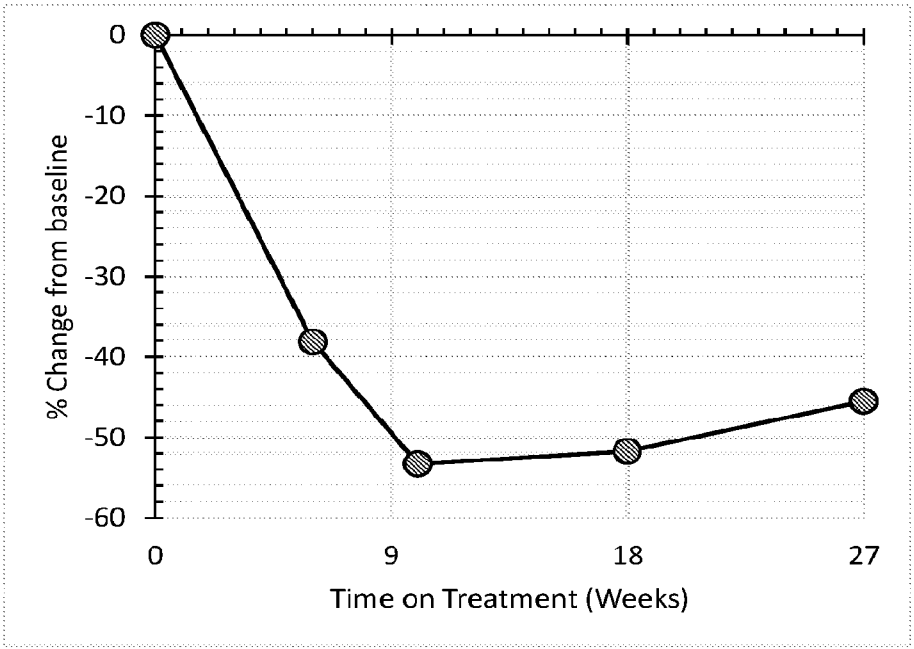

0
-10
-20
-30
-40
-50
-60
% Change from baseline
0
9
18
27
Time on Treatment (Weeks)

FIG. 71B

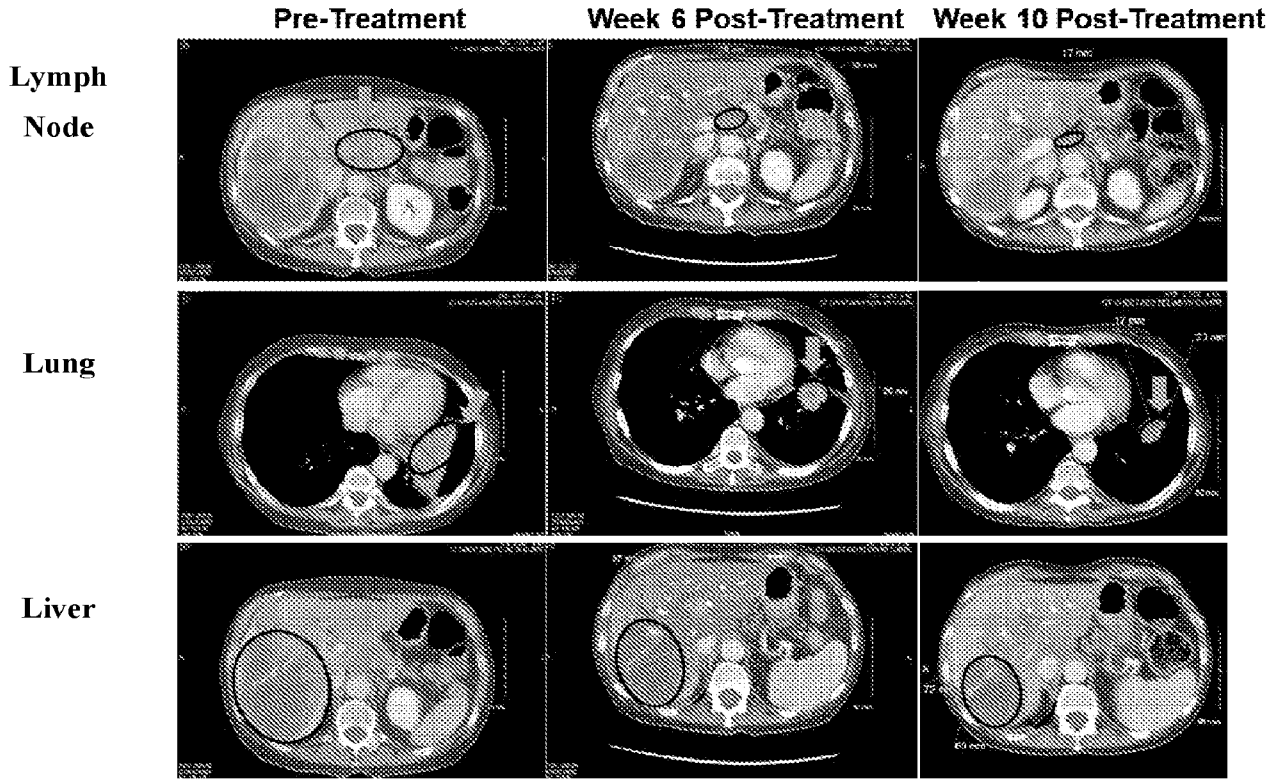

Pre-Treatment
Week 6 Post-Treatment
Week 10 Post-Treatment
Lymph Node
Lung
Liver

FIG. 72A

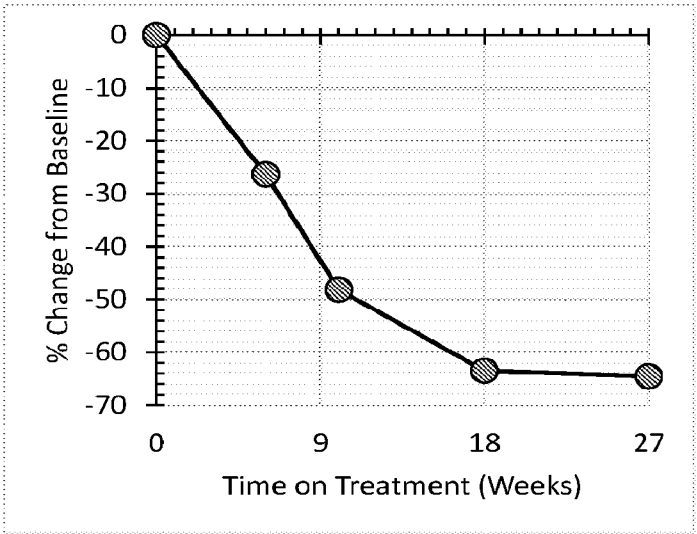


FIG. 72B

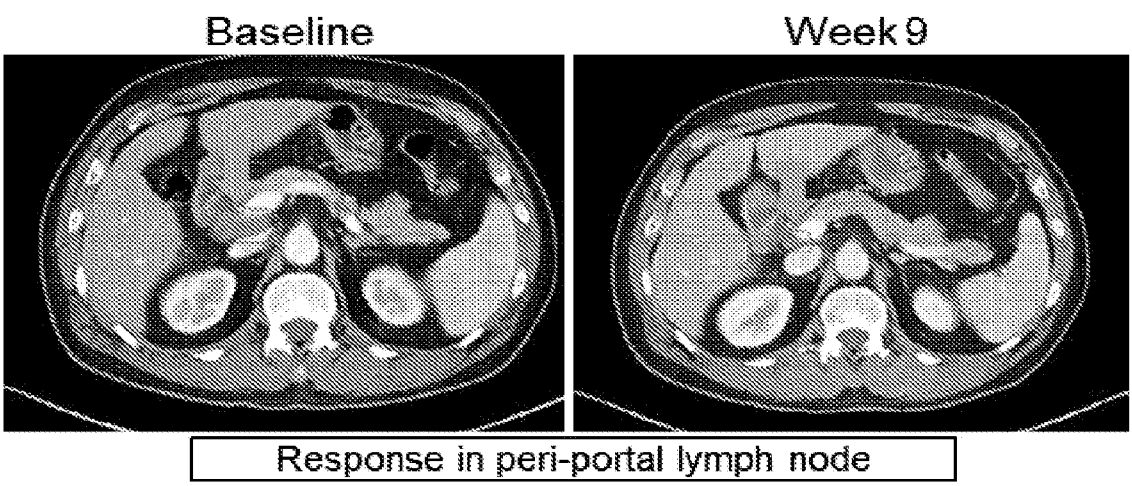


FIG. 73

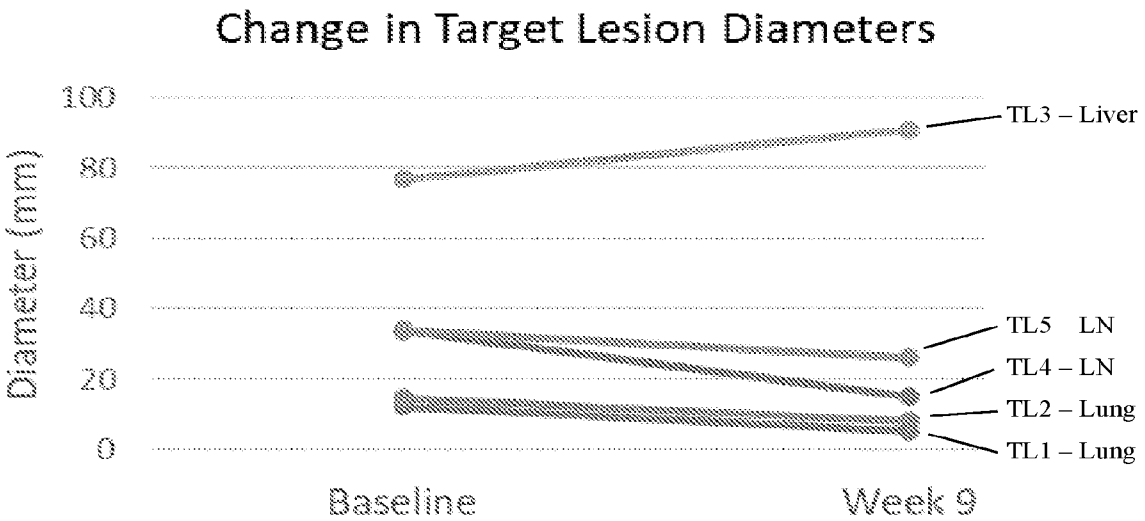

Change in Target Lesion Diameters
Diameter (mm)
100
80
60
40
20
0
Baseline
Week 9
TL3 – Liver
TL5 LN
TL4 – LN
TL2 – Lung
TL1 – Lung

FIG. 74A

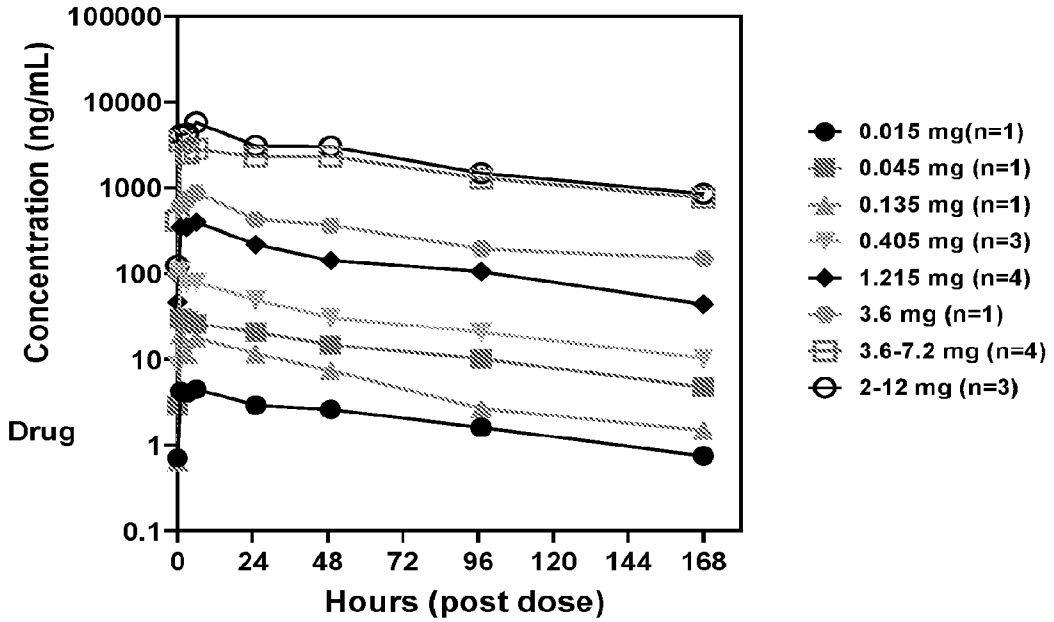


FIG. 74B

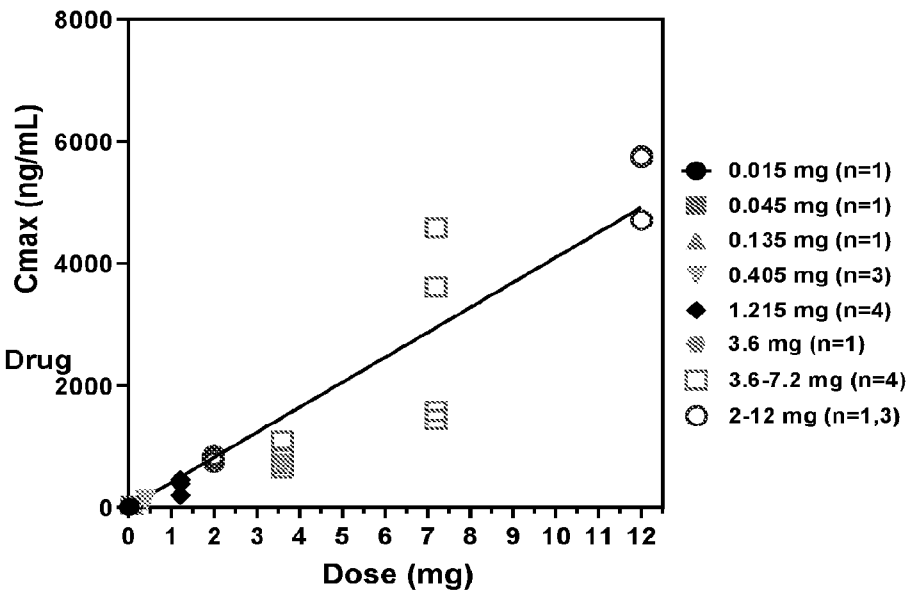


FIG. 75A

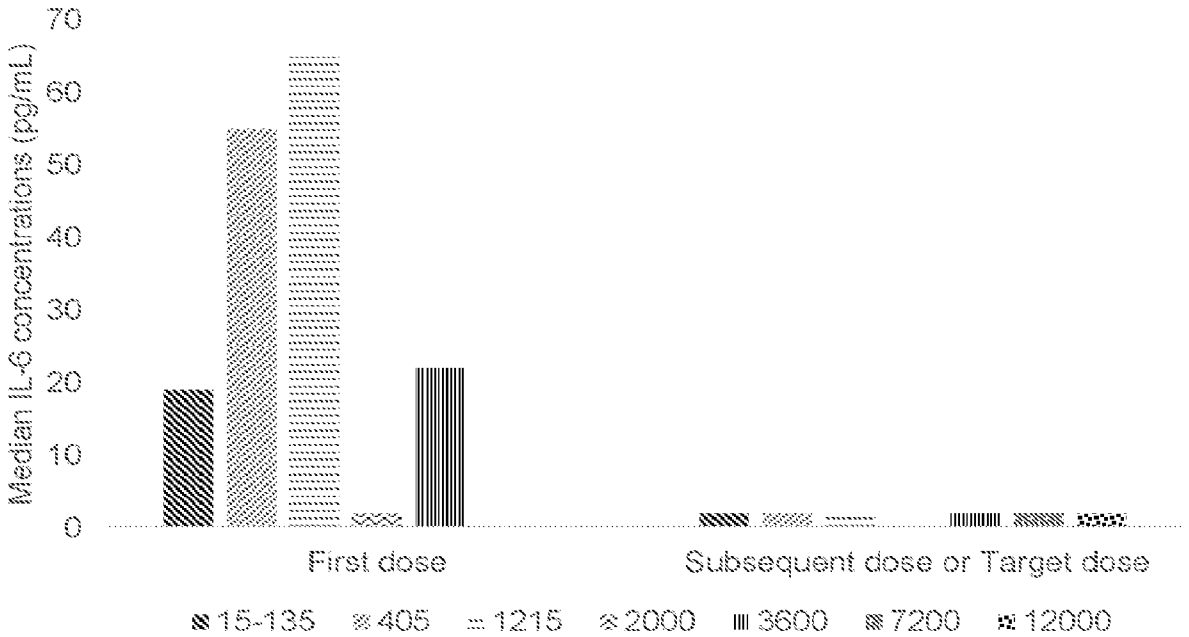


FIG. 75B

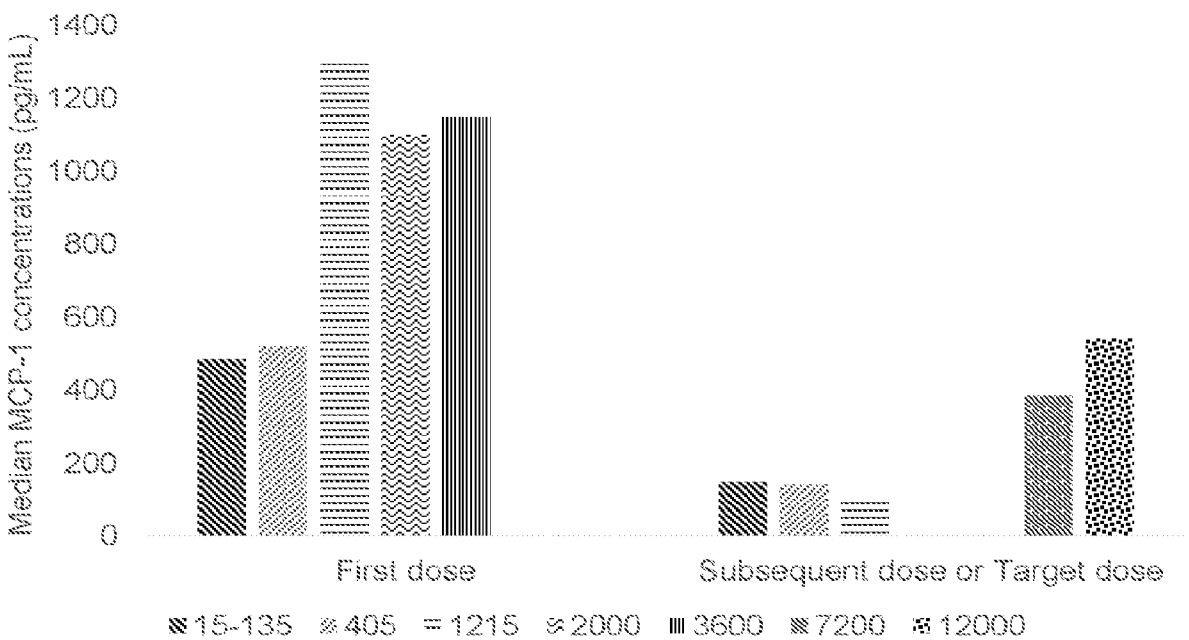
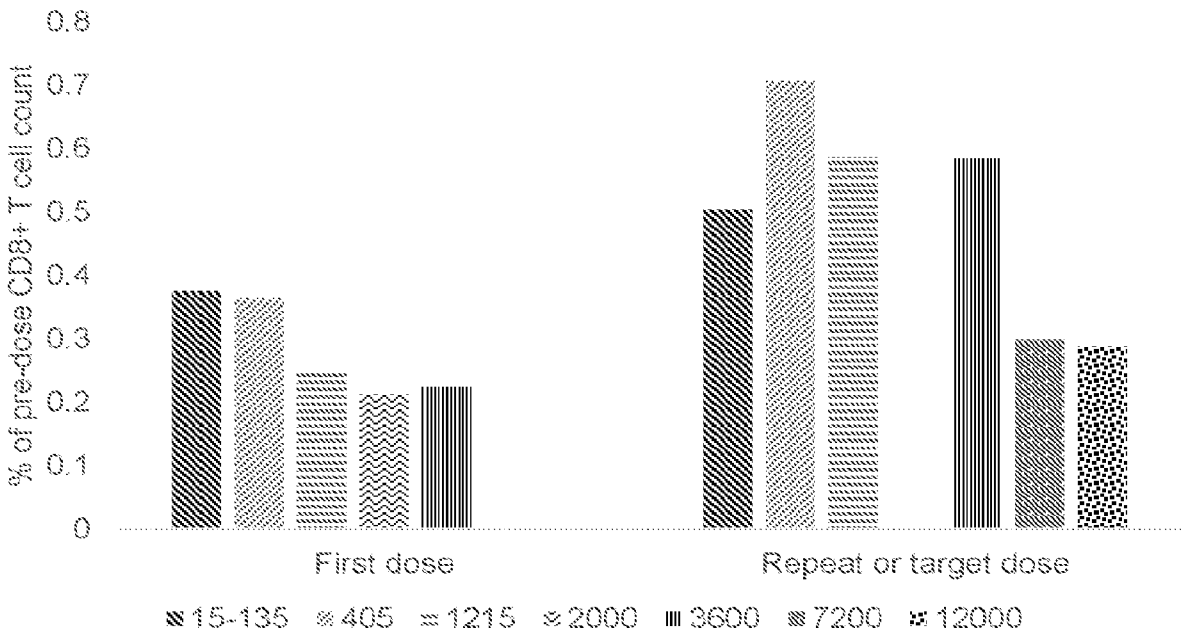


FIG. 75C


0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
% of pre-dose CD8+ T cell count
First dose
Repeat or target dose
15-135
405
1215
2000
3600
7200
12000

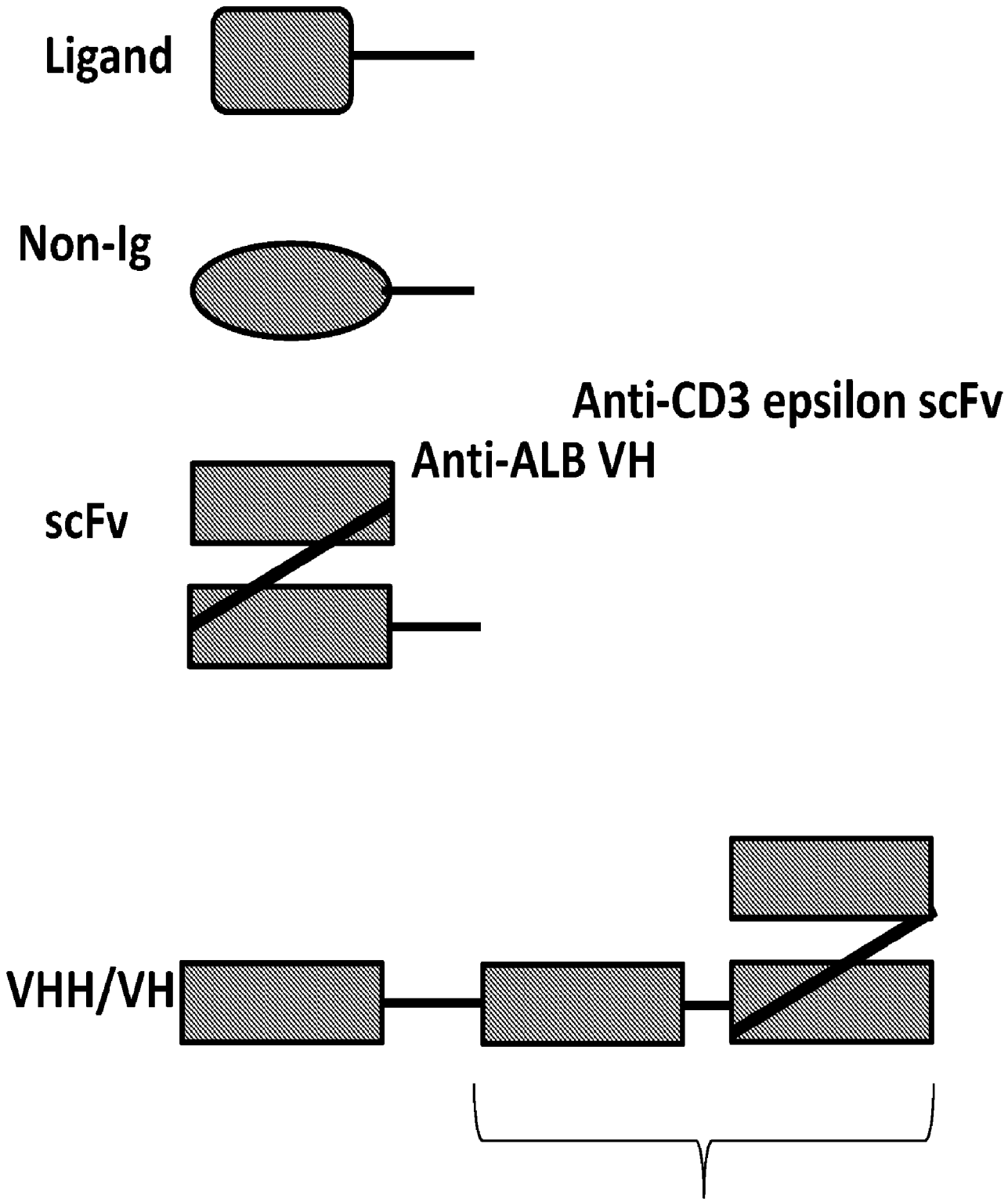

Ligand
Non-Ig
Anti-CD3 epsilon scFv
Anti-ALB VH
scFv
VHH/VH
DLL3 Binder
Constant Core

FIG. 1