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Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3064331 A1 2018/12/06

(21) 3 064 331

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/06/01
(87) Date publication PCT/PCT Publication Date: 2018/12/06
(85) Entrée phase nationale/National Entry: 2019/11/20
(86) N° demande PCT/PCT Application No.: IB 2018/000696
(87) N° publication PCT/PCT Publication No.: 2018/220446
(30) Priorités/Priorities: 2017/06/01 (US62/513,960); 2017/06/05 (US62/515,452); 2017/07/28 (US62/538,563); 2017/08/17 (US62/547,051); 2017/11/07 (US62/582,756); 2018/01/16 (US62/618,005)

(51) Cl.Int./Int.Cl. *A61K 39/395* (2006.01), *C07K 16/28* (2006.01)

(71) Demandeur/Applicant:
COMPUGEN LTD., IL

(72) Inventeurs/Inventors:
LIANG, SPENCER, IL;
LEUNG, LING, IL;
WHELAN, SARAH, IL;
KOTTURI, MAYA, IL;
MACHLENKIN, ARTHUR, IL;
OPHIR, ERAN, IL;
ALTEBER, ZOYA, IL;
...

(74) Agent: SMART & BIGGAR LLP

(54) Titre : THERAPIES A BASE D'ANTICORPS A TRIPLE COMBINAISON
(54) Title: TRIPLE COMBINATION ANTIBODY THERAPIES

Figure 1A

Human IgG1 constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1)
Human IgG1 D265A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2)
Human IgG1 N297A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 3)
Human IgG2 constant region
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVD
KTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV
HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4)
Human IgG3 constant region
ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVD
KRVELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEV1CV
VVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
(SEQ ID NO: 5)

Figure 1B
Human IgG4 constant region (Wild Type)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 6)

Human IgG4 constant region (S241P hinge mutant)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 7)

Human kappa light chain
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
SSPVTKSFNRGEC (SEQ ID NO: 8)

Human lambda light chain
GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS (SEQ ID NO: 9)

(57) Abrégé/Abstract:
The present invention is directed to triple combination therapies with anti-TIGIT antibodies, anti-PVRIG antibodies, and checkpoint inhibitors, including anti-PD-1 or anti- PD-L1 antibodies.

(21) 3 064 331

(13) A1

(72) Inventeurs(suite)/Inventors(continued): AZULAY, MEIR, IL; LOGRONIO, KATHRYN, IL; KUMAR, SANDEEP, IL; DESAI, RADHIKA, IL; CHAN, CHRISTOPHER, IL

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 December 2018 (06.12.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/220446 A9

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/28* (2006.01)

(21) International Application Number:
PCT/IB2018/000696

(22) International Filing Date:
01 June 2018 (01.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/513,960	01 June 2017 (01.06.2017)	US
62/515,452	05 June 2017 (05.06.2017)	US
62/538,563	28 July 2017 (28.07.2017)	US
62/547,051	17 August 2017 (17.08.2017)	US
62/582,756	07 November 2017 (07.11.2017)	US
62/618,005	16 January 2018 (16.01.2018)	US

(71) Applicant: **COMPUGEN LTD.** [IL/IL]; 26 Harokmim Street, 5885849 Holon (IL).

(72) Inventors: **LIANG, Spencer**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **LEUNG, Ling**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **WHELAN, Sarah**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **KOTTURI, Maya**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **MACHLENKIN, Arthur**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **OPHIR, Eran**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **ALTEBER, Zoya**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **AZULAY, Meir**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **LOGRONIO, Kathryn**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **KUMAR, Sandeep**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **DESAI, Radhika**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL). **CHAN, Christopher**; c/o Compugen Ltd., 26 Harokmim Street, 5885849 Holon (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,

(54) Title: TRIPLE COMBINATION ANTIBODY THERAPIES

Figure 1A

Human IgG1 constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1)
Human IgG1 D265A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV[A]VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2)
Human IgG1 N297A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY[A]STYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 3)
Human IgG2 constant region
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVD
KTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV
HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4)
Human IgG3 constant region
ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KRVELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
(SEQ ID NO: 5)

Figure 1B
Human IgG4 constant region (Wild Type)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 6)

Human IgG4 constant region (S241P hinge mutant)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPC[P]CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 7)

Human kappa light chain
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
SSPVTKSFNRGEC (SEQ ID NO: 8)

Human lambda light chain
GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS (SEQ ID NO: 9)

(57) **Abstract:** The present invention is directed to triple combination therapies with anti-TIGIT antibodies, anti-PVRIG antibodies, and checkpoint inhibitors, including anti-PD-1 or anti- PD-L1 antibodies.

[Continued on next page]

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KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
22 August 2019 (22.08.2019)

(15) Information about Correction:
see Notice of 22 August 2019 (22.08.2019)

TRIPLE COMBINATION ANTIBODY THERAPIES

CROSS REFERENCE TO RELATED APPLICAITONS

[0001] This application claims priority under 35 U.S.C. §119 to U.S. Patent Application Nos. 62/513,960 filed June 1, 2017, 62/515,452 filed June 5, 2017, 62/538,563 filed July 28, 2017, 62/547,051 filed August 17, 2017, 62/582,756 filed November 7, 2017 and 62/618,005 filed January 16, 2018, all of which are expressly incorporated herein by reference in their entireties.

I. BACKGROUND OF THE INVENTION

[0002] TIGIT is a coinhibitory receptor that is highly expressed on effector & regulatory (Treg) CD4+ T cells, effector CD8+ T cells, and NK cells. TIGIT has been shown to attenuate immune response by (1) direct signaling, (2) inducing ligand signaling, and (3) competition with and disruption of signaling by the costimulatory receptor CD226 (also known as DNAM-1). TIGIT signaling has been the most well-studied in NK cells, where it has been demonstrated that engagement with its cognate ligand, poliovirus receptor (PVR, also known as CD155) directly suppresses NK cell cytotoxicity through its cytoplasmic ITIM domain. Knockout of the TIGIT gene or antibody blockade of the TIGIT/PVR interaction has shown to enhance NK cell killing in vitro, as well as to exacerbate autoimmune diseases in vivo. In addition to its direct effects on T- and NK cells, TIGIT can induce PVR-mediated signaling in dendritic or tumor cells, leading to the increase in production of anti-inflammatory cytokines such as IL10. In T-cells TIGIT can also inhibit lymphocyte responses by disrupting homodimerization of the costimulatory receptor CD226, and by competing with it for binding to PVR.

[0003] TIGIT is highly expressed on lymphocytes, including Tumor Infiltrating Lymphocytes (TILs) and Tregs, that infiltrate different types of tumors. PVR is also broadly expressed in tumors, suggesting that the TIGIT-PVR signaling axis may be a dominant immune escape mechanism for cancer. Notably, TIGIT expression is tightly correlated with the expression of another important coinhibitory receptor, PD1. TIGIT and PD1 are co-expressed on the TILs of numerous human and murine tumors. Unlike TIGIT and CTLA4,

PD1 inhibition of T cell responses does not involve competition for ligand binding with a costimulatory receptor.

[0004] The immune checkpoint, poliovirus receptor related immunoglobulin domain containing (PVRIG, also known as CD112R) represents a new inhibitory receptor within the TIGIT family of receptors. PVRIG binds with high affinity to its cognate ligand, poliovirus receptor-related 2 (PVRL2, also known as CD112 or nectin-2) to deliver an inhibitory signal through its ITIM motif within T and NK cells. The affinity of TIGIT to PVR and of PVRIG to PVRL2 is higher than the affinity of CD226 to either PVR or PVRL2, suggesting TIGIT and PVRIG can outcompete PVR and PVRL2 from CD226 and providing an indirect mechanism by which TIGIT and PVRIG can reduce lymphocyte function. Thus, two receptors with the same family, TIGIT and PVRIG, deliver inhibitory signals to dampen T and NK cell responses.

[0005] Accordingly, TIGIT and PVRIG are attractive for triple therapy combinations with checkpoint inhibitors, including anti-PD-1 antibodies.

II. BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides methods and compositions comprising combinations of the TIGIT antibodies as disclosed herein and as provided in the claims with PVRIG antibodies and checkpoint inhibitors, including anti-PD-1 antibodies. The present invention also provides for nucleic acids encoding said antibodies and compositions thereof.

[0007] The present invention provides a method of treating cancer said patient comprising: a) providing a biopsy from said patient comprising tumor cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with

a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0008] In some embodiments of the method, anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P) and CHA.9.547.13.H4(S241P).

[0009] In some embodiments of the method, anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0010] In some embodiments of the method, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.

[0011] In some embodiments of the method, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0012] In some embodiments of the method, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P);

CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0013] In some embodiments of the method, the antibodies are administered simultaneously.

[0014] In some embodiments of the method, the antibodies are administered sequentially.

[0015] In some embodiments of the method, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS). In some embodiments of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS). In some embodiments of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, and MSI-high cancer.

[0016] The present invention also provides a method of treating cancer said patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-1 antibody.

[0017] In some embodiments of the method, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0018] In some embodiments of the method, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0019] In some embodiments of the method, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab and nivolumab.

[0020] In some embodiments of the method, the triple combination therapy comprises the administration of an anti-PD-1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0021] In some embodiments of the method, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P),

nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0022] In some embodiments of the method, the antibodies are administered simultaneously.

[0023] In some embodiments of the method, the antibodies are administered sequentially.

[0024] In some embodiments of the method, the cancer for the triple combination therapy is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS)..

In some embodiments of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0025] The present invention also provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; and b) a container comprising a unit dosage of an anti- PVRIG antibody.

[0026] The present invention also provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; b) a container comprising a unit dosage of an anti- PVRIG antibody; and c) a container comprising an anti-PD-1 antibody.

[0027] In a further aspect, the invention provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein; v) PD-L1 protein; vi) PVRL2; and vi) a relevant isotype control for the antibodies in i)-vi); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1, PVRL2 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either TIGIT or PVR, and for either PVRIG or PVRL2, and for either PD-1 or PD-L1, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[0028] In a further aspect, the invention provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVR protein; iii) PD-1 protein; iv) PD-L1 protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVR, PD-1, and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is $\geq$ 1% for all 4 receptors, e) administering antibodies to TIGIT and PD-1 to said patient.

[0029] In an additional aspect, the invention provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) PD-1 protein; iv) PD-L1 protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, PD-1 and PD-L1,

determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is ≥ 1% for all 4 receptors, e) administering antibodies to PVRIG and PD-1 to said patient.

[0030] In a further aspect, the invention provides methods comprising a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) TIGIT protein; iv) PVR protein; and v) a relevant isotype control for the antibodies in i)-iv); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is ≥ 1% for all 4 receptors, e) administering antibodies to PVRIG and TIGIT to said patient.

[0031] In an additional aspect, the invention provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) TIGIT protein; iii) PVRL2 protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, TIGIT, PVRL2, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is ≥ 1% for all 5 receptors, e) administering antibodies to PVRIG, TIGIT, and PD-1 to said patient.

[0032] In a further aspect, the invention provides methods comprising a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PVRL2 protein; iii) TIGIT protein; iv) PVR protein; v) PD-1; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is ≥ 1% for all 4 receptors, e) administering antibodies to PVRIG, TIGIT, and PD-1 to said patient.

[0033] In some embodiments, the present invention provides a method of treating cancer in a patient comprising: a) providing a biopsy from said patient comprising tumor

cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0034] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0035] 3 In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0036] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0037] In some embodiments, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0038] In some embodiments, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0039] In some embodiments, the anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, Cemiplimab and nivolumab.

[0040] 8 In some embodiments, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P);

CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0041] In some embodiments, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), and CHA.9.547.13.H4(S241P), and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0042] In some embodiments, the antibodies are administered simultaneously.

[0043] In some embodiments, the antibodies are administered sequentially.

[0044] In some embodiments, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer,

cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0045] In some embodiments, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0046] In some embodiments, the present invention provides a method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-1 antibody.

[0047] In some embodiments, the anti-TIGIT antibody is an antibody chosen from at least oneof CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0048] In some embodiments, the said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0049] 1 In some embodiments, the anti-PD-1 antibody is an antibody selected from the group consisting of pembrolizumab, cemiplimab, and nivolumab.

[0050] In some embodiments, the triple combination therapy comprises the administration of an anti-PD-1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0051] In some embodiments, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

[0052] In some embodiments, the antibodies are administered simultaneously.

[0053] In some embodiments, the antibodies are administered sequentially.

[0054] In some embodiments, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL),

Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0055] In some embodiments, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0056] In some embodiments, the present invention provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; and b) a container comprising a unit dosage of an anti-PVRIG antibody.

[0057] In some embodiments, the present invention provides a pharmaceutical dose kit comprising: a) a container comprising a unit dosage of an anti-TIGIT antibody; b) a container comprising a unit dosage of an anti-PVRIG antibody; and c) a container comprising an anti-PD-1 antibody.

[0058] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0059] In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0060] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0061] In some embodiments, the present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the

percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[0062] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0063] In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0064] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0065] In some embodiments, the TIGIT antibody is CPA.9.086.

[0066] In some embodiments, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0067] In some embodiments, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0068] In some embodiments, the present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) TIGIT protein; iii) PVRL2 protein; iv) PD-1 protein; v) PD-L1 protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, TIGIT, PVRL2, PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to PVRIG and PD-1 to said patient.

[0069] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0070] In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0071] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0072] In some embodiments, the anti-PD-L1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0073] In some embodiments, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0074] In some embodiments, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0075] In some embodiments, the TIGIT antibody is CPA.9.086.

[0076] In some embodiments, the present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; ii) PD-1 protein; iii) PVRL2 protein; iv) TIGIT protein; v) PVR protein; and vi) a relevant isotype control for the antibodies in i)-v); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG, PVRL2, TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for all 5 receptors, e) administering antibodies to PVRIG and TIGIT to said patient.

[0077] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0078] In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0079] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[0080] In some embodiments, the anti-PD-L1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0081] In some embodiments, the PVRIG antibody is CHA.7.518.1.H4(S241P).

[0082] In some embodiments, the TIGIT antibody is CPA9.086.

[0083] In some embodiments, the PD-1 antibody is selected from pembrolizumab and nivolumab.

[0084] In some embodiments, the present invention provides a method of treating cancer in a patient comprising: a) providing a biopsy from said patient comprising tumor cells; b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy; c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-L1 antibody; and d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

[0085] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

[0086] In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

[0087] In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

[0088] In some embodiments, the anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0089] In some embodiments, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0090] 58. A method according to any one of claims 52 to 57, wherein said anti-PD-L1 antibody is an antibody chosen from at least one of atezolizumab, avelumab, and durvalumab.

[0091] In some embodiments, the double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[0092] In some embodiments, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, avelumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

[0093] In some embodiments, the antibodies are administered simultaneously.

[0094] In some embodiments, the antibodies are administered sequentially.

[0095] In some embodiments, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0096] In some embodiments, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[0097] In some embodiments, the present invention provides a method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-L1 antibody.

[0098] In some embodiments, the anti-TIGIT antibody is an antibody chosen from at least oneof CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

[0099] In some embodiments, the anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[00100] In some embodiments, the anti-PD-L1 antibody is an antibody selected from the group consisting of atezolizumab, avelumab, and durvalumab.

[00101] In some embodiments, the triple combination therapy comprises the administration of an anti-PD-L1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and

CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

[00102] In some embodiments, the triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, avelumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

[00103] In some embodiments, the antibodies are administered simultaneously.

[00104] In some embodiments, the antibodies are administered sequentially.

[00105] In some embodiments, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer

(squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[00106] In some embodiments, the cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

III. BRIEF DESCRIPTION OF THE DRAWINGS

[00107] Figure 1A-1B depicts the amino acid sequences of the constant domains of human IgG1 (with some useful amino acid substitutions), IgG2, IgG3, IgG4, IgG4 with a hinge variant that finds particular use in the present invention, and the constant domains of the kappa and lambda light chains.

[00108] Figure 2 depicts the sequence of human and cynomolgus macaque (referred to as cyno) TIGIT, PVRIG and PD-1 proteins.

[00109] Figure 3A-3SSS depicts the sequences of four anti-TIGIT antibodies that block the interaction of TIGIT and PVR, CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P) and CHA.9.547.13.H4(S241P), as well as benchmark antibodies, BM26 and BM29.,and numerous other anti-TIGIT antibodies.

[00110] Figure 4A-4C shows the FACS K_D results of anti-TIGIT antibodies (CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P), as well as benchmark antibodies, BM26 and BM29, binding to human (A), cynomolgus (B), and mouse (C) TIGIT over-expressing Expi293 HEK cells.

[00111] Figure 5A-5F depicts the sequences of two anti-PVRIG antibodies, CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P). Other PVRIG antibodies are provided in Figure 63.

[00112] Figure 6 shows the binding of CHA.7.518.1.H4(S241P) to PVRIG by flow cytometry. (A) Binding to PVRIG over-expressing HEK293 cells. CHA.7.518.1.H4(S241P) binds human and cynomolgus PVRIG over-expressing HEK293 cells but not the mouse PVRIG over-expressing or parental HEK293 cells. (B) Binding of CHA.7.518.1.H4(S241P) to Jurkat cells. Specific binding is observed for CHA.7.518.1.H4(S241P) but not for an irrelevant isotype control antibody. Dissociation constant (K_D) for CHA.7.518.1.H4(S241P) binding to targets expressed on cells are listed in the table.

[00113] Figure 7A-7F depicts the sequences of two anti-PD-1 antibodies.

[00114] Figure 8 shows the expression of PVRIG, TIGIT, PD1 on CMVpp65 reactive T cells, as described in experiments of Example 1. (A) Gating strategy for detection of tetramer-stained CMV-CTLs. The gating hierarchy and tetramer positive cells in three donors are shown. The lymphocytes were gated in the FS/SS quadrant (upper left) followed by the selection of singlets, followed by the removal of CD14-CD19-CD56- cells, followed by CD3+ CD8+ positive cells. Within the CD3+ CD8+ positive population, the percentage of cells that bind each tetramer is determined in individual donors. Staining results using the HLA-A*02:01 CMV tetramer are shown. (B) The expression of PVRIG, TIGIT and PD-1 on the CMVpp65 reactive T cells expanded from 3 donors is shown.

[00115] Figure 9 shows the kinetics of PVRIG, TIGIT and PD-1 expression on CD8 + CMV+ T cells, as described in experiments of Example 1. (A) Percent pp65 tetramer positive of CD8 T cells after 0, 72, 144, 216 and 288 hours of stimulation with IL-2, IL-7 and CMV pp65 peptide is shown. (B) TIGIT, (C) CHA.7.518.1.H4(S241P), (D) PD-1 expression on CMVpp65 reactive CD8 T-cells at distinct time points after stimulation. (n=3)

[00116] Figure 10 shows the expression of PVRL2, PVR, PDL1 and HLA-A2 on the Colo205 and Panc.04.05 cells was evaluated by flow cytometry, as described in experiments of Example 1. The number in the upper right hand corner denotes the percentage of the ligand (PVRL2, PVR, PDL1) or HLA-A2 expressed on the tumor cell lines in comparison to the isotype control antibody.

[00117] Figure 11A-11D shows the effect of inhibitory receptor blockade on CMVpp65 reactive CD8 T cells in co-culture with cancer cell lines, as described in

experiments of Example 1. CMVpp65 reactive T cells for 2 donors (Donor 4 and Donor 156 were co-cultured with 0.03 ug/ml CMVpp65 peptide loaded Panc.04.05 or Colo205 for 24hr in the presence of 10ug/ml CHA.7.518.1.H4(S241P), anti-TIGIT, anti-PD-1, or isotype control either alone or in combination. (A) CHA.7.518.1.H4(S241P), anti-TIGIT or anti-PD1 antibodies tested alone, in dual combination, or in triple combination. (B) CHA.7.518.1.H4(S241P) and anti-TIGIT antibodies tested alone or in combination. (C) CHA.7.518.1.H4(S241P) and anti-PD1 antibodies tested alone or in combination. (D) Anti-TIGIT and anti-PD1 antibodies tested alone or in combination. Conditioned media were assayed for cytokine secretion. The bar graphs show the average + standard deviation for IFN-γ, with each dot representing a technical replicate. Data are representative of n > 2 experiments.

[00118] Figure 12 shows the expression of PVRIG on cells from dissociated tumors, as described in experiments of Example 2. (A) Samples were grouped based on the tumor type as defined by the pathology report. For each sample, expression of PVRIG is shown on CD4+ T cells, CD8+ T cells, CD4-CD8- T cells, and on NK cells. Each dot within a column represents an individual sample. Samples with a MFIr value above 1 denotes expression of PVRIG was detected. The median is depicted by the middle line and the upper and lower quartiles are depicted by the grey space above and below the median line. (B) Across all tumor samples examined, the expression of PVRIG on CD4+ T cells, CD8+ T cells, CD4-CD8- T cells, and on NK cells is shown. The median is depicted by the middle line and the upper and lower quartiles are depicted by the light and dark grey space above and below the median line. The whiskers depict 1.5 times the interquartile range. (C) Representative FACS histograms for PVRIG (blue) compared to isotype control (red) are shown for 4 cell subsets isolated from a lung and kidney tumor.

[00119] Figure 13 shows the correlation analysis of PD1, TIGIT, and PVRIG expression on CD4+ and CD8+ T cells from dissociated endometrial tumors, as described in experiments of Example 2. For each endometrial sample, a MFIr was calculated for PVRIG, PD1, and TIGIT on CD4 and CD8 T cells. A Spearman's correlation analysis was performed and a r2 and p value reported.

[00120] Figure 14 shows the co-expression analysis of PD1, TIGIT, and PVRIG expression on CD8+ T cells from a dissociated lung and kidney cancer sample, as described in experiments of Example 2.

[00121] Figure 15 shows a comparison of PVRIG expression on T cells from dissociated tumors with matched NAT, as described in experiments of Example 2. (A) Matched tumor and normal adjacent tissues from colon/stomach/rectal, endometrium/uterine, kidney, lung, and ovarian tumors were assessed for PVRIG expression on CD4 and CD8 T cells. Each line represents a matched donor. A paired Student's t-test was performed on all samples comparing NAT vs tumor expression of PVRIG on CD4 and CD8 T cells. (B) PVRIG fold change (in NAT vs tumor) is plotted vs PD1 fold change for CD4 and CD8 T cells. A spearman's correlation analysis was done and r value and p value is shown.

[00122] Figure 16 shows the expression of PVRL2 on immune and non-immune subsets from all dissociated tumor samples, as described in experiments of Example 2. The expression of PVRL2 on various cell subsets derived from tumors is shown. MFIr values above 1 denote expression of PVRL2 was detected. The median is depicted by the middle line and the upper and lower quartiles are depicted by the light and dark grey space above and below the median line. The whiskers depict 1.5 times the interquartile range.

[00123] Figure 17 shows the expression of PVRL2 on non-immune subsets from dissociated tumors, as described in experiments of Example 2. Samples were grouped based on the tumor type as defined by the pathology report. For each sample, expression of PVRL2 is shown on CD45- non-immune cells. Each dot represents an individual sample. The median is depicted by the middle line and the upper and lower quartiles are depicted by the grey space above and below the median line.

[00124] Figure 18 shows the expression of PVRL2 on myeloid cell subsets from dissociated tumors, as described in experiments of Example 2. Samples were grouped based on the tumor type as defined by the pathology report. For each sample, expression of PVRL2 is shown on myeloid cells which include monocytes, mDC, and pDC populations. Each dot represents an individual sample. The median is depicted by the middle line and

the upper and lower quartiles are depicted by the grey space above and below the median line.

[00125] Figure 19 shows a comparison of PVRL2 expression on monocytes and CD45- tumor cells from dissociated tumors and matched NAT, as described in experiments of Example 2. (A) Matched tumor and normal adjacent tissues from colon/stomach/rectal, endometrium/uterine, kidney, lung, and ovarian tumors were assessed for PVRL2 expression on CD45- cells and on monocytes. Each line represents a matched donor. A paired Student's t-test was performed on all samples comparing NAT vs tumor expression of PVRL2 on CD45- cells and on monocytes cells. (B) PVRL2 fold change (in NAT vs tumor) is plotted vs PD-L1 fold change for CD45- cells and for monocytes. A spearman's correlation analysis was done and r value and p value is shown.

[00126] Figure 20 depicts the co-expression of PVRIG on T cells with PVRL2 on monocytes and CD45- cells in tumor tissues, as described in experiments of Example 2. From the same sample, the expression of PVRIG on CD8 T cells and PVRL2 on monocytes or CD45- cells was plotted. Tumor types were grouped and each dot represents an individual tumor. Reference lines were drawn at MFIr value of 2.

[00127] Figure 21A-21B depicts the expression of PVRL2 and PD-L1 in colon, skin, and breast cancers, as described in experiments of Example 3.

[00128] Figure 22 depicts the expression of PVRL2 in PD-L1 negative and PD-L1 positive tumors, as described in experiments of Example 3. Based on PD-L1 staining, tumors were categorized as PD-L1 Negative (No staining of PD-L1 observed in either duplicate cores for each tumor) or PD-L1 Positive (Positive staining observed in both duplicate cores for each tumor. A) Expression of PVRL2 was analyzed and shown for each cancer type. B) Of the PD-L1 negative tumors, the number of PVRL2 expressing samples (PVRL2 partial positive or greater/total samples) for each cancer type is shown.

[00129] Figure 23 shows the expression of PVRL2 and PD-L1 at the invasive front of the tumor, as described in experiments of Example 3. A. In this tumor sample, PVRL2 was expressed on both immune cells and tumor cells at the invasive front, as delineated by the

blue and red lines. B) In this tumor sample, PD-L1 was expressed in the immune compartment.

[00130] Figure 24 shows antitumor responses of mono, dual and triple combination antibody treatments in the CT26 tumor model, as described in experiments of Example 4. Groups of 10-15 Balb/c mice were subcutaneously injected with $5x10^5$ CT26 cells. Mice were treated x2 weekly for 3 weeks, starting at day 7 post inoculation with the designated antibody combination. A) Tumor volumes of all tested groups were measured x2 weekly, including positive control group (anti-PDL-1 + anti-CTLA-4 antibodies). The TGIs and p-values of the triple combination group compared to the indicated groups summarized in the table. . B) Survival proportions of assigned groups. C) Spider plots showing individuals response over treatment groups, while PR indicates partial responders with tumor size not exceeding $1000mm^3$. Figure 25 depicts expression profiles for PVRIG and PVRL2, as well as PD-L1 in various human tumors, as described in experiments of Examples 2 and 3.

[00131] Figure 26 depicts in vivo data regarding the use of an anti-PVRIG antibody in TIGIT-/- mice or the combination of anti-PVRIG and anti-PD-1 antibodies in wild type Balb/c mice to reduce syngeneic tumor growth, as described in experiments of Example 4.

[00132] Figure 27. PVRIG is expressed highest on cytotoxic lymphocyte subsets from human cancer. A) Expression of PVRIG on leukocyte cell subsets from 5-8 healthy donor PBMCs is shown. PVRIG expression is defined as the ratio of PVRIG MFI relative to isotype control MFI. B) Expression of PVRIG, TIGIT, CD96, and PD-1 on peripheral blood Tregs as compared to CD8 T cell subsets from 5 healthy donor PBMCs is shown. C) CMV pp65 specific T cells from 3 healthy donors were expanded in vitro with pp65 (495 - 503) peptide, IL-2 and IL-7 for up to 7 days. Expression of TIGIT (blue) and PVRIG (black) on HLA-A2/pp65 (495 - 503) tetramer positive cells is shown. D) Human T cells were cultured with allogeneic DCs and expression of TIGIT and PVRIG shown on $CD4^+$ T cells on day 0, 1, 2, and 7 post activation. E) Representative FACS plots showing expression of PVRIG (blue) compared to isotype control (red) on TILS (CD4 T cells, CD8 T cells, and NK cells) from a representative lung and kidney cancer. F) Co-expression of PVRIG, TIGIT, and PD-1 on CD4 and CD8 TILS from a lung cancer sample is shown. G) Expression of PVRIG on $CD8^+$ and $CD4^+$ TILS from dissociated human tumors of various cancer types is shown. Each dot

represents a distinct tumor from an individual patient. H) Relative expression on CD8 TILs vs Treg TILS for PVRIG, TIGIT, and PD-1 from endometrial, kidney, and lung tumors was assessed. For each tumor, the fold expression on CD8 TILS was normalized to fold expression on Treg TILS and plotted. For A, B, C, G, and H, mean ± SEM is shown by the error bars.

[00133] Figure 28A-Figure 28F. PVRL2 expression is enhanced in the tumor microenvironment. A) PVRL2 expression was assessed by IHC on lung, ovarian/endometrial, breast, colon, and kidney tumors. For each tumor, 2 cores were assessed by 2 independent observers. Representative staining for each descriptor is shown in Figure B) A representative melanoma tumor showing PVRL2 expression on tumor cells and in the immune cells in the stroma is shown. C) PVRL2 expression from dissociated tumors was examined by FACS on $CD45^-$, $CD14^+$ TAMs, and $CD14^-CD33^{hi}$ mDC cell subsets. Mean ± SEM is shown for each cancer type. D) Representative FACS plots for PVRL2 expression (blue) as compared to IgG (red) are shown for a lung cancer. E) For tumor samples where we were able to assess both PVRIG and PVRL2 expression, PVRIG expression on CD8 T cells is plotted versus PVRL2 expression on $CD14^+$ TAMS for each tumor. Each dot represents an individual tumor sample. Red line represents a 2 fold expression of PVRIG or PVRL2 compared to IgG.

[00134] Figure 29. Distinct regulation of PVRL2 and PD-L1 on tumor cells. A) Expression of PD-L1 and PVRL2 was assessed by IHC on serial sections. Expression of PVRL2 on PD-L1 negative (left) and PD-L1 positive (tumors) is shown. PD-L1 negative tumors were defined as no staining observed on duplicate cores for a given tumor. PD-L1 positive staining was defined as at least partial positive on both duplicate cores of a give tumor. The number of PVRL2 positive tumors from PD-L1 positive and PD-L1 negative tumors is shown in the table (positive/total). B, C) Representative expression of a $PVRL2^+PD\text{-}L1^-$ endometrial (B) tumor and a $PVRL2^+PD\text{-}L1^-$ lung (C) tumor. D) Immature BM-DCs were cultured with the indicated stimuli and PVR, PVRL2, PD-L1 expression assessed by FACS on day 2 of culture. For each condition, expression was normalized to media only control condition. E) Expression of PVR, PVRL2, and PD-L1 on HT-29 cells

treated with IFN-γ or media alone is shown. PD-L1 or PVRL2 is shown in blue and IgG isotype control staining is shown in red.

[00135] Figure 30. CHA.7.518.1.H4(S241P) is a high affinity antibody that enhances T cell activation. A) Binding of CHA.7.518.1.H4(S241P) or IgG isotype control to HEK293 PVRIG or HEK293 parental cells by FACS is shown. FACS KD values are shown for the binding of CHA.7.518.1.H4(S241P) to HEK293 hPVRIG, HEK293 cPVRIG, and Jurkat cells. B) CHA.7.518.1.H4(S241P) disrupts the binding of PVRL2 Fc to HEK293 cells ectopically expressing PVRIG. Mean ± Std Dev of triplicate values is shown. C) CHA.7.518.1.H4(S241P) blocks the binding of PVRIG Fc to HEK293 cells that endogenously express PVRL2. D) Human CD4 T cells were co-cultured with aAPC CHO cells expressing a cell surface bound anti-CD3 antibody and hPVRL2 in the presence of 10 μg/ml anti-PVRIG antibody and human IgG isotype control antibodies. The effect of anti-PVRIG Ab on proliferation of CD4 T cells isolated from 11 different donors is shown. Bars depicted mean ± SEM. E) gp100 specific T cell lines (TIL-209, TIL-463) were co-cultured with CHO cells engineered to express HLA-A2 and PVRL2 along with 10 μg/ml anti-PVRIG or IgG isotype control antibody. IFN-γ and TNF-α production was tested at 24 hours post co-culture. Mean ± Std Dev of triplicate values is shown. Percent change in IFN-γ and TNF-α for each condition relative to isotype control is depicted by the number above each bar. F) Expression of PVR, PVRL2, and PD-L1 (red) relative to IgG (blue) on MEL624, Colo205, and Panc.05.04 cells is shown. For the T cells, expression of PVRIG, TIGIT, and PD-1 (red) relative to IgG (blue) on TIL-209 and TIL-463 gp100 specific T cells, and on CMVpp65 specific T cells is shown. To expand CMVpp65 reactive T cells, PBMCs were cultured with pp65 (495-503) peptide, IL-2, and IL-7 for 10 days. Expression of PVRIG, TIGIT, PD-1 is shown on HLA-A2/pp65 tetramer positive cells. G) gp100 specific T cells (TIL-209, TIL-463) expanded from TILS derived from melanoma tumors were co-cultured with MEL624 cells in the presence of 10 μg/ml of the indicated antibodies. IFN-γ concentration in the conditioned media was determined at 24hrs. H, I) Expanded CMVpp65 specific T cells were co-cultured with Colo205 and Panc.05.04 cells, CMVpp65 peptide, and the indicated antibodies at 10 μg/ml. IFN-γ concentration in the conditioned media was determined at 24 hrs. For E, G, H, I, average ± Std Dev of triplicates is shown. Percent change in IFN-γ for each condition relative to isotype control is depicted by the number above each bar.

[00136] Figure 31. PVRIG deficient mice have increased T cell function. A) RNA expression of PVRIG as measured by qRT-PCR from purified mouse immune cell subsets was assessed. Relative expression to housekeeping was determined by ΔCt method. B) pmel $CD8^+$ TCR transgenic T cells were activated with gp100 (25-33) and PVRIG and TIGIT RNA transcript levels assessed by qRT-PCR at the indicated time points. Graph shows mean ± SEM of results from 5 different experiments. C) Spleens were harvested from $PVRIG^{-/-}$ and WT littermates and analyzed by flow cytometry for expression of PVRIG on NK, $CD4^+$ and $CD8^+$ T cells ("Resting" cells). In addition, $CD3^+$ T cells were isolated from splenocytes and activated for 11 days with anti-CD3/anti-CD28 beads. Following the activation, PVRIG expression on $CD4^+$ and $CD8^+$ T cells ("activated" cells) was analyzed by flow cytometry. Each dot represents cells derived from an individual mouse. D) WT and $PVRIG^{-/-}$ derived splenocytes were labeled with Cell Proliferation Dye eFluor450 and were cultured in the presence of Control-Fc (mouse IgG2a) or with mouse PVRL2 Fc. After 4 d of culture, cell division was analyzed by flow cytometry. Representative FACS plots from an experiment (left) and the summary of percentage inhibition by PVRL2 Fc (defined as % proliferation Control-Fc subtracted from % proliferation PVRL2 Fc) 3 independent experiments (right) are presented. * indicate p-value < 0.05, paired student's t-test for the change in proliferation in the presence of PVRL2-FC relative to proliferation in the presence of protein control in WT versus $PVRIG^{-/-}$ T cells E) pmel $CD8^+$ T cells derived from pmel $PVRIG^{-/-}$ or pmel PVRIG WT mice were activated for 11 days with their cognate peptide and IL2. Activated pmel $CD8^+$ cells were then co-cultured with B16-Db/gp100 cells for 18 hours and following the co-culture were evaluated for CD107 expression and for cytokine production. Four independent experiments are presented as indicated by each paired dot. * indicate p-value<0.05, Student's t-test comparing $PVRIG^{-/-}$ versus WT.

[00137] Figure 32. PVRIG deficiency results in reduced tumor growth and increased CD8 effector T cell mechanism. (A) C57BL/6 WT or $PVRIG^{-/-}$ mice were subcutaneously injected with 5×10^5 MC38 cells. Tumor volumes were measured x2 weekly. * indicate p-value<0.05 for WT mice versus $PVRIG^{-/-}$ mice (ANOVA). (B) Individual tumor growth curves are shown. One representative experiment out of 2 performed is shown. (C) C57BL/6 WT or $PVRIG^{-/-}$ mice were subcutaneously injected with 5×10^5 MC38 cells. At day 14 post-inoculation, mice were treated with anti-PD-L1, x2 weekly for 2 weeks. Tumor volumes

were measured x2 weekly. p-value= 0.052 for WT mice versus PVRIG$^{-/-}$ mice, both treated with anti-PD-L1. (D) Individual tumor growth curves are shown. One representative experiment out of 2 performed is shown. (E) Frequency of CD8^{+} IFN-γ^{+} TNF-α^{+} effector cells in tumor-draining lymph nodes from 4 treatment groups on day 18 is shown. (F) Total number of CD8+ IFN-γ+TNF-α+ effector cells per mg tumor tissue on day 18 is shown. (G-H) Total TILS score and Cytotoxic T cells score relative to TILs, derived from nSolver 3.0 advanced analysis of the mouse pan-cancer immune codeset panel (Nanostring Technologies, Seattle, WA) run on CD45^{+} enriched cells from MC38 day 18 TILs isolated from 2 treatment groups per wild-type and PVRIG deficient mice.

[00138] Figure 33. Antagonistic anti-PVRIG antibodies synergistically inhibit tumor grown in combination of PD-1 inhibitors or TIGIT genetic deficiency. A) Binding of mPVRL2 Fc fusion protein to mPVRIG HEK293 engineered cells that were pre-incubated with serial dilutions of anti-mPVRIG mAb or IgG isotype control Ab is shown. B) BALB/c mice were subcutaneously injected with 5×10^{5} CT26 cells. On day 14 post inoculation, mice were sacrificed and spleen, draining lymph nodes and tumors were harvested. Cells were analyzed by flow cytometry for expression of PVRIG on CD3^{+}CD4^{+} T cells, CD3^{+}CD8^{+} T cells, CD3^{-}CD49b^{+} NK cells, CD11b^{+} Gr-1^{+} Myeloid-Derived-Suppressor Cells (MDSC) and CD11b^{+}F4/80^{+} macrophages. C, D) BALB/c mice were subcutaneously injected with 5×10^{5} CT26 cells. At day 7 post inoculation mice were treated with anti-PD-L1 and/or anti-PVRIG Ab, 2x weekly for 3 weeks (arrows indicate Ab treatment). C) Tumor volumes are shown. *** indicate p-value < 0.001 (ANOVA) for anti-PD-L1+Rat IgG2b compared to anti-PD-L1+aPVRIG treated groups. Arrows indicate when antibodies were dosed. D. Survival analysis of complete responder's mice. * indicate p value < 0.05 (Log-rank test) for anti-PD-L1 + Rat IgG2b compared to anti-PD-L1 + anti-PVRIG treated groups. One representative study of 3 studies are shown. E. C57BL/6 or TIGIT$^{-/-}$ mice were subcutaneously injected with 1×10^{5} B16/Db-hmgp100 cells. Mice were treated 2x weekly for 3 weeks with the designated mAb starting on the day of inoculation (day 0). E. Tumor volumes were measured 2x weekly and average $\pm$ SEM is shown. Tumor growth inhibition as measured at indicated days compared to control WT+mIgG1 isotype control. *** indicate p-value<0.001 for TIGIT$^{-/-}$ + aPVRIG compared to WT + mIgG1 isotype control. Arrows indicate when

antibodies were dosed. F. Individual tumor growth curves for each mouse is shown. One representative experiment out of 2 performed is shown.

[00139] Figure 34. PVRIG is expressed on T and NK cells of TILS in human cancer. A) Expression of PVRIG, TIGIT, CD96, and PD-1 on CD4 T cell subsets from healthy donor PBMCs is shown. Mean ± SEM is shown. B) Human T cells were co-cultured with allogeneic PBMCs and expression of PVRIG protein on CD4 and CD8 T cells shown (top). C) Tumors were dissociated and single cells were activated with anti-CD3 and anti-CD28. Expression of PVRIG (blue) relative to IgG isotype control (red) was assessed on day 0 (directly ex vivo) and day 5 post activation. D) Expression of PVRIG on NK cells from dissociated human tumors is shown. Each dot represents a distinct tumor from an individual patient. Mean ± 95% confidence internal is shown. D) Dissociated tumor cells were activated with anti-CD3 and anti-CD28 beads for 5 days. Expression of PVRIG (blue) relative to IgG control (red) on CD4 and CD8 T cells on day 0 directly ex vivo and on day 5 post activation is shown for 2 dissociated tumor samples. E) Expression of PVRIG was assessed on CD4 and CD8 T cells from dissociated tumors and from dissociated donor-matched normal adjacent tissue. Each line represents matched tissues obtained from an individual patient. A paired student's t-test was performed. F) A correlation analysis of the magnitude of PVRIG, TIGIT, and PD-1 fold expression relative to IgG isotype control on CD4 and CD8 T cells from tumors is shown. Each dot represents an individual tumor sample. A Spearman's correlation coefficient and p value are shown.

[00140] Figure 35. Expression of PVRL2 is enhanced in colon, skin, and breast cancers. A) Photomicrographs showing the binding of Sigma anti human PVRL2 antibody to FFPE sections of positive cells, CHO-S human PVRL2 (right) compare to negative cells, CHO-S (left), following antigen retrieval at pH9. B) Anti-PVRL2 antibody was tested on a panel of $PVRL2^+$ (HT29, MCF7, PC3, PANC1, RT4, NCI-H1573) and $PVRL2^-$ (Jurkat, OPM2, Daudi, CA46) cell lines. C-F) Example expression of PVRL2 in lung normal and cancer tissues. C) Normal tissue showing no staining. D) Lung Adenocarcinoma showing partial positive staining. E) Lung adenocarcinoma showing positive staining. F) Lung adenocarcinoma showing strong positive staining.

[00141] Figure 36. PVRL2 is upregulated on TAMs and CD45$^-$ cells in the tumor as compared to normal adjacent tissue. Expression of PVRL2 on CD45$^-$ cells and TAMs from donor matched tumor and normal adjacent tissue is shown. A paired student's t-test p value is shown.

[00142] Figure 37. PVRIG and PVRL2 are co-expressed in the same tumor sample. PVRIG expression on CD4 T cells (A) and NK cells (B) is plotted against PVRL2 expression on TAMS for an individual tumor.

[00143] Figure 38. Activity of CHA.7.518.1.H4(S241P) on human T cells. A) Expression of PVRIG on CD4 T cells activated with CHO cells expressing cell surface bound anti-CD3 and PVRL2. B) Expression of HLA-A2, B-2m, and PVRL2 are shown on CHO-S parental and engineered CHO-S cell lines. Fold expression relative to isotype is depicted by the number. C) CHO cells ectopically expressing cell surface bound anti-CD3 and PVRL2 were co-cultured with purified CD8 T cells in the presence of varying concentrations of anti-PVRIG Ab or relevant IgG control. % Proliferation is shown. Each dot represents an average of triplicate values. D) CHO cells ectopically expression HLA-A2/B2m and PVRL2 were co-cultured with 2 gp100 specific T cell lines (TIL F4, TIL 209) in the presence of 1 ug/ml gp100 and varying concentrations of anti-PVRIG antibody or relevant IgG control. TNF-α concentrations on day 3 of co-culture is down. Each value represents an average of triplicates.

[00144] Figure 39. Characterization of mPVRIG binding interactions and a surrogate anti-mPVRIG antibody. A, B) Binding of mPVRIG to mPVRL2 was assessed by surface plasmon resonance. C) Soluble receptor Fc or control proteins were incubated in a dose response with immobilized mPVRL2 HIS in an ELISA format. Bound receptor Fc is shown. D) Soluble PVRL2 HIS protein was incubated in a dose response with PVRIG Fc or DNAM Fc coated plates. E) Binding of mPVRIG Fc or control Fc fusion protein to B16-F10 cell line transfected with mPVRL2 siRNA, mPVRsRNA, or scrambled siRNA transfection is shown. F) Affinity characterization of rat anti-mouse PVRIG mAb was performed by examining the binding of anti-mPVRIG to HEK293 cells overexpressing mPVRIG. G) Affinity characterization of rat anti-mouse PVRIG mAb was performed by examining the of anti-mPVRIG to D10.G4.1 cell line endogenously expressing mPVRIG vs isotype control rat IgG

is shown. H) Binding of anti-mPVRIG to D10.G4.1 cells transfected with mouse PVRIG-siRNA (green histogram) vs scr siRNA (orange histogram). I) Binding of mPVRIG Fc pre-incubated with anti-mPVRIG Ab to B16-F10 cells, which endogenously express PVRL2

[00145] Figure 40. Generation of transgenic PVRIG and TIGIT knockout mice. The PVRIG conditional knockout and Tigit knockout mouse lines were generated by Ozgene Pty Ltd (Bentley WA, Australia). A) The targeting construct in which PVRIG exons 1 to 4 were floxed was electroporated into a C57BL/6 ES cell line, Bruce4 (Koentgen et al., Int Immunol 5: 957-964, 1993). B) The targeting construct in which the coding region of Tigit exon 1 (including the ATG) and exons 2 and 3 were replaced with an FRT-flanked neo cassette was electroporated into a C57BL/6 ES cell line, Bruce4. Homologous recombinant ES cell clones were identified by Southern hybridization and injected into goGermline blastocysts (Koentgen et al., genesis 54: 326–333, 2016). Male chimeric mice were obtained and crossed to C57BL/6J females to establish heterozygous germline offspring on C57BL/6 background. The germline mice were crossed to a ubiquitous FLP C57BL/6 mouse line to remove the FRT flanked selectable marker cassette and generate the conditional or knockout alleles (for PVRIG and Tigit, respectively). For PVRIG knockout, mice were further crossed to a ubiquitous Cre C57BL/6 mouse line to remove the loxP flanked exons and generate the knockout allele.

[00146] Figure 41. PVRIG knockout mice are immune-phenotypically similar to wild-type mice. Mice (n= 5 per wild-type and PVRIG knockout cohorts) were euthanized prior to venous blood being collected in anti-coagulant-coated tubes and harvesting of organs. Single cells were recovered from freshly harvested bone marrow, thymus, spleen, cutaneous and mesenteric lymph nodes. Cells were stained with fluorochrome-conjugated surface marker antibodies and acquired on a BD LSR Fortessa flow cytometer. Panels illustrate comparable frequencies of myeloid cells (A), dendritic cells (B), B cells (C), T cells (D), CD4 T cells (E), CD8 T cells (F), and NK cells (G) across lymphoid tissue types. (H-I) Whole venous blood was run on a Hemavet 950 veterinary hematology system to compare differential counts and frequencies of blood cell subsets from wild-type and PVRIG deficient mice.

[00147] Figure 42. Increased T cell effector function in PVRIG$^{-/-}$ mice treated with anti-PDL1 compared to WT with anti-PD-L1. MC38 tumors were inoculated into WT or PVRIG$^{-/-}$ mice and were subsequently treated with anti-PD-L1 or rat IgG2b isotype control. On day 18, CD45+ tumor infiltrating lymphocytes were purified from tumors, RNA extracted, and transcript profiling performed. Several T cell related genes are shown, with each dot representing an individual mouse. Student's t test p values are shown.

[00148] Figure 43. Anti-TIGIT and anti-PVRIG antibodies induce tumor cell killing. An in vitro co-culture assay with human CMV-specific CD8+ T cells expanded was utilized to assess the effect of the benchmark anti-TIGIT antibody and CHA.7.518.1.H4(S241P) on antigen-specific tumor cell killing. HLA-A2+ target cell lines used in the assay were the Mel624 (A) and Panc05.04 (B). Synagis hIgG4 is the isotype control antibody. Luciferase activity in the target cells was measured with the Bio-Glo luciferase substrate. Representative data (n≥2) shows the percent specific killing (mean +/- standard deviation) of Mel624 or Panc05.04 cells after a 16 hour co-culture with human CMV-specific CD8+ T cells from three different donors.

[00149] Figure 44. Dose-dependent tumor cell killing of anti-TIGIT antibodies with CHA.7.518.1.H4(S241P). An in vitro co-culture assay with human CMV-specific CD8+ T cells was utilized to assess the effect of two different anti-TIGIT antibodies, BM26 and CPA.9.086 when combined with CHA.7.518.1.H4(S241P) on antigen-specific Mel624 cell killing. Luciferase activity in the target cells was measured with the Bio-Glo luciferase substrate. Representative data (n≥2) shows the percent specific killing (mean +/- standard deviation) of Mel624 cells after a 16 hour co-culture with human CMV-specific CD8+ T cells from one donor.

[00150] Figure 45. CPA.9.086 CDR sequences, IMGT and Kabat numbering.

[00151] Figure 46. Anti-TIGIT hIgG4 + CHA.7.518.1.H4(S241P) combination induces tumor cell killing. Co-culture of CMV-reactive CD8+ T cells with Mel624 PVR, PVRL2 & luciferase OE Single dose of 10 μg/ml anti-TIGIT Ab and 10 μg/ml CHA.7.518.1.H4(S241P) with CMV-reactive donor 4, while dose titration starting at 0.5 μg/ml aTIGIT Ab and 10 μg/ml CHA.7.518.1.H4(S241P) with CMV-reactive donor 156.

[00152] Figure 47. Anti-TIGIT antibodies augment IFN-γ when combined with an anti-PD-1 antibody. An in vitro co-culture assay with human CMV-specific CD8+ T cells was utilized to assess the effect of CPA.9.086 compared to the benchmark antibodies, BM26 and BM29, on antigen-specific cytokine secretion in combination with an anti-PD-1 antibody, pembrolizumab. The target cell line used in the assay was the HLA-A2+ pancreatic adenocarcinoma cells, Panc.05.04 that endogenously expresses human PVR and PD-L1. Panc.05.04 cells were pulsed with the CMV pp65 peptide at 0.01 μg/ml at 37 °C for 1 hour. Cells were then washed and plated at 50,000 cells/well in 96-well round-bottom tissue culture treated plates. Anti-human TIGIT antibodies or the isotype control hIgG4 antibody (anti-Synagis) were added at a concentration of 0.1 μg/ml in combination with the anti-PD-1 antibody (hatched bars) or a control hIgG4 isotype antibody at 10 μg/ml (solid bars). Human CMV-specific CD8+ T cells from a single donor were expanded according to the protocol above. 50,000 human CD8+ T cells were added to each well. Co-cultures were incubated at 37 °C with 5% CO_2 for 24 hours. The amount of human IFN-γ in the co-culture supernatant was measured by flow cytometry using a cytometric bead assay (BD Biosciences).

[00153] Figure 48 depicts expression profiling of PVRIG/TIGIT axis in tumors; lung and endometrial cancers are high for both PVRIG-PVRL2 and TIGIT-PVR pathway. (A, B) PVRIG and TIGIT expression were analyzed on $CD4^+$ and $CD8^+$ T cells from dissociated human tumors by FACS. Fold expression was calculated by dividing the MFI of PVRIG or TIGIT by the MFI of the IgG control. Grey line = No expression detected. Each orange dot is a distinct tumor sample and median of samples shown by the blue bar. C, D) Expression of PVRIG on $CD8^+$ T cells vs PVRL2 on $CD45^-$ cells or TIGIT on $CD8^+$ T cells vs PVR on $CD45^-$ cells is plotted from dissociated tumors. Each dot represents an individual tumor sample.

[00154] Figure 49 depicts expression data for PD-1, PVRIG and TIGIT on CD8 T cells, which shows that PVRIG+TIGIT+PD-1+CD8+TILs are highly prevalent and have an exhausted profile. A) TILS from human cancers were stained for PD1, PVRIG, and TIGIT expression on CD8 T cells. The percentage of cells that express combinations of PD-1, PVRIG, or TIGIT on CD8+ T cells was determined by Boolean gating. B) Representative PD-1, PVRIG, and TIGIT expression on CD4+ and CD8+ T cells from a lung tumor are shown.

C) TILS from human cancers were stained for cell surface PD1, PVRIG, and TIGIT on CD8+ T cells, permeabilized, and stained for Eomes and T-bet. Within each cell subset, the percentage of Eomes+T-bet- cells are shown. A paired Student's t-test was performed and p values shown. D) Representative FACS plots showing Eomes and T-bet expression on PD-1, PVRIG, or TIGIT expressing CD8 T cells from an ovarian and bladder tumor are shown. E) Percentage of Eomes+T-bet- cells expressing cells based on PD-1, PVRIG, and TIGIT expression was determined. Thus, PVRIG expression correlates with Eomes+T-bet- transcription factor expression, a phenotype known to be associated with T cell exhaustion. Triple positive PVRIG+TIGIT+PD-1+ cells were also high in percentage of Eomes+T-bet- cells.

[00155] Figure 50 shows that PVRL2 is induced in cancer and expressed in PD-L1$^-$ tumors. A) PVRL2 expression was assessed by IHC on lung, ovarian/endometrial, breast, colon, kidney, and skin tumors. Bars depict mean $\pm$ SEM. For each tumor, 2 cores were assessed by a pathologist and scored based on prevalence and intensity of membranous staining on tumor cells. For each tumor, the average score of 2 cores is shown. B) Expression of PD-L1 and PVRL2 was assessed by IHC on serial sections. Tumors were grouped based on tissue type and expression of PVRL2 on PD-L1 negative and PD-L1 positive is shown. PD-L1 negative tumors were defined as no membranous staining on tumor or immune cells from either duplicate cores for a given tumor. PD-L1 positive staining was defined as membranous staining on at least 1 core of a tumor. Bars depict mean $\pm$ SEM for each group. C) Representative expression of a PVRL2+PD-L1- endometrioid carcinoma tumor and a PVRL2+PD-L1- lung tumor.

[00156] Figure 51 shows that anti-PVRIG/TIGIT/PD-1 synergistically increases T cell function. (A) CMVpp65 CD8 T cells were stained for TIGIT/PD-1/PVRIG expression, and tumor cell lines were stained for PD-L1, HLA-A2, PVR & PVRL2. Representative FACs histograms are shown. B) CMVpp65 specific T cells were co-cultured with Panc0504 & Colo205 cells, CMVpp65 peptide and the indicated antibodies at 10 ug/ml. IFN-γ concentration in the conditioned media was determined at 18hrs. Percentages above bar graphs is % increase in IFN-γ secretion over isotype IgG.

[00157] Figure 52 shows that the blockade of the PVRIG-PVRL2 interaction induces PD-1 and TIGIT expression. CMVpp65 specific T cells from 1-2 donors were co-cultured with Panc0504, CMVpp65 peptide, and the indicated antibodies at 10 ug/ml for 18 hours. Cells were then stained for FACs and the percentage of cells PD-1, TIGIT, and LAG3 for each treatment condition is shown. Representative histograms for each receptor is shown. Red = Isotype, Blue = Target expression. A) TIGIT expression was induced by CHA7.518.1.H4(S241P) or anti-PD1 treatment. (B) PD-1 expression was induced by CHA7.518.1.H4(S241P) and/or CPA.9.083.H4(S241P). (C) LAG-3 expression was not induced by CHA7.518.1.H4(S241P), anti-TIGIT, or anti-PD-1.

[00158] Figure 53. Tumors obtained within 24hrs of surgical resection were dissociated and purified CD3+ TILS co-cultured with MEL624 cells expressing surface bound anti-CD3 and the indicated antibodies at 10 ug/ml. IFN-γ concentration in the conditioned media was determined at 72hrs. % change in IFN-γ for each condition relative to hIgG4 is shown.

[00159] Figure 54. PVRIG ANTIBODY BLOCKADE OR DEFICIENCY RESULT IN REDUCED TUMOR GROWTH. PVRIG antibody blockade or deficiency inhibit tumor growth. A) BALB/c mice were subcutaneously injected with 5×105 CT26 cells. At day 7 post inoculation mice were treated with anti-PD-L1 and/or anti-PVRIG antibodies, twice weekly for 3 weeks. Tumor volumes are shown. n=10 mice per group. Mean $^{+}$/- SEM is shown. *** Indicates p-value <0.001 (ANOVA with repeated measures) for anti-PD-L1 $^{+}$ Rat IgG2b compared to anti-PD-L1 $^{+}$ anti-PVRIG treated groups. B) C57BL/6 WT or PVRIG-/- mice were subcutaneously injected with 5×105 MC38 cells. n=10 mice per group. Mean $^{+}$/- SEM is shown. *Indicates p-value < 0.05 for WT mice versus PVRIG-/- mice (ANOVA with repeated measures). Individual tumor growth curves are also shown. Representative data from n=2 experiments.

[00160] Figure 55. EXPRESSION PROFILING OF PVRIG/TIGIT AXIS IN HUMAN TUMORS. Lung and endometrial cancers are high for both PVRIG-PVRL2 and TIGIT-PVR pathway. (A, B) PVRIG and TIGIT expression were analyzed on $CD4^{+}$ and $CD8^{+}$ T cells from dissociated human tumors by FACS. Fold expression was calculated by dividing the MFI of PVRIG or TIGIT by the MFI of the IgG control. Grey line = No expression detected. Each orange dot is a distinct tumor sample and median of samples shown by the blue bar.

C, D) Expression of PVRIG on $CD8^+$ T cells vs PVRL2 on CD45- cells or TIGIT on $CD8^+$ T cells vs PVR on CD45- cells is plotted from dissociated human tumors. Each dot represents an individual tumor sample.

[00161] Figure 56. PVRIG+TIGIT+PD1+ CELLS ARE THE HIGHEST % AND MOST EXHAUSTED OF CD8+ TILS. PVRIG+TIGIT+PD1+ CD8+ TILs are highly prevalent and have an exhausted phenotype. A) $CD8^+$ TILs from human cancers were stained for PD-1, PVRIG, and TIGIT. The percentage of $CD8^+$ TILs that express combinations of PD-1, PVRIG, or TIGIT on $CD8^+$ T cells was determined by Boolean gating. Each dot represents an individual tumor sample. B) $CD8^+$ TILs from human cancers were stained for cell surface PD1, PVRIG, and TIGIT, permeabilized, and stained for intracellular Eomes and T-bet. The percentage of $Eomes^+$T-bet- $CD8^+$ T cells are shown. A paired Student's t-test was performed and p-values shown. C) The percentage of $Eomes^+$T-bet- $CD8^+$ T cells expressing PD-1, PVRIG, and TIGIT was determined across multiple human cancers.

[00162] Figure 57. RELATIVE EXPRESSION OF PVRL2 VERSUS PVR VARIES BY TUMOR TYPE. Relative RNA and protein expression of PVRL2 and PVR across different human tumors. RNA expression of PVRL2 and PVR from the TCGA was plotted as a ratio of PVRL2 relative to PVR across multiple human tumors (left hand panel). Tumors with higher PVRL2 RNA expression compared to PVR include breast, ovarian, prostate, endometrial, bladder, pancreatic and lung. The ratio of protein expression (gMFI) of PVRL2 relative to PVR on CD45- tumor cells is plotted from dissociated human tumors (right hand panel). Each dot represents an individual tumor sample. Tumors with higher PVRL2 protein expression compared to PVR include ovary, breast, endometrial, lung, prostate, oral cavity and stomach. Higher RNA expression correlates with higher protein levels for PVRL2 across several tumors, including breast, ovarian, endometrial, prostate, and lung cancers.

[00163] Figure 58. PVRL2+PVR- TUMOR CELLS AND APCs EXIST IN HUMAN TUMORS. PVRL2+PVR- tumor cells and APCs are present in human tumors. PVRL2 and PVR expression from dissociated tumors determined by FACS on A) CD45- tumor cells, and B) cDC2 ($CD1c^+CD14$-HLA-$DR^{hi}Lin^-CD141^-$) and $CD14^+$ TAMs is plotted. $PVRL2^+PVR$- tumor cells and APCs are represented as red dots in the percent positive plots.

Representative FACS plots for PVRL2 and PVR expression (blue) as compared to an IgG isotype control (red) are shown for ovarian and endometrial tumors.

[00164] Figure 59. CHA7.518.1.H4(S241P) + CPA.9.083.H4(S241P) COMBO HAS ACTIVITY ≥ PEMBROLIZUMAB ON PRIMARY CD3+ TILS. CHA7.518.1.H4(S241P) and/or CPA.9.083.H4(S241P) have similar or greater potency than Pembrolizumab on freshly isolated human TILs. Human tumors obtained within 24 hours of surgical resection were dissociated and $CD3^+$ TILs were purified. Isolated $CD3^+$ TILs were co-cultured with a modified Mel-624 tumor cell line, expressing surface bound anti-CD3, and the indicated antibodies at 10 μg/ml. IFN-γ secretion in the conditioned media was measured at 72 hours. The percentage change in IFN-γ for each treatment over the hIgG isotype control is shown.

[00165] Figure 60. BLOCKADE OF PVRIG/PVRL2 INDUCES PD-1 AND TIGIT EXPRESSION. Blockade of PVRIG/PVRL2 induces PD-1 & TIGIT expression. $CMVpp65^-$ specific $CD8^+$ T cells from 2 donors were co-cultured with Panc.05.04, CMVpp65 peptide, and the indicated antibodies at 10 μg/ml for 18 hrs. Cells were stained and the percentage of A) $TIGIT^+$, B) $PD\text{-}1^+$, and C) $LAG3^+$ $CD8^+$ T cells following each treatment is shown.

[00166] Figure 61A-61C. TRIPLE COMBINATION SHOWED IMPROVED ANTITUMOR EFFICACY. A) Growth kinetics of CT26 tumors in a minimal disease model. Groups of 10 female Balb/c were inoculated with CT26 cells in the right flank. I.p. antibody administration began when tumors reached a desired mean volume (30-60mm^3). Mice were treated with anti-TIGIT mIgG1 or anti-PVRIG mIgG1 at 10mg/kg, anti-PD-L1 mIgG1 at 3mg/kg, and control isotype at 10mg/kg either as dual or triple combination, 3 times biweekly for a total of 6 doses. TGI with anti-TIGIT mIgG1 in combination was calculated by % TGI = [1-(average tumor volume of test article divided by average tumor volume of control article) *100]. The asterisk (***, ****) indicate $p<0.001$ or $p<0.0001$, respectively, for differences between dual or triple combination over isotype control, versus dual or triple combination group by 2-way ANOVA. B) Spider plots of individual tumor volumes of each mouse in the three treatment groups were measured until tumor volumes of >1500mm^3 or 45 days (study endpoints) were reached. C) Kaplan-Meier survival curves of mice treated in the three different treatment groups. A log-rank (Mantel-Cox) test revealed a p-value

<0.0001, a 90% survival in mice treated triple antibody combination versus 40% survival in mice in dual antibody combination treatment.

[00167] Figure 62A-62I depicts the sequences of exemplary anti-PD-L1 antibodies.

[00168] Figure 63A-63AAAA depicts the sequences of numerous exemplary PVRIG antibodies.

IV. DETAILED DESCRIPTION OF THE INVENTION

A. Introduction

[00169] Therapeutic antibodies directed against immune checkpoint inhibitors such as PD-1 are showing great promise in limited circumstances in the clinic for the treatment of cancer. Cancer can be considered as an inability of the patient to recognize and eliminate cancerous cells. In many instances, these transformed (e.g. cancerous) cells counteract immunosurveillance. There are natural control mechanisms that limit T-cell activation in the body to prevent unrestrained T-cell activity, which can be exploited by cancerous cells to evade or suppress the immune response. Restoring the capacity of immune effector cells-especially T cells-to recognize and eliminate cancer is the goal of immunotherapy. The field of immuno-oncology, sometimes referred to as "immunotherapy" is rapidly evolving, with several recent approvals of T cell checkpoint inhibitory antibodies such as Yervoy®, Keytruda® and Opdivo®. These antibodies are generally referred to as "checkpoint inhibitors" because they block normally negative regulators of T cell immunity. It is generally understood that a variety of immunomodulatory signals, both costimulatory and coinhibitory, can be used to orchestrate an optimal antigen-specific immune response.

[00170] Generally, these monoclonal antibodies bind to checkpoint inhibitor proteins such as CTLA-4 and PD-1, which under normal circumstances prevent or suppress activation of cytotoxic T cells (CTLs). By inhibiting the checkpoint protein, for example through the use of antibodies that bind these proteins, an increased T cell response against tumors can be achieved. That is, these cancer checkpoint proteins suppress the immune response; when the proteins are blocked, for example using antibodies to the checkpoint

protein, the immune system is activated, leading to immune stimulation, resulting in treatment of conditions such as cancer and infectious disease.

[00171] The present invention is directed to compositions and methods of using several anti-checkpoint inhibitors in combination, so as to result in better patient outcomes. In particular, combinations of anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies are contemplated. Furthermore, these methods are particularly useful in combination with an evaluation of PD-L1 expression levels from the patient tumor. If the percentage of PD-L1 positive tumor cells or immune cells is greater than 1% (>1%) compared to the same tumor cells stained with antibody relevant isotype control antibody for the antibodies used then a triple combination of anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies should be administered. Whereas, patients with a frequency of PD-L1 positive tumor cells or immune cells below 1% (<1%) compared to the isotype control should be administered a double combination of anti-TIGIT and anti-PVRIG antibodies.

[00172] As discussed herein, TIGIT is a co-inhibitory receptor that is highly expressed on effector & regulatory (Treg) CD4+ T cells, effector CD8+ T cells, and NK cells. TIGIT has been shown to attenuate immune response by (1) direct signaling, (2) inducing ligand signaling, and (3) competition with and disruption of signaling by the costimulatory receptor CD226 (also known as DNAM-1).

[00173] Human Poliovirus Receptor Related Immunoglobulin Domain Containing Protein, or "PVRIG", is expressed on the cell surface of NK and T-cells and shares several similarities to other known immune checkpoints. PVRIG has been validated as a checkpoint inhibitor, see USSNs 62/118,208, 62/141,120, 62/235,823, 62/376,334, 15/048,967, 62/376,335, 62/417,217 and 62/477,974, all of which are expressly incorporated herein by reference in their entirety and in particular for the sequences of the antibodies, figures and figure legends therein. As shown in those documents, PVRL2 was identified/confirmed to be the counterpart of PVRIG. Antibodies that bind to PVRIG were generated, and then a subset of those were identified that both bind to PVRIG and block the interaction of PVRIG and PVLR2. When PVRIG is bound by its ligand (PVRL2), an inhibitory signal is elicited which acts to attenuate the immune response of NK and T-cells against a target cell (i.e. analogous

to PD-1/PDL1). Blocking the binding of PVRL2 to PVRIG shuts-off this inhibitory signal of PVRIG and as a result modulates the immune response of NK and T-cells.

[00174] PD-1, or "programmed cell death protein 1", is a known checkpoint inhibitor. There are two approved anti-PD-1 antibodies, pembrolizumab (Keytruda®), cemiplimab (REGN2810), and nivolumab (Opdivo®) and many more in development (including, but not limited to, pidilizumab, BAP049 clones as listed in WO2015/112900 (the sequences of which are expressly incorporated herein by reference), antibody 317-4B6 as listed in WO2015/035606 (the sequence of which is expressly incorporated herein by reference), antibody APE2058 as listed in US2016/0075783 (the sequence of which is expressly incorporated herein by reference).

[00175] There are three approved anti-PD-L1 antibodies, atezolizumab (TECENTRIQ®), avelumab (BAVENCIO®), and durvalumab, as well as other anti-PD-L1 antibodies in development.

[00176] Functional effects of the combinations of these antibodies on NK and T-cells can be assessed in vitro (and in some cases in vivo, as described more fully below) by measuring changes in the following parameters: proliferation, cytokine release and cell-surface makers. Accordingly, functional effects of the anti- TIGIT antibodies on NK, effector T, and Treg cells can be assessed in vitro (and in some cases, in vivo, as described more fully below) by measuring changes in the following parameters: proliferation, cytokine release and cell-surface receptors. For NK cells, increases in cell proliferation, cytotoxicity (ability to kill target cells as measured by increases in CD107a, granzyme, and perforin expression, or by directly measuring target cells killing), cytokine production (e.g. IFN-γ and TNF), and cell surface receptor expression (e.g. CD25) is indicative of immune modulation, e.g. enhanced killing of cancer cells. For effector T and Treg-cells, increases in proliferation, increases in expression of cell surface receptors of activation (e.g. CD25, CD69, CD137, and PD-1), cytotoxicity (ability to kill target cells, as mentioned above), and cytokine production (e.g. IL-2, IL-4, IL-6, IFN-γ, TNF-α, IL-10, IL-17A) are indicative of immune modulation, e.g. enhanced killing of cancer cells. Accordingly, assessment of treatment can be done using assays that evaluate one or more of the following: (i) increases in immune response, (ii) increases in activation of $\alpha\beta$ and/or $\gamma\delta$ T cells, (iii) increases in

cytotoxic T cell activity, (iv) increases in NK and/or NKT cell activity, (v) alleviation of αβ and/or γδ T-cell suppression, (vi) increases in pro-inflammatory cytokine secretion, (vii) increases in IL-2 secretion; (viii) increases in interferon-γ production, (ix) increases in Th1 response, (x) decreases in Th2 response, (xi) decreases or eliminates cell number and/or activity of at least one of regulatory T cells.

[00177] In particular, any one of the assays shown in Example 1 can be used to measure T cell activation and/or suppression of T cell inhibition.

[00178] Thus, in some embodiments the invention provides the use of combination therapies of anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies (or just anti-TIGIT and anti-PVRIG antibodies in some cases as outlined herein) to perform one or more of the following in a subject in need thereof: (a) upregulating pro-inflammatory cytokines; (b) increasing T-cell proliferation and/or expansion; (c) increasing interferon- or TNF-α production by T-cells; (d) increasing IL-2 secretion; (e) stimulating antibody responses; (f) inhibiting cancer cell growth; (g) promoting antigenic specific T cell immunity; (h) promoting CD4+ and/or CD8+ T cell activation; (i) alleviating Treg-mediated-cell suppression; (j) promoting NK cell activity; (k) promoting apoptosis or lysis of cancer cells; and/or (l) cytotoxic or cytostatic effect on cancer cells.

[00179] Accordingly, the present invention provides anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies for use in combination therapies, and in conjunction with diagnostic assays measuring the levels of one or more of TIGIT, PVRIG and PD-1 expression, and/or measuring the levels of the ligands of TIGIT (e.g., PVR), PVRIG (PVRL2) and PD-1 (PD-L1).

B. Definitions

[00180] In order that the application may be more completely understood, several definitions are set forth below. Such definitions are meant to encompass grammatical equivalents.

[00181] By "ablation" herein is meant a decrease or removal of activity. In some embodiments, it is useful to remove activity from the constant domains of the antibodies. Thus for example, "ablating FcγR binding" means the Fc region amino acid variant has less than 50% starting binding as compared to an Fc region not containing the specific variant,

with less than 70-80-90-95-98% loss of activity being preferred, and in general, with the activity being below the level of detectable binding in a Biacore assay. As shown in Figure 1, one ablation variant in the IgG1 constant region is the N297A variant, which removes the native glycosylation site and significantly reduces the FcγRIIIa binding and thus reduces the antibody dependent cell-mediated cytotoxicity (ADCC).

[00182] By "antigen binding domain" or "ABD" herein is meant a set of six **C**omplementary **D**etermining **R**egions (CDRs) that, when present as part of a polypeptide sequence, specifically binds a target antigen as discussed herein. Thus, a "TIGIT antigen binding domain" binds TIGIT antigen (the sequence of which is shown in Figure 2) as outlined herein. As is known in the art, these CDRs are generally present as a first set of variable heavy CDRs (vhCDRs or V_HCDRs) and a second set of variable light CDRs (vlCDRs or V_LCDRs), each comprising three CDRs: vhCDR1, vhCDR2, vhCDR3 for the heavy chain and vlCDR1, vlCDR2 and vlCDR3 for the light. The CDRs are present in the variable heavy and variable light domains, respectively, and together form an Fv region. Thus, in some cases, the six CDRs of the antigen binding domain are contributed by a variable heavy and variable light chain. In a "Fab" format, the set of 6 CDRs are contributed by two different polypeptide sequences, the variable heavy domain (vh or V_H; containing the vhCDR1, vhCDR2 and vhCDR3) and the variable light domain (vl or V_L; containing the vlCDR1, vlCDR2 and vlCDR3), with the C-terminus of the vh domain being attached to the N-terminus of the CH1 domain of the heavy chain and the C-terminus of the vl domain being attached to the N-terminus of the constant light domain (and thus forming the light chain).

[00183] By "modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence or an alteration to a moiety chemically linked to a protein. For example, a modification may be an altered carbohydrate or PEG structure attached to a protein. By "amino acid modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence. For clarity, unless otherwise noted, the amino acid modification is always to an amino acid coded for by DNA, e.g. the 20 amino acids that have codons in DNA and RNA.

[00184] By "amino acid substitution" or "substitution" herein is meant the replacement of an amino acid at a particular position in a parent polypeptide sequence with a different amino acid. In particular, in some embodiments, the substitution is to an amino acid that is not naturally occurring at the particular position, either not naturally occurring within the organism or in any organism. For example, the substitution N297A refers to a variant polypeptide, in this case an Fc variant, in which the asparagine at position 297 is replaced with alanine. For clarity, a protein which has been engineered to change the nucleic acid coding sequence but not change the starting amino acid (for example exchanging CGG (encoding arginine) to CGA (still encoding arginine) to increase host organism expression levels) is not an "amino acid substitution"; that is, despite the creation of a new gene encoding the same protein, if the protein has the same amino acid at the particular position that it started with, it is not an amino acid substitution.

[00185] By "amino acid insertion" or "insertion" as used herein is meant the addition of an amino acid sequence at a particular position in a parent polypeptide sequence. For example, -233E or 233E designates an insertion of glutamic acid after position 233 and before position 234. Additionally, -233ADE or A233ADE designates an insertion of AlaAspGlu after position 233 and before position 234.

[00186] By "amino acid deletion" or "deletion" as used herein is meant the removal of an amino acid sequence at a particular position in a parent polypeptide sequence. For example, E233- or E233#, E233() or E233del designates a deletion of glutamic acid at position 233. Additionally, EDA233- or EDA233# designates a deletion of the sequence GluAspAla that begins at position 233.

[00187] By "variant protein" or "protein variant", or "variant" as used herein is meant a protein that differs from that of a parent protein by virtue of at least one amino acid modification. Protein variant may refer to the protein itself, a composition comprising the protein, or the amino sequence that encodes it. Preferably, the protein variant has at least one amino acid modification compared to the parent protein, e.g. from about one to about seventy amino acid modifications, and preferably from about one to about five amino acid modifications compared to the parent. As described below, in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a human wild type sequence,

such as the Fc region from IgG1, IgG2, IgG3 or IgG4, although human sequences with variants can also serve as “parent polypeptides”. The protein variant sequence herein will preferably possess at least about 80% identity with a parent protein sequence, and most preferably at least about 90% identity, more preferably at least about 95-98-99% identity. Variant protein can refer to the variant protein itself, compositions comprising the protein variant, or the DNA sequence that encodes it. Accordingly, by "antibody variant" or "variant antibody" as used herein is meant an antibody that differs from a parent antibody by virtue of at least one amino acid modification, "IgG variant" or "variant IgG" as used herein is meant an antibody that differs from a parent IgG (again, in many cases, from a human IgG sequence) by virtue of at least one amino acid modification, and "immunoglobulin variant" or "variant immunoglobulin" as used herein is meant an immunoglobulin sequence that differs from that of a parent immunoglobulin sequence by virtue of at least one amino acid modification. "Fc variant" or "variant Fc" as used herein is meant a protein comprising an amino acid modification in an Fc domain. The Fc variants of the present invention are defined according to the amino acid modifications that compose them. Thus, for example, S241P or S228P is a hinge variant with the substitution proline at position 228 relative to the parent IgG4 hinge polypeptide, wherein the numbering S228P is according to the EU index and the S241P is the Kabat numbering. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody (Edelman et al., 1969, Proc Natl Acad Sci USA 63:78-85, hereby entirely incorporated by reference.) The modification can be an addition, deletion, or substitution. Substitutions can include naturally occurring amino acids and, in some cases, synthetic amino acids. Examples include U.S. Pat. No. 6,586,207; WO 98/48032; WO 03/073238; US2004-0214988A1; WO 05/35727A2; WO 05/74524A2; J. W. Chin et al., (2002), Journal of the American Chemical Society 124:9026-9027; J. W. Chin, & P. G. Schultz, (2002), ChemBioChem 11:1135-1137; J. W. Chin, et al., (2002), PICAS United States of America 99:11020-11024; and, L. Wang, & P. G. Schultz, (2002), Chem. 1-10, all entirely incorporated by reference.

[00188] As used herein, "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. The peptidyl group may comprise naturally occurring amino acids and peptide bonds, or synthetic peptidomimetic structures, i.e. "analogs", such as peptoids (see Simon et al., PNAS

USA 89(20):9367 (1992), entirely incorporated by reference). The amino acids may either be naturally occurring or synthetic (e.g. not an amino acid that is coded for by DNA); as will be appreciated by those in the art. For example, homo-phenylalanine, citrulline, ornithine and noreleucine are considered synthetic amino acids for the purposes of the invention, and both D- and L-(R or S) configured amino acids may be utilized. The variants of the present invention may comprise modifications that include the use of synthetic amino acids incorporated using, for example, the technologies developed by Schultz and colleagues, including but not limited to methods described by Cropp & Shultz, 2004, Trends Genet. 20(12):625-30, Anderson et al., 2004, Proc Natl Acad Sci USA 101 (2):7566-71, Zhang et al., 2003, 303(5656):371-3, and Chin et al., 2003, Science 301(5635):964-7, all entirely incorporated by reference. In addition, polypeptides may include synthetic derivatization of one or more side chains or termini, glycosylation, PEGylation, circular permutation, cyclization, linkers to other molecules, fusion to proteins or protein domains, and addition of peptide tags or labels.

[00189] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Asparagine 297 (also referred to as Asn297 or N297) is a residue at position 297 in the human antibody IgG1.

[00190] By "Fab" or "Fab region" as used herein is meant the polypeptide that comprises the VH, CH1, VL, and CL immunoglobulin domains. Fab may refer to this region in isolation, or this region in the context of a full length antibody or antibody fragment.

[00191] By "Fv" or "Fv fragment" or "Fv region" as used herein is meant a polypeptide that comprises the VL and VH domains of a single antibody. As will be appreciated by those in the art, these generally are made up of two chains.

[00192] By “single chain Fv” or “scFv” herein is meant a variable heavy domain covalently attached to a variable light domain, generally using a scFv linker as discussed herein, to form a scFv or scFv domain. A scFv domain can be in either orientation from N- to C-terminus (vh-linker-vl or vl-linker-vh). In general, the linker is a scFv linker as is generally known in the art, with the linker peptide predominantly including the following amino acid residues: Gly, Ser, Ala, or Thr. The linker peptide should have a length that is adequate to link two molecules in such a way that they assume the correct conformation

relative to one another so that they retain the desired activity. In one embodiment, the linker is from about 1 to 50 amino acids in length, preferably about 1 to 30 amino acids in length. In one embodiment, linkers of 1 to 20 amino acids in length may be used, with from about 5 to about 10 amino acids finding use in some embodiments. Useful linkers include glycine-serine polymers, including for example (GS)n, (GSGGS)n, (GGGGS)n, and (GGGS)n, where n is an integer of at least one (and generally from 3 to 4), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Alternatively, a variety of nonproteinaceous polymers, including but not limited to polyethylene glycol (PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers, that is may find use as linkers.

[00193] By "IgG subclass modification" or “isotype modification” as used herein is meant an amino acid modification that converts one amino acid of one IgG isotype to the corresponding amino acid in a different, aligned IgG isotype. For example, because IgG1 comprises a tyrosine and IgG2 a phenylalanine at EU position 296, a F296Y substitution in IgG2 is considered an IgG subclass modification. Similarly, because IgG1 has a proline at position 241 and IgG4 has a serine there, an IgG4 molecule with a S241P is considered an IgG subclass modification. Note that subclass modifications are considered amino acid substitutions herein.

[00194] By "non-naturally occurring modification" as used herein is meant an amino acid modification that is not isotypic. For example, because none of the IgGs comprise an asparagine at position 297, the substitution N297A in IgG1, IgG2, IgG3, or IgG4 (or hybrids thereof) is considered a non-naturally occurring modification.

[00195] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids that are coded for by DNA and RNA.

[00196] By "effector function" as used herein is meant a biochemical event that results from the interaction of an antibody Fc region with an Fc receptor or ligand. Effector functions include but are not limited to ADCC, ADCP, and CDC. In many cases, it is desirable to ablate most or all effector functions using either different IgG isotypes (e.g. IgG4) or amino acid substitutions in the Fc domain; however, preserving binding to the

FcRn receptor is desirable, as this contributes to the half-life of the antibodies in human serum.

[00197] By "IgG Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an IgG antibody to form an Fc/Fc ligand complex. Fc ligands include but are not limited to FcγRIs, FcγRIIs, FcγRIIIs, FcRn, C1q, C3, mannan binding lectin, mannose receptor, staphylococcal protein A, streptococcal protein G, and viral FcγR. Fc ligands also include Fc receptor homologs (FcRH), which are a family of Fc receptors that are homologous to the FcγRs (Davis et al., 2002, Immunological Reviews 190:123-136, entirely incorporated by reference). Fc ligands may include undiscovered molecules that bind Fc. Particular IgG Fc ligands are FcRn and Fc gamma receptors. By "Fc ligand" as used herein is meant a molecule, preferably a polypeptide, from any organism that binds to the Fc region of an antibody to form an Fc/Fc ligand complex.

[00198] By "parent polypeptide" as used herein is meant a starting polypeptide that is subsequently modified to generate a variant. The parent polypeptide may be a naturally occurring polypeptide, or a variant or engineered version of a naturally occurring polypeptide. Parent polypeptide may refer to the polypeptide itself, compositions that comprise the parent polypeptide, or the amino acid sequence that encodes it. Accordingly, by "parent immunoglobulin" as used herein is meant an unmodified immunoglobulin polypeptide that is modified to generate a variant, and by "parent antibody" as used herein is meant an unmodified antibody that is modified to generate a variant antibody. It should be noted that "parent antibody" includes known commercial, recombinantly produced antibodies as outlined below.

[00199] By “Fc” or “Fc region” or “Fc domain” as used herein is meant the polypeptide comprising the constant region of an antibody excluding the first constant region immunoglobulin domain and in some cases, part of the hinge. Thus Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM, Fc may include the J chain. For IgG, the Fc domain comprises immunoglobulin domains Cγ2 and Cγ3 (Cγ2 and Cγ3) and the lower

hinge region between Cγ1 (Cγ1) and Cγ2 (Cγ2). Although the boundaries of the Fc region may vary, the human IgG heavy chain Fc region is usually defined to include residues C226 or P230 to its carboxyl-terminus, wherein the numbering is according to the EU index as in Kabat. In some embodiments, as is more fully described below, amino acid modifications are made to the Fc region, for example to alter binding to one or more FcγR receptors or to the FcRn receptor.

[00200] By “heavy constant region” herein is meant the CH1-hinge-CH2-CH3 portion of an antibody.

[00201] By "position" as used herein is meant a location in the sequence of a protein. Positions may be numbered sequentially, or according to an established format, for example the EU index for antibody numbering.

[00202] By "target antigen" as used herein is meant the molecule that is bound specifically by the variable region of a given antibody. The target antigen of interest herein is TIGIT, usually human TIGIT and optionally cyno TIGIT, the sequences of which are shown in .

[00203] By "target cell" as used herein is meant a cell that expresses a target antigen.

[00204] By "variable region" as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the Vκ (V.kappa), Vλ (V.lamda), and/or VH genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively.

[00205] By "wild type or WT" herein is meant an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A WT protein has an amino acid sequence or a nucleotide sequence that has not been intentionally modified.

[00206] The antibodies of the present invention are generally isolated or recombinant. “Isolated,” when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a cell or cell culture from which it was expressed. Ordinarily, an isolated polypeptide will be prepared by at least one purification step. An “isolated antibody,” refers to an antibody which is substantially free of other antibodies having different antigenic specificities. “Recombinant”

means the antibodies are generated using recombinant nucleic acid techniques in exogeneous host cells.

[00207] "Specific binding" or "specifically binds to" or is "specific for" a particular antigen or an epitope means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target.

[00208] Specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KD for an antigen or epitope of at least about 10^{-9} M, at least about 10^{-10} M, at least about 10^{-11} M, at least about 10^{-12} M, at least about 10^{-13} M, at least about 10^{-14} M, at least about 10^{-15} M, where KD refers to a dissociation rate of a particular antibody-antigen interaction. Typically, an antibody that specifically binds an antigen will have a KD that is 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for a control molecule relative to the antigen or epitope.

[00209] Also, specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KA or Ka for an antigen or epitope of at least 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for the epitope relative to a control, where KA or Ka refers to an association rate of a particular antibody-antigen interaction. Binding affinity is generally measured using surface plasmon resonance (e.g. Biacore assay) and flow cytometry with antigen-expressing cells.

V. Antibodies

[00210] As is discussed below, the term "antibody" is used generally. Traditional antibody structural units typically comprise a tetramer. Each tetramer is typically composed of two identical pairs of polypeptide chains, each pair having one "light" (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). Human light chains are classified as kappa and lambda light chains. The present invention is directed to antibodies that generally are based on the IgG class, which has several subclasses, including, but not limited to IgG1,

IgG2, IgG3, and IgG4. In general, IgG1, IgG2 and IgG4 are used more frequently than IgG3. It should be noted that IgG1 has different allotypes with polymorphisms at 356 (D or E) and 358 (L or M). The sequences depicted herein use the 356D/358M allotype, however the other allotype is included herein. That is, any sequence inclusive of an IgG1 Fc domain included herein can have 356E/358L replacing the 356D/358M allotype.

[00211] The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition, generally referred to in the art and herein as the "Fv domain" or "Fv region". In the variable region, three loops are gathered for each of the V domains of the heavy chain and light chain to form an antigen-binding site. Each of the loops is referred to as a complementarity-determining region (hereinafter referred to as a "CDR"), in which the variation in the amino acid sequence is most significant. "Variable" refers to the fact that certain segments of the variable region differ extensively in sequence among antibodies. Variability within the variable region is not evenly distributed. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-15 amino acids long or longer.

[00212] Each VH and VL is composed of three hypervariable regions ("complementary determining regions," "CDRs") and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4.

[00213] The hypervariable region generally encompasses amino acid residues from about amino acid residues 24-34 (LCDR1; "L" denotes light chain), 50-56 (LCDR2) and 89-97 (LCDR3) in the light chain variable region and around about 31-35B (HCDR1; "H" denotes heavy chain), 50-65 (HCDR2), and 95-102 (HCDR3) in the heavy chain variable region; Kabat et al., SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991) and/or those residues forming a hypervariable loop (e.g. residues 26-32 (LCDR1), 50-52 (LCDR2) and 91-96 (LCDR3) in the light chain variable region and 26-32 (HCDR1), 53-55 (HCDR2) and 96-

101 (HCDR3) in the heavy chain variable region; Chothia and Lesk (1987) J. Mol. Biol. 196:901-917. Specific CDRs of the invention are described below.

[00214] As will be appreciated by those in the art, the exact numbering and placement of the CDRs can be different among different numbering systems. However, it should be understood that the disclosure of a variable heavy and/or variable light sequence includes the disclosure of the associated (inherent) CDRs. Accordingly, the disclosure of each variable heavy region is a disclosure of the vhCDRs (e.g. vhCDR1, vhCDR2 and vhCDR3) and the disclosure of each variable light region is a disclosure of the vlCDRs (e.g. vlCDR1, vlCDR2 and vlCDR3). A useful comparison of CDR numbering is as below, see Lafranc et al., Dev. Comp. Immunol. 27(1):55-77 (2003):

	Kabat+Clothia	IMGT	Kabat	AbM	Chothia	Contact
vhCDR1	26-35	27-38	31-35	26-35	26-32	30-35
vhCDR2	50-65	56-65	50-65	50-58	53-55	47-58
vhCDR3	95-102	105-117	95-102	95-102	96-101	93-101
vlCDR1	24-34	27-38	24-34	24-34	26-32	30-36
vlCDR2	50-56	56-65	50-56	50-56	50-52	46-55
vlCDR3	89-97	105-117	89-97	89-97	91-96	89-96

[00215] Throughout the present specification, the Kabat numbering system is generally used when referring to a residue in the variable domain (approximately, residues 1-107 of the light chain variable region and residues 1-113 of the heavy chain variable region) and the hinge and the EU numbering system for Fc regions (e.g, Kabat et al., supra (1991)).

[00216] The present invention provides a large number of different CDR sets. In this case, a "full CDR set" comprises the three variable light and three variable heavy CDRs, e.g. a vlCDR1, vlCDR2, vlCDR3, vhCDR1, vhCDR2 and vhCDR3. These can be part of a larger variable light or variable heavy domain, respectfully. In addition, as more fully outlined herein, the variable heavy and variable light domains can be on separate polypeptide

chains, when a heavy and light chain is used, or on a single polypeptide chain in the case of scFv sequences.

[00217] The CDRs contribute to the formation of the antigen-binding, or more specifically, epitope binding site of antibodies. "Epitope" refers to a determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. Epitopes are groupings of molecules such as amino acids or sugar side chains and usually have specific structural characteristics, as well as specific charge characteristics. A single antigen may have more than one epitope.

[00218] The epitope may comprise amino acid residues directly involved in the binding (also called immunodominant component of the epitope) and other amino acid residues, which are not directly involved in the binding, such as amino acid residues which are effectively blocked by the specifically antigen binding peptide; in other words, the amino acid residue is within the footprint of the specifically antigen binding peptide.

[00219] Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. Conformational and nonconformational epitopes may be distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[00220] An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Antibodies that recognize the same epitope can be verified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen, for example "binning." As outlined below, the invention not only includes the enumerated antigen binding domains and antibodies herein, but those that compete for binding with the epitopes bound by the enumerated antigen binding domains.

[00221] The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Kabat et al. collected numerous primary sequences of the variable regions of heavy chains and light chains. Based on the degree of

conservation of the sequences, they classified individual primary sequences into the CDR and the framework and made a list thereof (see SEQUENCES OF IMMUNOLOGICAL INTEREST, 5th edition, NIH publication, No. 91-3242, E.A. Kabat et al., entirely incorporated by reference).

[00222] In the IgG subclass of immunoglobulins, there are several immunoglobulin domains in the heavy chain. By "immunoglobulin (Ig) domain" herein is meant a region of an immunoglobulin having a distinct tertiary structure. Of interest in the present invention are the heavy chain domains, including, the constant heavy (CH) domains and the hinge domains. In the context of IgG antibodies, the IgG isotypes each have three CH regions. Accordingly, "CH" domains in the context of IgG are as follows: "CH1" refers to positions 118-220 according to the EU index as in Kabat. "CH2" refers to positions 237-340 according to the EU index as in Kabat, and "CH3" refers to positions 341-447 according to the EU index as in Kabat. As shown herein and described below, the pI variants can be in one or more of the CH regions, as well as the hinge region, discussed below.

[00223] Another type of Ig domain of the heavy chain is the hinge region. By "hinge" or "hinge region" or "antibody hinge region" or "immunoglobulin hinge region" herein is meant the flexible polypeptide comprising the amino acids between the first and second constant domains of an antibody. Structurally, the IgG CH1 domain ends at EU position 220, and the IgG CH2 domain begins at residue EU position 237. Thus for IgG the antibody hinge is herein defined to include positions 221 (D221 in IgG1) to 236 (G236 in IgG1), wherein the numbering is according to the EU index as in Kabat. In some embodiments, for example in the context of an Fc region, the lower hinge is included, with the "lower hinge" generally referring to positions 226 or 230.

[00224] The light chain generally comprises two domains, the variable light domain (containing the light chain CDRs and together with the variable heavy domains forming the Fv region), and a constant light chain region (often referred to as CL or Cκ).

[00225] Another region of interest for additional substitutions, outlined below, is the Fc region.

A. Chimeric and Humanized Antibodies

[00226] In some embodiments, the antibodies herein can be derived from a mixture from different species, e.g. a chimeric antibody and/or a humanized antibody. In general, both "chimeric antibodies" and "humanized antibodies" refer to antibodies that combine regions from more than one species. For example, "chimeric antibodies" traditionally comprise variable region(s) from a mouse (or rat, in some cases) and the constant region(s) from a human. "Humanized antibodies" generally refer to non-human antibodies that have had the variable-domain framework regions swapped for sequences found in human antibodies. Generally, in a humanized antibody, the entire antibody, except the CDRs, is encoded by a polynucleotide of human origin or is identical to such an antibody except within its CDRs. The CDRs, some or all of which are encoded by nucleic acids originating in a non-human organism, are grafted into the beta-sheet framework of a human antibody variable region to create an antibody, the specificity of which is determined by the engrafted CDRs. The creation of such antibodies is described in, e.g., WO 92/11018, Jones, 1986, Nature 321:522-525, Verhoeyen et al., 1988, Science 239:1534-1536, all entirely incorporated by reference. "Backmutation" of selected acceptor framework residues to the corresponding donor residues is often required to regain affinity that is lost in the initial grafted construct (US 5530101; US 5585089; US 5693761; US 5693762; US 6180370; US 5859205; US 5821337; US 6054297; US 6407213, all entirely incorporated by reference). The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region, typically that of a human immunoglobulin, and thus will typically comprise a human Fc region. Humanized antibodies can also be generated using mice with a genetically engineered immune system. Roque et al., 2004, Biotechnol. Prog. 20:639-654, entirely incorporated by reference. A variety of techniques and methods for humanizing and reshaping non-human antibodies are well known in the art (See Tsurushita & Vasquez, 2004, Humanization of Monoclonal Antibodies, Molecular Biology of B Cells, 533-545, Elsevier Science (USA), and references cited therein, all entirely incorporated by reference). Humanization methods include but are not limited to methods described in Jones et al., 1986, Nature 321:522-525; Riechmann et al.,1988; Nature 332:323-329; Verhoeyen et al., 1988, Science, 239:1534-1536; Queen et al., 1989, Proc Natl Acad Sci, USA 86:10029-33; He et al., 1998, J. Immunol. 160: 1029-1035; Carter et al., 1992, Proc Natl Acad Sci USA 89:4285-9, Presta et al., 1997, Cancer Res. 57(20):4593-9; Gorman et al., 1991, Proc. Natl. Acad. Sci. USA

88:4181-4185; O'Connor et al., 1998, Protein Eng 11:321-8, all entirely incorporated by reference. Humanization or other methods of reducing the immunogenicity of nonhuman antibody variable regions may include resurfacing methods, as described for example in Roguska et al., 1994, Proc. Natl. Acad. Sci. USA 91:969-973, entirely incorporated by reference.

[00227] In certain embodiments, the antibodies of the invention comprise a heavy chain variable region from a particular germline heavy chain immunoglobulin gene and/or a light chain variable region from a particular germline light chain immunoglobulin gene (with optional mutations as is generally described herein). For example, such antibodies may comprise or consist of a human antibody comprising heavy or light chain variable regions that are "the product of" or "derived from" a particular germline sequence. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (i.e., greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally-occurring somatic mutations or intentional introduction of site-directed mutation. However, a humanized antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the antibody as being derived from human sequences when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a humanized antibody may be at least 95, 96, 97, 98 or 99%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a humanized antibody derived from a particular human germline sequence will display no more than 10-20 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the humanized antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene (again, prior to

the introduction of any variants herein; that is, the number of variants is generally low, prior to the introduction of the variants of the invention).

[00228] In one embodiment, the parent antibody has been affinity matured, as is known in the art. Structure-based methods may be employed for humanization and affinity maturation, for example as described in USSN 11/004,590. Selection based methods may be employed to humanize and/or affinity mature antibody variable regions, including but not limited to methods described in Wu et al., 1999, J. Mol. Biol. 294:151-162; Baca et al., 1997, J. Biol. Chem. 272(16):10678-10684; Rosok et al., 1996, J. Biol. Chem. 271(37): 22611-22618; Rader et al., 1998, Proc. Natl. Acad. Sci. USA 95: 8910-8915; Krauss et al., 2003, Protein Engineering 16(10):753-759, all entirely incorporated by reference. Other humanization methods may involve the grafting of only parts of the CDRs, including but not limited to methods described in USSN 09/810,510; Tan et al., 2002, J. Immunol. 169:1119-1125; De Pascalis et al., 2002, J. Immunol. 169:3076-3084, all entirely incorporated by reference.

B. Specific anti-TIGIT antibodies

[00229] The invention provides antigen binding domains, including full length antibodies, which contain a number of specific, enumerated sets of 6 CDRs and defined variable heavy (vh, VH or V_H) and variable light (vl, VL or V_L), that bind to TIGIT.

[00230] In one embodiment, the anti-TIGIT antibody is an antibody comprising a set of six CDRs (vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3) from CPA.9.083.H4(S241P) as depicted in Figure 3. In one embodiment, the anti-TIGIT antibody is an antibody comprising the variable heavy (vh) and variable light (vl) domains from CPA.9.083.H4(S241P) as depicted in Figure 3, linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). In one embodiment, the anti-TIGIT antibody is CPA.9.083.H4(S241P).

[00231] In one embodiment, the anti-TIGIT antibody is an antibody comprising a set of six CDRs (vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3) from CPA.9.086.H4(S241P) as depicted in Figure 3. In one embodiment, the anti-TIGIT antibody is an antibody comprising the variable heavy (vh) and variable light (vl) domains from CPA.9.086.H4(S241P) as depicted in Figure 3, linked to a human IgG constant domain of

IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). In one embodiment, the anti-TIGIT antibody is CPA.9.086.H4(S241P).

[00232] In one embodiment, the anti-TIGIT antibody is an antibody comprising a set of six CDRs (vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3) from CHA.9.547.7.H4(S241P) as depicted in Figure 3. In one embodiment, the anti-TIGIT antibody is an antibody comprising the variable heavy (vh) and variable light (vl) domains from CHA.9.547.7.H4(S241P) as depicted in Figure 3, linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). In one embodiment, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P).

[00233] In one embodiment, the anti-TIGIT antibody is an antibody comprising a set of six CDRs (vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3) from CHA.9.547.13.H4(S241P) as depicted in Figure 3. In one embodiment, the anti-TIGIT antibody is an antibody comprising the variable heavy (vh) and variable light (vl) domains from CHA.9.547.13.H4(S241P) as depicted in Figure 3, linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). In one embodiment, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P).

[00234] Further anti-TIGIT antibodies that find use in combinations with anti-PVRIG antibodies as outlined herein are those in Figure 4 of USSN 62/513,916, entitled "Anti-TIGIT Antibodies and Methods of Use", filed on June 1, 2017, by assignee Compugen, as well as those included in Figure 3.

C. Additional Anti-TIGIT Antibodies for Use in Combination Therapy

[00235] Additional anti-TIGIT antibodies that can be used in combination with anti-PVRIG antibodies and optionally anti-PD-1 antibodies as outlined herein are also included. As discussed more fully below, anti-TIGIT antibodies show particular efficacy in combination with anti-PVRIG antibodies. Thus, in some embodiments, alternative anti-TIGIT antibodies are used in combination with anti-PVRIG antibodies outlined herein, and in particular either of CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00236] Accordingly, in one embodiment, anti-TIGIT antibodies as outlined in US Patent No. 9,499,596, (hereby incorporated by reference in its entirety and specifically for

the SEQ ID NO:s listed below) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a light chain sequence of SEQ ID NO:21 and a heavy chain sequence of SEQ ID NO:22 (from USP9,499,596) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Additionally, an anti-TIGIT antibody having a light chain sequence of SEQ ID NO:29 and a heavy chain sequence of SEQ ID NO:30 (from USP9,499,596) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00237] Similarly, in one embodiment, anti-TIGIT antibodies as outlined in WO 2016/191643 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences of the OMP-313M32 antibody) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a light chain sequence of SEQ ID NO:72 and a heavy chain sequence of SEQ ID NO:70 (from WO 2016/191643) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00238] Accordingly, in one embodiment, anti-TIGIT antibodies as outlined in WO 2017/053748 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:36 and a variable heavy chain sequence of SEQ ID NO:34 (from WO 2017/053748) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Additionally, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:36 and a variable heavy chain sequence of SEQ ID NO:35 (from WO 2017/053748) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Additionally, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:38 and a variable heavy chain sequence of SEQ ID NO:37 (from WO 2017/053748) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Additionally, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:40 and a variable heavy chain sequence of SEQ ID NO:39 (from WO 2017/053748) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In one embodiment, anti-TIGIT antibodies include the Genentech

antibody, MTIG7192A, currently in clinical trials (*see*, the World Wide Web at clinicaltrials.gov/ct2/show/NCT02794571?term=MTIG7192A&rank=1). In one embodiment, an MTIG7192A anti-TIGIT antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00239] Similarly, in one embodiment, anti-TIGIT antibodies as outlined in WO2016/191643 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences of the OMP-313M32 antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a light chain sequence of SEQ ID NO:72 and a heavy chain sequence of SEQ ID NO:70 (from WO2016/191643) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In one embodiment, anti-TIGIT antibodies include the Oncomed antibody, OMP-313M32, currently in clinical trials (*see*, the World Wide Web at clinicaltrials.gov/ct2/show/NCT03119428?term=OMP-313M32&rank=1). In one embodiment, an OMP-313M32 anti-TIGIT antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00240] Additionally, in one embodiment, anti-TIGIT antibodies as outlined in WO 2016/028656 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences of the MEB125.31C6.A1.205 VH4/VL1 (VH of SEQ ID NO:127, VL of SEQ ID NO:130 with a human IgG1 constant domain), MEB 125.31C6.A1.205 VH5/VL4 (VH of SEQ ID NO:128, VL of SEQ ID NO:133 and a human IgG1 constant region) and MEB125.31.C6,A1.205 VH5/VL3 (VH of SEQ ID NO:128, VL of SEQ ID NO:132 and a human IgG1 constant region) antibodies) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody MEB125.31C6.A1.205 VH4/VL1 (VH of SEQ ID NO:127, VL of SEQ ID NO:130 with a human IgG1 constant domain) (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody MEB 125.31C6.A1.205 VH5/VL4 (VH of SEQ ID NO:128, VL of SEQ ID NO:133 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody MEB125.31.C6.A1.205 VH5/VL3 (VH of SEQ ID NO:128, VL of SEQ ID NO:132 and a

human IgG1 constant region) (from WO2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:7, VL of SEQ ID NO:8 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:63, VL of SEQ ID NO:64 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:94, VL of SEQ ID NO:95 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:126, VL of SEQ ID NO:131 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:128, VL of SEQ ID NO:131 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:125, VL of SEQ ID NO:133 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:126, VL of SEQ ID NO:130 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:125, VL of SEQ ID NO:132 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:143, VL of SEQ ID NO:145 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:144, VL of SEQ ID NO:146 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody comprising the VH of SEQ ID NO:149, VL of SEQ ID NO:151 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an

anti-TIGIT antibody comprising the VH of SEQ ID NO:150, VL of SEQ ID NO:152 and a human IgG1 constant region (from WO 2016/028656) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00241] Additionally, in one embodiment, anti-TIGIT antibodies as outlined in WO 2017/030823 hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:8 and a variable heavy chain sequence of SEQ ID NO:7 (from WO 2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:13 and a variable heavy chain sequence of SEQ ID NO:9 (from WO 2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:24 and a variable heavy chain sequence of SEQ ID NO:23 (from WO 2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:29 and a variable heavy chain sequence of SEQ ID NO:25 (from WO 2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In some embodiments, an anti-TIGIT antibody having a variable light chain selected from sequences of SEQ ID NO:s 14, 15, 16, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 ,75, 76, 77, 78, 79, or 80 and a variable heavy chain sequence of SEQ ID NO:s 10, 11 ,12, 48, 49, 50, 51, 52, 53, 54, 55, or 56 (from WO 2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In some embodiments, an anti-TIGIT antibody having a variable light chain selected from sequences of SEQ ID NO:s 14, 15, 16, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 ,75, 76, 77, 78, 79, or 80 and a variable heavy chain sequence of SEQ ID NO:s 10, 11 ,12, 48, 49, 50, 51, 52, 53, 54, 55, or 56 (from WO2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In some embodiments, an anti-TIGIT antibody having a variable light chain selected from sequences of SEQ ID NO:s 30, 31, or 32 and a variable heavy chain sequence of SEQ ID NO: 26, 27, 28, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, or 112 (from WO2017/030823) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In one embodiment, anti-TIGIT

antibodies include the Merck antibody, MK-7684, currently in clinical trials (*see*, the World Wide Web at clinicaltrials.gov/ct2/show/NCT02964013?term=MK-7684&rank=1). In one embodiment, an MK-7684 anti-TIGIT antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00242] Accordingly, in one embodiment, anti-TIGIT antibodies as outlined in US Patent Appl. No. 2016/0176963 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:s 6, 9, 11, or 13 and a variable heavy chain sequence of SEQ ID NO:s 2, 3, 4, 5, 7, 8, 10, or 12 (from US2016/0176963) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:s 6 and a variable heavy chain sequence of SEQ ID NO:s 2, 3, 4, or 5 (from US2016/0176963) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO:s 9 and a variable heavy chain sequence of SEQ ID NO:s 7 or 8 (from US2016/0176963) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO: 11 and a variable heavy chain sequence of SEQ ID NO: 10 (from US2016/0176963) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody having a variable light chain sequence of SEQ ID NO: 13 and a variable heavy chain sequence of SEQ ID NO: 12 (from US2016/0176963) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In one embodiment, anti-TIGIT antibodies include the BMS antibody, BMS-98620, currently in clinical trials (*see*, the World Wide Web at clinicaltrials.gov/ct2/show/NCT02913313?term=BMS-986207&rank=1). In one embodiment, an BMS-98620 anti-TIGIT antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00243] In one embodiment, anti-TIGIT antibodies include the Arcus Bio antibody, AB154. In one embodiment, an AB154 anti-TIGIT antibody can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00244] Additionally, in one embodiment, anti-TIGIT antibodies as outlined in WO 2017/037707 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences of the SEQ ID NO:s listed below, and in particular for the VSIG9#1 antibody (SEQ ID NO:7 VH and SEQ ID NO: 8 VL) and the 258-csl#4 antibody (SEQ ID NO:18 VH and SEQ ID NO: 19 VL). Specifically, the anti-TIGIT antibody VSIG9#1 antibody (from WO2017/037707; SEQ ID NO:7 VH and SEQ ID NO: 8 VL) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 258-csl#4 (from WO2017/037707; SEQ ID NO:18 VH and SEQ ID NO: 19 VL) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00245] Additionally, in one embodiment, anti-TIGIT antibodies as outlined in WO 2017/059095 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences disclosed therein. Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 13 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 12 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 14 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 15 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 9 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 10 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 1 1 and a V_L sequence of SEQ ID NO: 26 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of

SEQ ID NO: 99 and a light chain of SEQ ID NO: 92; or (it) a heavy chain of SEQ ID NO: 100 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 97 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 98 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 101 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 102 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 103 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 104 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 90 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 91 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 93 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 94 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a heavy chain of SEQ ID NO: 95 and a light chain of SEQ ID NO: 92; or (ii) a heavy chain of SEQ ID NO: 96 and a light chain of SEQ ID NO: 92 (from WO 2017/059095) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).Additionally, in one embodiment, anti-TIGIT antibodies as outlined in WO 2016/106302 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences of the particular sequences disclosed therein. Specifically, the anti-TIGIT antibody comprising a heavy chain sequence selected from SEQ ID NOs: 2, 3, 4, 5, 7, 8, 10 or 12 (from WO 2016/106302) and a light chain sequence from SEQ ID NOs: 6, 9, 11, or 13 (from WO 2016/106302) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 22G2 (from WO 2016/106302) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the

anti-TIGIT antibody 11G11 (from WO 2016/106302) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 15A6 (from WO 2016/106302) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00246] Additionally, in one embodiment, anti-TIGIT antibodies as outlined in U.S. Patent Publication No. 2017281764 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences disclosed therein. Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 10 and a V_L sequence of SEQ ID NO: 14 (from US 2017281764) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 18 and a V_L sequence of SEQ ID NO: 22 (from US 2017281764) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 26 and a V_L sequence of SEQ ID NO: 30 (from US 2017281764) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 35 and a V_L sequence of SEQ ID NO: 37 (from US 2017281764) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 34 and a V_L sequence of SEQ ID NO: 36 (from US 2017281764) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00247] In another embodiment, anti-TIGIT antibodies as outlined in International Patent Publication No. WO 2015/009856 (hereby incorporated by reference in its entirety and specifically for the SEQ ID NO:s listed below, and in particular for the sequences disclosed therein (see, also International Patent Publication No. WO 2016/011264). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 15 and a V_L sequence of SEQ ID NO: 13 (from WO 2015/009856) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody comprising a V_H sequence of SEQ ID NO: 16 and a V_L sequence of SEQ ID NO: 14 (from WO 2015/009856) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00248] In some embodiments, the anti-TIGIT antibody is an antibody described in any of U.S. Patent Application No. 20170037133, International Patent Publication No. WO 2017/048824, a MBSA43 (commercially available from eBioscience), is anti-TIGIT antibody pab2197 or pab2196 (U.S. Patent Application No. 2017/0081409), EOS084448, CASC-674 (available from Adimab LLC). Specifically, an anti-TIGIT antibody as described in U.S. Patent Application No. 2017/0037133 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, an anti-TIGIT antibody as described in International Patent Publication No. WO 2017/048824 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MBSA43 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody pab2197 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody pab2196 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody EOS084448 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody CASC-674 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00249] In some embodiments, the anti-TIGIT antibody is an antibody described in U.S. Patent No. 9,713,364 (incorporated herein by reference in its entirety). In some embodiments, the anti-TIGIT antibody is PTZ-201 (ASP8374). Specifically, the anti-TIGIT antibody PTZ-201 (ASP8374) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). In some embodiments, the anti-TIGIT antibody is an antibody selected from the group consisting of MAB1, MAB2, MAB3, MAB4, MAB5, MAB6, MAB7, MAB8, MAB9, MAB10, MAB11, MAB12, MAB13, MAB14, MAB15, MAB16, MAB17, MAB18, 40 MAB19, MAB20, or MAB21, as described in U.S. Patent No. 9,713,364. Specifically, the anti-TIGIT antibody MAB1 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB2 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB3 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB4 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

Specifically, the anti-TIGIT antibody MAB5 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB6 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB7 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB8 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB9 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB10 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB11 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB12 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB13 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB14 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB15 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB16 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB17 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB18 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB19 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB20 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody MAB21 from U.S. Patent No. 9,713,364 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00250] In some embodiments, the anti-TIGIT antibody is 10A7, 1F4, 14A6, 28H5, 31C6, 15A6, 22G2, 11G11, and/or 10D7, the contents of each of which are incorporated herein by reference in their entirety. Specifically, the anti-TIGIT antibody 10A7 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 1F4 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 14A6 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 28H5 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 31C6 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 15A6 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 22G2 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 11G11 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P). Specifically, the anti-TIGIT antibody 10D7 can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00251] In some embodiments, the anti-TIGIT antibody is one of those described in International Patent Publication WO 2016/028656, incorporated herein in its entirety. Specifically, the anti-TIGIT antibodies are provided in International Patent Publication No. WO 2016/028656 (and reproduced herein in Figure 3) can be combined with CHA.7.538.1.2.H4(S241P) or CHA.7.518.1.H4(S241P).

[00252] The anti-TIGIT antibodies described herein can find use according to the triple combination therapy methods of the invention are labeled as follows. Such TIGIT antibodies have reference numbers, for example "CPA.9.086". This represents the combination of the variable heavy and variable light chains, as depicted in Figure 3, for example, with the understanding that these antibodies include two heavy chains and two light chains. "CPA.9.086.VH" refers to the variable heavy portion of CPA. 9. 086, while "CPA. 9. 086.VL" is the variable light chain. "CPA. 9. 086.vhCDR1", "CPA. 9. 086.vhCDR2", "CPA. 9. 086.vhCDR3", "CPA. 9. 086.vlCDR1", "CPA. 9. 086.vlCDR2", and "CPA. 9. 086.vlCDR3", refers to the CDRs are indicated. "CPA. 9. 086.HC" refers to the entire heavy chain (e.g. variable and constant domain) of this molecule, and "CPA. 9. 086.LC" refers to

the entire light chain (e.g. variable and constant domain) of the same molecule. In general, the human kappa light chain is used for the constant domain of each phage (or humanized hybridoma) antibody herein, although in some embodiments the lambda light constant domain is used. "CPA. 9. 086.H1" refers to a full length antibody comprising the variable heavy and light domains, including the constant domain of **H**uman IgG**1** (hence, the H1; IgG1, IgG2, IgG3 and IgG4 sequences are shown in Figures 1, for example). Accordingly, "CPA. 9. 086.H2" would be the CPA. 9. 086 variable domains linked to a **H**uman IgG**2.** "CPA. 9. 086.H3" would be the CPA. 9. 086 variable domains linked to a **H**uman IgG**3**, and "CPA. 9. 086.H4" would be the CPA. 9. 086 variable domains linked to a **H**uman IgG**4**. Note that in some cases, the human IgGs may have additional mutations, such are described below, and this can be annotated. For example, in many embodiments, there may be a S241P mutation in the human IgG4, and this can be annotated as "CPA.9.086.H4(S241P)" for example. The human IgG4 sequence with this S241P hinge variant is shown in Figure 1. Other potential variants are IgG1(N297A), (or other variants that ablate glycosylation at this site and thus many of the effector functions associated with FcγRIIIa binding), and IgG1(D265A), which reduces binding to FcγR receptors. The anti-TIGIT antibodies for use in the present invention can comprise any of the TIGIT antibody domain sequences. The anti-TIGIT antibodies for use in the present invention can comprise any of the TIGIT antigen binding domains.

[00253] The invention further provides variable heavy and light domains as well as full length heavy and light chains.

[00254] In some embodiments, the invention provides scFvs that bind to TIGIT comprising a variable heavy domain and a variable light domain linked by an scFv linker as outlined above. The VL and VH domains can be in either orientation, e.g. from N- to C-terminus "VH-linker-VL" or "VL-linker" VH". These are named by their component parts; for example, "scFv-CPA. 9.086.VH-linker-VL" or "scFv-CPA.9.086.VL-linker-VH." Thus, "scFv-CPA.9.086" can be in either orientation. The anti-TIGIT antibodies for use in the present invention can comprise any scFvs that bind to TIGIT. The anti-TIGIT antibodies for use in the present invention can comprise any scFvs that bind to TIGIT. The anti-TIGIT antibodies for use in the present invention can include any of the following:

[00255] CPA.9.018, CPA.9.018.VH, CPA.9.018.VL, CPA.9.018.HC, CPA.9.018.LC, CPA.9.018.H1, CPA.9.018.H2, CPA.9.018.H3, CPA.9.018.H4; CPA.9.018.H4(S241P);

CPA.9.018.vhCDR1, CPA.9.018.vhCDR2, CPA.9.018.vhCDR3, CPA.9.018.vlCDR1, CPA.9.018.vlCDR2, CPA.9.018.vlCDR3 and scFv-CPA.9.018;

[00256] CPA.9.027, CPA.9.027.VH, CPA.9.027.VL, CPA.9.027.HC, CPA.9.027.LC, CPA.9.027.H1, CPA.9.027.H2, CPA.9.027.H3, CPA.9.027.H4; CPA.9.018.H4(S241P); CPA.9.027.vhCDR1, CPA.9.027.vhCDR2, CPA.9.027.vhCDR3, CPA.9.027.vlCDR1, CPA.9.027.vlCDR2, CPA.9.027.vlCDR3 and scFv-CPA.9.027;

[00257] CPA.9.049, CPA.9.049.VH, CPA.9.049.VL, CPA.9.049.HC, CPA.9.049.LC, CPA.9.049.H1, CPA.9.049.H2, CPA.9.049.H3; CPA.9.049.H4; CPA.9.049.H4(S241P); CPA.9.049.vhCDR1, CPA.9.049.vhCDR2, CPA.9.049.vhCDR3, CPA.9.049.vlCDR1, CPA.9.049.vlCDR2, CPA.9.049.vlCDR3 and scFv-CPA.9.049;

[00258] CPA.9.057, CPA.9.057.VH, CPA.9.057.VL, CPA.9.057.HC, CPA.9.057.LC, CPA.9.057.H1, CPA.9.057.H2, CPA.9.057.H3; CPA.9.057.H4; CPA.9.057.H4(S241P); CPA.9.057.vhCDR1, CPA.9.057.vhCDR2, CPA.9.057.vhCDR3, CPA.9.057.vlCDR1, CPA.9.057.vlCDR2, CPA.9.057.vlCDR3 and scFv-CPA.9.057;

[00259] CPA.9.059, CPA.9.059.VH, CPA.9.059.VL, CPA.9.059.HC, CPA.9.059.LC, CPA.9.059.H1, CPA.9.059.H2, CPA.9.059.H3; CPA.9.059.H4; CPA.9.059.H4(S241P); CPA.9.059.vhCDR1, CPA.9.059.vhCDR2, CPA.9.059.vhCDR3, CPA.9.059.vlCDR1, CPA.9.059.vlCDR2, CPA.9.059.vlCDR3 and scFv-CPA.9.059;

[00260] CPA.9.083, CPA.9.083.VH, CPA.9.083.VL, CPA.9.083.HC, CPA.9.083.LC, CPA.9.083.H1, CPA.9.083.H2, CPA.9.083.H3; CPA.9.083.H4; CPA.9.083.H4(S241P); CPA.9.083.vhCDR1, CPA.9.083.vhCDR2, CPA.9.083.vhCDR3, CPA.9.083.vlCDR1, CPA.9.083.vlCDR2, CPA.9.083.vlCDR3 and scFv-CPA.9.083;

[00261] CPA.9.086, CPA.9.086.VH, CPA.9.086.VL, CPA.9.086.HC, CPA.9.086.LC, CPA.9.086.H1, CPA.9.086.H2, CPA.9.086.H3; CPA.9.086.H4; CPA.9.086.H4(S241P); CPA.9.086.vhCDR1, CPA.9.086.vhCDR2, CPA.9.086.vhCDR3, CPA.9.086.vlCDR1, CPA.9.086.vlCDR2, CPA.9.086.vlCDR3 and scFv-CPA.9.086;

[00262] CPA.9.089, CPA.9.089.VH, CPA.9.089.VL, CPA.9.089.HC, CPA.9.089.LC, CPA.9.089.H1, CPA.9.089.H2, CPA.9.089.H3; CPA.9.089.H4; CPA.9.089.H4(S241P); CPA.9.089.vhCDR1, CPA.9.089.vhCDR2, CPA.9.089.vhCDR3, CPA.9.089.vlCDR1, CPA.9.089.vlCDR2, CPA.9.089.vlCDR3 and scFv-CPA.9.089;

[00263] CPA.9.093, CPA.9.093.VH, CPA.9.093.VL, CPA.9.093.HC, CPA.9.093.LC, CPA.9.093.H1, CPA.9.093.H2, CPA.9.093.H3; CPA.9.093.H4; CPA.9.093.H4(S241P); CPA.9.093.vhCDR1, CPA.9.093.vhCDR2, CPA.9.093.vhCDR3, CPA.9.093.vlCDR1, CPA.9.093.vlCDR2, CPA.9.093.vlCDR3 and scFv-CPA.9.093;

[00264] CPA.9.101, CPA.9.101.VH, CPA.9.101.VL, CPA.9.101.HC, CPA.9.101.LC, CPA.9.101.H1, CPA.9.101.H2, CPA.9.101.H3; CPA.9.101.H4; CPA.9.101.H4(S241P); CPA.9.101.vhCDR1, CPA.9.101.vhCDR2, CPA.9.101.vhCDR3, CPA.9.101.vlCDR1, CPA.9.101.vlCDR2, CPA.9.101.vlCDR3 and scFv-CPA.9.101; and

[00265] CPA.9.103, CPA.9.103.VH, CPA.9.103.VL, CPA.9.103.HC, CPA.9.103.LC, CPA.9.103.H1, CPA.9.103.H2, CPA.9.103.H3; CPA.9.103.H4; CPA.9.103.H4(S241P); CPA.9.103.vhCDR1, CPA.9.103.vhCDR2, CPA.9.103.vhCDR3, CPA.9.103.vlCDR1, CPA.9.103.vlCDR2, CPA.9.103.vlCDR3 and scFv-CPA.9.103.

[00266] Furthermore, the present invention provides a number of CHA antibodies, which are murine antibodies generated from hybridomas. As is well known the art, the six CDRs are useful when put into either human framework variable heavy and variable light regions or when the variable heavy and light domains are humanized. Accordingly, the present invention provides antibodies, usually full length or scFv domains, that comprise the following sets of CDRs, the sequences of which are shown in Figure 3 and/or the sequence listing:

[00267] CHA.9.536.1, CHA.9.536.1.VH, CHA.9.536.1.VL, CHA.9.536.1.HC, CHA.9.536.1.LC, CHA.9.536.1.H1, CHA.9.536.1.H2, CHA.9.536.1.H3; CHA.9.536.1.H4, CHA.9.536.1.H4(S241P), CHA.9.536.1.vhCDR1, CHA.9.536.1.vhCDR2, CHA.9.536.1.vhCDR3, CHA.9.536.1.vlCDR1, CHA.9.536.1.vlCDR2 and CHA.9.536.1.vhCDR3;

[00268] CHA.9.536.3, CHA.9.536.3.VH, CHA.9.536.3.VL, CHA.9.536.3.HC, CHA.9.536.3.LC, CHA.9.536.3.H1, CHA.9.536.3.H2, CHA.9.536.3.H3; CHA.9.536.3.H4, CHA.9.536.3.H4(S241P); CHA.9.536.3.vhCDR1, CHA.9.536.3.vhCDR2, CHA.9.536.3.vhCDR3, CHA.9.536.3.vlCDR1, CHA.9.536.3.vlCDR2 and CHA.9.536.3.vhCDR3;

[00269] CHA.9.536.4, CHA.9.536.4.VH, CHA.9.536.4.VL, CHA.9.536.4.HC, CHA.9.536.4.LC, CHA.9.536.4.H1, CHA.9.536.4.H2, CHA.9.536.4.H3; CHA.9.536.4.H4,

CHA.9.536.4.H4(S241P), CHA.9.536.4.vhCDR1, CHA.9.536.4.vhCDR2, CHA.9.536.4.vhCDR3, CHA.9.536.4.vlCDR1, CHA.9.536.4.vlCDR2 and CHA.9.536.4.vhCDR3;

[00270] CHA.9.536.5, CHA.9.536.5.VH, CHA.9.536.5.VL, CHA.9.536.5.HC, CHA.9.536.5.LC, CHA.9.536.5.H1, CHA.9.536.5.H2, CHA.9.536.5.H3; CHA.9.536.5.H4, CHA.9.536.5.H4(S241P), CHA.9.536.5.vhCDR1, CHA.9.536.5.vhCDR2, CHA.9.536.5.vhCDR3, CHA.9.536.5.vlCDR1, CHA.9.536.5.vlCDR2 and CHA.9.536.5.vhCDR3;

[00271] CHA.9.536.6, CHA.9.536.6.VH, CHA.9.536.6.VL, CHA.9.536.6.HC, CHA.9.536.6.LC, CHA.9.536.6.H1, CHA.9.536.6.H2, CHA.9.536.6.H3; CHA.9.536.6.H4, CHA.9.536.6.vhCDR1, CHA.9.536.6.vhCDR2, CHA.9.536.6.vhCDR3, CHA.9.536.6.vlCDR1, CHA.9.536.6.vlCDR2 and CHA.9.536.6.vhCDR3;

[00272] CHA.9.536.7, CHA.9.536.7.VH, CHA.9.536.7.VL, CHA.9.536.7.HC, CHA.9.536.7.LC, CHA.9.536.7.H1, CHA.9.536.7.H2, CHA.9.536.7.H3; CHA.9.536.7.H4, CHA.9.536.5.H4(S241P); CHA.9.536.7.vhCDR1, CHA.9.536.7.vhCDR2, CHA.9.536.7.vhCDR3, CHA.9.536.7.vlCDR1, CHA.9.536.7.vlCDR2 and CHA.9.536.7.vhCDR3;

[00273] CHA.9.536.8, CHA.9.536.8.VH, CHA.9.536.8.VL, CHA.9.536.8.HC, CHA.9.536.8.LC, CHA.9.536.8.H1, CHA.9.536.8.H2, CHA.9.536.8.H3; CHA.9.536.8.H4, CHA.9.536.8.H4(S241P), CHA.9.536.8.vhCDR1, CHA.9.536.8.vhCDR2, CHA.9.536.8.vhCDR3, CHA.9.536.8.vlCDR1, CHA.9.536.8.vlCDR2 and CHA.9.536.8.vhCDR3;

[00274] CHA.9.560.1, CHA. 9.560.1VH, CHA. 9.560.1.VL, CHA. 9.560.1.HC, CHA. 9.560.1.LC, CHA. 9.560.1.H1, CHA. 9.560.1.H2, CHA. 9.560.1.H3; CHA. 9.560.1.H4, CHA. 9.560.1.H4(S241P), CHA. 9.560.1.vhCDR1, CHA. 9.560.1.vhCDR2, CHA. 9.560.1.vhCDR3, CHA. 9.560.1.vlCDR1, CHA. 9.560.1.vlCDR2 and CHA. 9.560.1.vhCDR3;

[00275] CHA.9.560.3, CHA. 9.560. 3VH, CHA. 9.560. 3.VL, CHA. 9.560. 3.HC, CHA. 9.560. 3.LC, CHA. 9.560. 3.H1, CHA. 9.560. 3.H2, CHA. 9.560. 3.H3; CHA.9.560.3.H4, CHA.9.560.3.H4(S241P); CHA. 9.560. 3.vhCDR1, CHA. 9.560.

3.vhCDR2, CHA. 9.560. 3.vhCDR3, CHA. 9.560. 3.vlCDR1, CHA. 9.560. 3.vlCDR2 and CHA. 9.560. 3.vhCDR3;

[00276] CHA.9.560.4, CHA. 9.560. 4VH, CHA. 9.560. 4.VL, CHA. 9.560. 4.HC, CHA. 9.560. 4.LC, CHA. 9.560. 4.H1, CHA. 9.560. 4.H2, CHA. 9.560. 4.H3; CHA.9.560.4.H4, CHA.9.560.4.H4(S241P), CHA. 9.560. 4.vhCDR1, CHA. 9.560. 4.vhCDR2, CHA. 9.560. 4.vhCDR3, CHA. 9.560. 4.vlCDR1, CHA. 9.560. 4.vlCDR2 and CHA. 9.560. 4.vhCDR3;

[00277] CHA.9.560.5, CHA. 9.560. 5VH, CHA. 9.560. 5.VL, CHA. 9.560. 5.HC, CHA. 9.560. 5.LC, CHA. 9.560. 5.H1, CHA. 9.560. 5.H2, CHA. 9.560. 5.H3; CHA. 9.560. 5.H4, CHA. 9.560. 5.vhCDR1, CHA. 9.560. 5.vhCDR2, CHA. 9.560. 5.vhCDR3, CHA. 9.560. 5.vlCDR1, CHA. 9.560. 5.vlCDR2 and CHA. 9.560. 5.vhCDR3;

[00278] CHA.9.560.6, CHA. 9.560. 6VH, CHA. 9.560. 6.VL, CHA. 9.560. 6.HC, CHA. 9.560. 6.LC, CHA. 9.560. 6.H1, CHA. 9.560. 6.H2, CHA. 9.560. 6.H3; CHA.9.560.6.H4, CHA.9.560.6.H4(S241P), CHA. 9.560. 6.vhCDR1, CHA. 9.560. 6.vhCDR2, CHA. 9.560. 6.vhCDR3, CHA. 9.560. 6.vlCDR1, CHA. 9.560. 6.vlCDR2 and CHA. 9.560. 6.vhCDR3;

[00279] CHA.9.560.7, CHA. 9.560. 7VH, CHA. 9.560. 7.VL, CHA. 9.560. 7.HC, CHA. 9.560. 7.LC, CHA. 9.560. 7.H1, CHA. 9.560. 7.H2, CHA. 9.560. 7.H3; CHA.9.560.7.H4; CHA.9.560.7.H4(S241P); CHA. 9.560. 7.vhCDR1, CHA. 9.560. 7.vhCDR2, CHA. 9.560. 7.vhCDR3, CHA. 9.560. 7.vlCDR1, CHA. 9.560. 7.vlCDR2 and CHA. 9.560. 7.vhCDR3;

[00280] CHA.9.560.8, CHA. 9.560. 8VH, CHA. 9.560. 8.VL, CHA. 9.560. 8.HC, CHA. 9.560. 8.LC, CHA. 9.560. 8.H1, CHA. 9.560. 8.H2, CHA. 9.560. 8.H3; CHA.9.560.8.H4, CHA.9.560.8.H4(S241P); CHA. 9.560. 8.vhCDR1, CHA. 9.560. 8.vhCDR2, CHA. 9.560. 8.vhCDR3, CHA. 9.560. 8.vlCDR1, CHA. 9.560. 8.vlCDR2 and CHA. 9.560. 8.vhCDR3;

[00281] CHA.9.546.1, CHA. 9. 546.1VH, CHA. 9. 546.1.VL, CHA. 9. 546.1.HC, CHA. 9. 546.1.LC, CHA. 9. 546.1.H1, CHA. 9. 546.1.H2, CHA. 9. 546.1.H3; CHA.9.546.1.H4, CHA.9.546.1.H4(S241P), CHA. 9. 546.1.vhCDR1, CHA. 9. 546.1.vhCDR2, CHA. 9. 546.1.vhCDR3, CHA. 9. 546.1.vlCDR1, CHA. 9. 546.1.vlCDR2 and CHA. 9. 546.1.vhCDR3;

[00282] CHA.9.547.1, CHA. 9. 547.1VH, CHA. 9. 547.1.VL, CHA. 9. 547.1.HC, CHA. 9. 547.1.LC, CHA. 9. 547.1.H1, CHA. 9. 547.1.H2, CHA. 9. 547.1.H3; CHA.9.547.1.H4, CHA.9.547.1.H4(S241P), CHA. 9. 547.1.vhCDR1, CHA. 9. 547.1.vhCDR2, CHA. 9. 547.1.vhCDR3, CHA. 9. 547.1.vlCDR1, CHA. 9. 547.1.vlCDR2 and CHA. 9. 547.1.vhCDR3;

[00283] CHA.9.547.2, CHA. 9. 547. 2VH, CHA. 9. 547. 2.VL, CHA. 9. 547. 2.HC, CHA. 9. 547. 2.LC, CHA. 9. 547. 2.H1, CHA. 9. 547. 2.H2, CHA. 9. 547. 2.H3; CHA.9.547.2.H4, CHA.9.547.2.H4(S241P), CHA. 9. 547. 2.vhCDR1, CHA. 9. 547. 2.vhCDR2, CHA. 9. 547. 2.vhCDR3, CHA. 9. 547. 2.vlCDR1, CHA. 9. 547. 2.vlCDR2 and CHA. 9. 547. 2.vhCDR3;

[00284] CHA.9.547.3, CHA. 9. 547. 3VH, CHA. 9. 547. 3.VL, CHA. 9. 547. 3.HC, CHA. 9. 547. 3.LC, CHA. 9. 547. 3.H1, CHA. 9. 547. 3.H2, CHA. 9. 547. 3.H3; CHA.9.547.3.H4, CHA.9.547.3.H4(S241P), CHA. 9. 547. 3.vhCDR1, CHA. 9.547. 3.vhCDR2, CHA. 9. 547. 3.vhCDR3, CHA. 9. 547. 3.vlCDR1, CHA. 9. 547. 3.vlCDR2 and CHA. 9. 547. 3.vhCDR3;

[00285] CHA.9.547.4, CHA. 9. 547. 4VH, CHA. 9. 547. 4.VL, CHA. 9. 547. 4.HC, CHA. 9.547. 4.LC, CHA. 9. 547. 4.H1, CHA. 9. 547. 4.H2, CHA. 9. 547. 4.H3; CHA.9.547.4.H4, CHA.9.547.4.H4(S241P), CHA. 9. 547. 4.vhCDR1, CHA. 9. 547. 4.vhCDR2, CHA. 9. 547. 4.vhCDR3, CHA. 9. 547. 4.vlCDR1, CHA. 9. 547. 4.vlCDR2 and CHA. 9. 547. 4.vhCDR3;

[00286] CHA.9.547.6, CHA. 9. 547. 6 VH, CHA. 9. 547. 6.VL, CHA. 9. 547. 6.HC, CHA. 9. 547. 6.LC, CHA. 9. 547. 6.H1, CHA. 9. 547. 6.H2, CHA. 9. 547. 6.H3; CHA.9.547.6.H4, CHA.9.547.6.H4(S241P), CHA. 9. 547. 6.vhCDR1, CHA. 9. 547. 6.vhCDR2, CHA. 9. 547. 6.vhCDR3, CHA. 9. 547. 6.vlCDR1, CHA. 9. 547. 6.vlCDR2 and CHA. 9. 547. 6.vhCDR3;

[00287] CHA.9.547.7, CHA. 9. 547. 7VH, CHA. 9. 547. 7.VL, CHA. 9. 547. 7.HC, CHA. 9. 547. 7.LC, CHA. 9. 547. 7.H1, CHA. 9. 547. 7.H2, CHA. 9. 547. 7.H3; CHA.9.547.7.H4, CHA.9.547.7.H4(S241P), CHA. 9. 547. 7.vhCDR1, CHA. 9. 547. 7.vhCDR2, CHA. 9. 547. 7.vhCDR3, CHA. 9. 547. 7.vlCDR1, CHA. 9. 547. 7.vlCDR2 and CHA. 9. 547. 7.vhCDR3;

[00288] CHA.9.547.8, CHA. 9. 547. 8VH, CHA. 9. 547. 8.VL, CHA. 9. 547. 8.HC, CHA.9.547.8.LC, CHA. 9. 547. 8.H1, CHA. 9. 547. 8.H2, CHA. 9. 547. 8.H3; CHA.9.547.8.H4, CHA.9.547.8.H4(S241P), CHA. 9. 547. 8.vhCDR1, CHA. 9. 547. 8.vhCDR2, CHA. 9. 547. 8.vhCDR3, CHA. 9. 547. 8.vlCDR1, CHA. 9. 547. 8.vlCDR2 and CHA. 9. 547. 8.vhCDR3;

[00289] CHA.9.547.9, CHA.9.547.9, CHA.9.547.9VH, CHA.9.547.9.VL, CHA.9. 547.9.HC, CHA.9.547.9.LC, CHA.9.547.9.H1, CHA.9.547.9.H2, CHA.9.547.9.H3; CHA.9.547.9.H4, CHA.9.547.9.H4, CHA.9.547.9.H4(S241P), CHA.9.547.9.H4(S241P), CHA.9.547.9.vhCDR1, CHA.9.547.9.vhCDR2, CHA.9.547.9.vhCDR3, CHA.9.547.9.vlCDR1, CHA.9.547.9.vlCDR2 and CHA.9.547.9.vhCDR3;

[00290] CHA.9.547.13, CHA.9.547.13, CHA.9.547. 13VH, CHA.9. 547.13.VL, CHA.9. 547.13.HC, CHA. 9.547.13.LC, CHA. 9.547.13.H1, CHA.9.547.13.H2, CHA.9. 547.13.H3; CHA.9.547.13.H4, CHA.9.547.13.H4, CHA.9.547.13.H4(S241P), CHA.9.547.13.H4(S241P), CHA. 9. 547.13.vhCDR1, CHA.9.547.13.vhCDR2, CHA.9.547. 13.vhCDR3, CHA. 9. 547.13.vlCDR1, CHA. 9. 547.13.vlCDR2 and CHA. 9. 547. 13.vhCDR3;

[00291] CHA.9.541.1, CHA. 9. 541.1.VH, CHA. 9. 541.1.VL, CHA. 9. 541.1.HC, CHA. 9. 541.1.LC, CHA. 9. 541.1.H1, CHA. 9. 541.1.H2, CHA. 9. 541.1.H3; CHA.9.541.1.H4, CHA.9.541.1.H4(S241P), CHA. 9. 541.1.vhCDR1, CHA. 9. 541.1.vhCDR2, CHA. 9. 541.1.vhCDR3, CHA. 9. 541.1.vlCDR1, CHA. 9. 541.1.vlCDR2 and CHA. 9.541.1.vhCDR3;

[00292] CHA.9.541.3, CHA. 9. 541. 3.VH, CHA. 9. 541. 3.VL, CHA. 9. 541. 3.HC, CHA. 9. 541. 3.LC, CHA. 9. 541. 3.H1, CHA. 9. 541. 3.H2, CHA. 9. 541. 3.H3; CHA.9.541.3.H4, CHA.9.541.3.H4(S241P), CHA. 9. 541. 3.vhCDR1, CHA. 9. 541. 3.vhCDR2, CHA. 9. 541. 3.vhCDR3, CHA. 9. 541. 3.vlCDR1, CHA. 9. 541. 3.vlCDR2 and CHA. 9.541. 3.vhCDR3;

[00293] CHA.9.541.4, CHA. 9. 541.4.VH, CHA. 9. 541. 4.VL, CHA. 9. 541. 4.HC, CHA. 9. 541. 4.LC, CHA. 9. 541. 4.H1, CHA. 9. 541. 4.H2, CHA. 9. 541. 4.H3; CHA.9.541.4.H4, CHA.9.541.4.H4(S241P), CHA. 9. 541. 4.vhCDR1, CHA. 9. 541. 4.vhCDR2, CHA. 9. 541. 4.vhCDR3, CHA. 9. 541. 4.vlCDR1, CHA. 9. 541. 4.vlCDR2 and CHA. 9.541. 4.vhCDR3;

[00294] CHA.9.541.5, CHA. 9. 541. 5.VH, CHA. 9. 541. 5.VL, CHA. 9. 541. 5.HC, CHA. 9. 541. 5.LC, CHA. 9. 541. 5.H1, CHA. 9. 541. 5.H2, CHA. 9. 541. 5.H3; CHA.9.541.5.H4, CHA.9.541.5.H4(S241P), CHA. 9. 541. 5.vhCDR1, CHA. 9. 541. 5.vhCDR2, CHA. 9. 541. 5.vhCDR3, CHA. 9. 541. 5.vlCDR1, CHA. 9. 541. 5.vlCDR2 and CHA. 9.541. 5.vhCDR3;

[00295] CHA.9.541.6, CHA. 9. 541. 6.VH, CHA. 9. 541. 6.VL, CHA. 9. 541. 6.HC, CHA. 9. 541. 6.LC, CHA. 9. 541. 6.H1, CHA. 9. 541. 6.H2, CHA. 9. 541.6.H3; CHA.9.541.6.H4, CHA.9.541.6.H4(S241P), CHA. 9. 541. 6.vhCDR1, CHA. 9. 541. 6.vhCDR2, CHA. 9. 541. 6.vhCDR3, CHA. 9. 541. 6.vlCDR1, CHA. 9. 541. 6.vlCDR2 and CHA. 9.541. 6.vhCDR3;

[00296] CHA.9.541.7, CHA. 9. 541. 7.VH, CHA. 9. 541. 7.VL, CHA. 9. 541. 7.HC, CHA. 9. 541. 7.LC, CHA. 9. 541. 7.H1, CHA. 9. 541. 7.H2, CHA. 9. 541. 7.H3; CHA.9.541.7.H4, CHA.9.541.7.H4(S241P), CHA. 9. 541. 7.vhCDR1, CHA. 9. 541. 7.vhCDR2, CHA. 9. 541. 7.vhCDR3, CHA. 9. 541. 7.vlCDR1, CHA. 9. 541. 7.vlCDR2 and CHA. 9.541. 7.vhCDR3; and

[00297] CHA.9.541.8, CHA. 9. 541. 8.VH, CHA. 9. 541. 8.VL, CHA. 9. 541. 8.HC, CHA. 9. 541. 8.LC, CHA. 9. 541. 8.H1, CHA. 9. 541. 8.H2, CHA. 9. 541. 8.H3; CHA.9.541.8.H4, CHA.9.541.8.H4(S241P); CHA. 9. 541. 8vhCDR1, CHA. 9. 541. 8.vhCDR2, CHA. 9. 541. 8.vhCDR3, CHA. 9. 541. 8.vlCDR1, CHA. 9. 541. 8.vlCDR2 and CHA. 9.541. 8.vhCDR3.

[00298] In the case of scFvs comprising the CDRs of the antibodies above, these are labeled as scFvs that include a scFv comprising a variable heavy domain with the vhCDRs, a linker and a variable light domain with the vlCDRs, again as above in either orientation. Thus the invention includes the use of scFv-CHA.9.536.3.1, scFv-CHA.9.536.3, scFv-CHA.9.536.4, scFv-CHA.9.536.5, scFv-CHA.9.536.7, scFv-CHA.9.536.8, scFv-CHA.9.560.1, scFv-CHA.9.560.3, scFv-CHA.9.560.4, scFv-CHA.9.560.5, scFv-CHA.9.560.6, scFv-CHA.9.560.7, scFv-CHA.9.560.8, scFv-CHA.9.546.1, scFv-CHA.9.547.1, scFv-CHA.9.547.2, scFv-CHA.9.547.3, scFv-CHA.9.547.4, scFv-CHA.9.547.6, scFv-CHA.9.547.7, scFv-CHA.9.547.8, scFv-CHA.9.547.9, scFv-CHA.9.547.13, scFv-CHA.9.541.1, scFv-CHA.9.541.3, scFv-CHA.9.541.4, scFv-CHA.9.541.5, scFv-CHA.9.541.6, scFv-CHA.9.541.7 and scFv-CHA.9.541.8.

[00299] In addition, CHA.9.543 binds to TIGIT but does not block the TIGIT-PVR interaction.

[00300] As discussed herein, the invention further provides for the use of variants of the above components (CPA and CHA), including variants in the CDRs, as outlined above. Thus, the invention provides antibodies comprising a set of 6 CDRs as outlined herein that can contain one, two or three amino acid differences in the set of CDRs, as long as the antibody still binds to TIGIT. Suitable assays for testing whether an anti-TIGIT antibody that contains mutations as compared to the CDR sequences outlined herein are known in the art, such as Biacore assays.

[00301] In addition, the invention further provides for the use of variants of the above variable heavy and light chains. In this case, the variable heavy chains can be 80%, 90%, 95%, 98% or 99% identical to the "VH" sequences herein, and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. Variable light chains are provided that can be 80%, 90%, 95%, 98% or 99% identical to the "VL" sequences herein (and in particular CPA.9.086), and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. In these embodiments, the anti-TIGIT antibodies for use in the present invention still binds to TIGIT. Suitable assays for testing whether an anti-TIGIT antibody that contains mutations as compared to the CDR sequences outlined herein are known in the art, such as Biacore assays.

[00302] Similarly, heavy and light chains are provided that are 80%, 90%, 95%, 98% or 99% identical to the full length "HC" and "LC" sequences herein (and in particular CPA.9.086), and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. In these embodiments, the invention includes these variants as long as the anti-TIGIT antibody still binds to TIGIT. Suitable assays for testing whether an anti-TIGIT antibody that contains mutations as compared to the CDR sequences outlined herein are known in the art, such as Biacore assays.

[00303] In addition, the framework regions of the variable heavy and variable light chains of either the CPA or CHA antibodies herein can be humanized (or, in the case of the CHA antibodies, "rehumanized", to the extent that alternative humanization methods can be done) as is known in the art (with occasional variants generated in the CDRs as needed), and thus humanized variants of the VH and VL chains of Figure 23 can be generated (and in particular CPA.9.086). Furthermore, the humanized variable heavy and light domains can

then be fused with human constant regions, such as the constant regions from IgG1, IgG2, IgG3 and IgG4 (including IgG4(S241P)).

[00304] In particular, as is known in the art, murine VH and VL chains can be humanized as is known in the art, for example, using the IgBLAST program of the NCBI website, as outlined in Ye et al. Nucleic Acids Res. 41:W34-W40 (2013), herein incorporated by reference in its entirety for the humanization methods. IgBLAST takes a murine VH and/or VL sequence and compares it to a library of known human germline sequences. As shown herein, for the humanized sequences generated herein, the databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VL kappa genes (F+ORF, 74 germline sequences). An exemplary five CHA sequences were chosen: CHA.9.536, CHA9.560, CHA.9.546, CHA.9.547 and CHA.9.541 (see Figure 3). For this embodiment of the humanization, human germline IGHV1-46(allele1) was chosen for all 5 as the acceptor sequence and the human heavy chain IGHJ4(allele1) joining region (J gene). For three of four (CHA.7.518, CHA.7.530, CHA.7.538_1 and CHA.7.538_2), human germline IGKV1-39(allele 1) was chosen as the acceptor sequence and human light chain IGKJ2(allele1) (J gene) was chosen. The J gene was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system as www.imgt.org. CDRs were defined according to the AbM definition (see www.bioinfo.org.uk/abs/). In some embodiments, the anti-TIGIT antibodies for use in the present invention include TIGIT binding portions or antigen binding domains wherein the V_H and V_L sequences of different TIGIT binding portions or antigen binding domains can be "mixed and matched" to create other TIGIT binding portions or antigen binding domains. TIGIT binding of such "mixed and matched" anti-TIGIT antibodies can be tested using the binding assays described above. e.g., ELISAs or Biacore assays). In some embodiments, when V_H and V_L chains are mixed and matched, a V_H sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_H sequence. Likewise, in some embodiments, a V_L sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_L sequence. For example, the V_H and V_L sequences of homologous antibodies are particularly amenable for mixing and matching.

[00305] Accordingly, the anti-TIGIT antibodies for use in the present invention can comprise CDR amino acid sequences selected from the group consisting of (a) sequences as listed herein; (b) sequences that differ from those CDR amino acid sequences specified in (a) by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid substitutions; (c) amino acid sequences

having 90% or greater, 95% or greater, 98% or greater, or 99% or greater sequence identity to the sequences specified in (a) or (b); (d) a polypeptide having an amino acid sequence encoded by a polynucleotide having a nucleic acid sequence encoding the amino acids as listed herein. In particular, the anti-TIGIT antibody can comprise the antigen binding domain from the CPA.9.086 antibody which can have sequences selected from (a), (b), (c) or (d).

[00306] Additionally included in the definition of the anti-TIGIT antibodies for use in the present invention are antibodies that comprise TIGIT binding domains that share identity to the binding domains from the TIGIT antibodies enumerated herein. That is, in certain embodiments, an anti-TIGIT antibody according to the invention comprises heavy and light chain variable regions comprising amino acid sequences that are identical to all or part of the binding domains from the anti-TIGIT amino acid sequences of preferred anti-TIGIT antibodies, respectively, wherein the antibodies retain the desired functional properties of the parent anti-TIGIT antibodies. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology=# of identical positions/total # of positions X 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[00307] The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.,* 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available commercially), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[00308] In general, the percentage identity for comparison between TIGIT binding domains or antigen binding domains is at least 75%, at least 80%, at least 90%, with at least about 95%, 96%, 97%, 98% or 99% percent identity being preferred. The percentage

identity may be along the whole amino acid sequence, for example the entire heavy or light chain or along a portion of the chains. For example, included within the definition of the anti-TIGIT antibodies for use in the present invention are those whose TIGIT binding portion or antigen binding domains shares identity along the entire variable region (for example, where the identity is 95% or 98% identical along the variable regions), or along the entire constant region, or along just the Fc domain. In particular, the anti-TIGIT antibodies for use in the present invention include antibodies that have TIGIT binding portions or antigen binding domains with at least 75%, at least 80%, at least 90%, with at least about 95%, 96%, 97%, 98%, or 99% percent identity being preferred, with the CPA.9.086 antibody.

[00309] In addition, also included are sequences that may have the identical CDRs but changes in the framework portions of the variable domain (or entire heavy or light chain). For example, anti-TIGIT antibodies for use in the present invention include those with CDRs identical to those shown in Figure 3 but whose identity along the variable region can be lower, for example 95 or 98% percent identical. In particular, the invention provides for the use of anti-TIGIT antibodies that have TIGIT binding portions or antigen binding domains with identical CDRs to CPA.9.086 but with framework regions that are 95% or 98% identical to CPA.9.086.

D. Anti-TIGIT antibodies in combination with anti-PD-1 antibodies

[00310] In another embodiment, the invention provides combinations of the anti-TIGIT antibodies of the invention and anti-PD-1 antibodies. There are two approved anti-PD-1 antibodies, pembrolizumab (Keytruda®) and nivolumab (Opdivo®) and many more in development which can be used in combination with the anti-TIGIT antibodies of the invention.

[00311] Accordingly, the invention provides the specific combinations of: CPA.9.083.H4(S241P) as shown in Figure 3F with pembrolizumab; CPA.9.083.H4(S241P) as shown in Figure 3F with nivolumab; CPA.9.086.H4(S241P) as shown in Figure 3G with pembrolizumab; CPA.9.086.H4(S241P) as shown in Figure 3G with nivolumab; CHA.9.547.7H4(S241P) as shown in Figure 4HH with pembrolizumab; CHA.9.547.7H4(S241P) as shown in Figure 3HH with nivolumab; CHA.9.547.13.H4(S241P)

as shown in Figure 3VV with pembrolizumab and CHA.9.547.13.H4(S241P) as shown in Figure 3VV with nivolumab; all from Figure 4 of USSN 62/513,916, entitled "Anti-TIGIT Antibodies and Methods of Use", filed on June 1, 2017, by assignee Compugen. Other anti-TIGIT antibodies that can be combined with anti-PD-1 antibodies are provided in Figure 3 as well.

E. Specific anti-PVRIG antibodies

[00312] The invention provides antigen binding domains, including full length antibodies, which contain a number of specific, enumerated sets of 6 CDRs and defined variable heavy (vh, VH or V_H) and variable light (vl, VL or V_L), that bind to PVRIG.

[00313] In one embodiment, the anti- PVRIG antibody is an antibody comprising a set of six CDRs (vhCDR1, vhCDR2, vhCDR3, vlCDR1, vlCDR2 and vlCDR3) from CHA.7.518.1.H4(S241P) as depicted in Figure 5. In one embodiment, the anti-TIGIT antibody is an antibody comprising the variable heavy (vh) and variable light (vl) domains from CHA.7.518.1.H4(S241P) as depicted in Figure 5, linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). In one embodiment, the anti-TIGIT antibody is CHA.7.518.1.H4(S241P). In some embodiments, the anti-PVRIG antibody is an anti-PVRIG antibody as shown in Figure 5 or Figure 63.

[00314] In particular, the 2H6 anti-PVRIG antibody of Zhu et al., WO2017/041004, specifically incorporated herein by reference, can be used, which has a vhCDR1 of SEQ ID NO:6, a vhCDR2 of SEQ ID NO:7, a vhCDR3 of SEQ ID NO:8, a vlCDR1 of SEQ ID NO:9, a vlCDR2 of SEQ ID NO:10 and a vhCDR3 of SEQ ID NO:11 from WO2017/041004. The 2H6 anti-PVRIG antibody of Zhu et al. has a variable heavy domain comprising SEQ ID NO:6 and a variable light domain comprising SEQ ID NO:3, which can be linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). All SEQ IDs in this paragraph are from WO2017/041004 and are also provided in Figure 5.

[00315] In particular, the 334M5 anti-PVRIG antibody from WO2018/017864, specifically incorporated herein by reference, can be used, which has a vhCDR1 of SEQ ID NO:31, a vhCDR2 of SEQ ID NO:32, a vhCDR3 of SEQ ID NO:33, a vlCDR1 of SEQ ID NO:26, a vlCDR2 of SEQ ID NO:27, and a vhCDR3 of SEQ ID NO:28 from WO2018/017864.

The 334M5 anti-PVRIG antibody from WO2018/017864 has a variable heavy domain comprising SEQ ID NO:30 and a variable light domain comprising SEQ ID NO:25, which can be linked to a human IgG constant domain of IgG1, IgG2, IgG3, IgG4 and IgG4(S241P). All SEQ IDs in this paragraph are from WO2018/017864 and are also provided in Figure 5.

F. Additional anti-PVRIG antibodies

[00316] The PVRIG antibodies which can find use in according to the triple combinations of the present invention are labeled as follows. These PVRIG antibodies described herein are labeled as follows. The PVRIG antibodies have reference numbers, for example "CPA.7.013". This represents the combination of the variable heavy and variable light chains, as depicted in Figure 63, for example. "CPA.7.013.VH" refers to the variable heavy portion of CPA.7.013, while "CPA.7.013.VL" is the variable light chain. "CPA.7.013.vhCDR1", "CPA.7.013.vhCDR2", "CPA.7.013.vhCDR3", "CPA.7.013.vlCDR1", "CPA.7.013.vlCDR2", and "CPA.7.013.vlCDR3", refers to the CDRs are indicated. "CPA.7.013.HC" refers to the entire heavy chain (e.g. variable and constant domain) of this molecule, and "CPA.7.013.LC" refers to the entire light chain (e.g. variable and constant domain) of the same molecule. "CPA.7.013.H1" refers to a full length antibody comprising the variable heavy and light domains, including the constant domain of **H**uman IgG**1** (hence, the H1; IgG1, IgG2, IgG3 and IgG4, as provided in Figure 1, for example). Accordingly, "CPA.7.013.H2" would be the CPA.7.013 variable domains linked to a **H**uman IgG**2.** "CPA.7.013.H3" would be the CPA.7.013 variable domains linked to a **H**uman IgG**3**, and "CPA.7.013.H4" would be the CPA.7.013 variable domains linked to a **H**uman IgG**4**.

[00317] The PVRIG antibodies which can find use in according to the triple combinations of the present invention are labeled as follows. The antibodies have reference numbers, for example "CHA.7.518.1". This represents the combination of the variable heavy and variable light chains, as depicted in Figures 5 and 63, for example, with the understanding that these antibodies include two heavy chains and two light chains. "CPA. 7.518.1.VH" refers to the variable heavy portion of CPA. 7.518.1, while "CPA.7.518.1.VL" is the variable light chain. "CPA. 7.518.1.vhCDR1", "CPA.7.518.1.vhCDR2", "CPA. 7.518.1.vhCDR3", "CPA. 7.518.1.vlCDR1", "CPA. 7.518.1.vlCDR2", and "CPA. 7.518.1.vlCDR3", refers to the CDRs are indicated. "CPA. 7.518.1.HC" refers to the entire heavy chain (e.g. variable and constant domain) of this molecule, and "CPA. 7.518.1.LC"

refers to the entire light chain (e.g. variable and constant domain) of the same molecule. In general, the human kappa light chain is used for the constant domain of each phage (or humanized hybridoma) antibody herein, although in some embodiments the lambda light constant domain is used. "CPA. 7.518.1.H1" refers to a full-length antibody comprising the variable heavy and light domains, including the constant domain of **H**uman IgG**1** (hence, the H1; IgG1, IgG2, IgG3 and IgG4, as provided in Figure 1, for example). Accordingly, "CPA. 7.518.1.H2" would be the CPA. 7.518.1 variable domains linked to a **H**uman IgG**2.** "CPA. 7.518.1.H3" would be the CPA. 7.518.1 variable domains linked to a **H**uman IgG**3**, and "CPA. 7.518.1.H4" would be the CPA. 7.518.1 variable domains linked to a **H**uman IgG**4**. Note that in some cases, the human IgGs may have additional mutations, such are described below, and this can be annotated. For example, in many embodiments, there may be a S241P mutation in the human IgG4, and this can be annotated as "CPA. 7.518.1.H4(S241P)" for example. The human IgG4 sequence with this S241P hinge variant is shown in Figure 1. Other potential variants are IgG1(N297A), (or other variants that ablate glycosylation at this site and thus many of the effector functions associated with FcγRIIIa binding), and IgG1(D265A), which reduces binding to FcγR receptors. The anti-PVRIG antibodies for use in the present invention can comprise any of the PVRIG antibody sequences. The anti-PVRIG antibodies for use in the present invention can comprise any of the PVRIG antigen binding domain sequences.

[00318] The invention further provides variable heavy and light domains as well as full length heavy and light chains, any of which can be employed as part of the anti-PVRIG antibodies for use according to the present invention.

[00319] In some embodiments, the invention provides scFvs that bind to PVRIG comprising a variable heavy domain and a variable light domain linked by an scFv linker as outlined above. The VL and VH domains can be in either orientation, e.g. from N- to C-terminus "VH-linker-VL" or "VL-linker" VH". These are named by their component parts; for example, "scFv-CHA.7.518.1VH-linker-VL" or "scFv-CPA. 7.518.1.VL-linker-VH." Thus, "scFv-CPA. 7.518.1" can be in either orientation. The anti-PVRIG antibodies for use in the present invention can comprise an scFv that binds to PVRIG.

[00320] The invention provides antigen binding domains, including full length antibodies, which contain a number of specific, enumerated sets of 6 CDRs. The anti-

PVRIG antibodies for use in the present invention can comprise any of the sets of 6 CDRs from the PVRIG antibody sequences provided herein.

[0100] The invention further provides variable heavy and light domains as well as full length heavy and light chains.

[0101] In many embodiments, the anti-PVRIG antibodies for use in the present invention are human (derived from phage) and block binding of PVRIG and PVLR2. The anti-PVRIG antibodies of the invention can comprise a PVRIG antibody and/or antigen binding domain sequence capable of both binding and blocking the receptor-ligand interaction. The anti-PVRIG can comprise the CDRs from a PVRIG antibody sequence capable of both binding and blocking the receptor-ligand interaction. The CPA antibodies, as well as the CDR sequences, that both bind and block the receptor-ligand interaction are as below, with their components outlined as well, the sequences for which are shown in Figure 63:

[0102] CPA.7.001, CPA.7.001.VH, CPA.7.001.VL, CPA.7.001.HC, CPA.7.001.LC and CPA.7.001.H1, CPA.7.001.H2, CPA.7.001.H3, CPA.7.001.H4; CPA.7.001.vhCDR1, CPA.7.001.vhCDR2, CPA.7.001.vhCDR3, CPA.7.001.vlCDR1, CPA.7.001.vlCDR2, and CPA.7.001.vlCDR3;

[0103] CPA.7.003, CPA.7.003.VH, CPA.7.003.VL, CPA.7.003.HC, CPA.7.003.LC, CPA.7.003.H1, CPA.7.003.H2, CPA.7.003.H3, CPA.7.003.H4; CPA.7.003.vhCDR1, CPA.7.003.vhCDR2, CPA.7.003.vhCDR3, CPA.7.003.vlCDR1, CPA.7.003.vlCDR2, and CPA.7.003.vlCDR3;

[0104] CPA.7.004, CPA.7.004.VH, CPA.7.004.VL, CPA.7.004.HC, CPA.7.004.LC, CPA.7.004.H1, CPA.7.004.H2, CPA.7.004.H3 CPA.7.004.H4; CPA.7.004.vhCDR1, CPA.7.004.vhCDR2, CPA.7.004.vhCDR3, CPA.7.004.vlCDR1, CPA.7.004.vlCDR2, and CPA.7.004.vlCDR3;

[0105] CPA.7.006, CPA.7.006.VH, CPA.7.006.VL, CPA.7.006.HC, CPA.7.006.LC, CPA.7.006.H1, CPA.7.006.H2, CPA.7.006.H3 CPA.7.006.H4; CPA.7.006.vhCDR1, CPA.7.006.vhCDR2, CPA.7.006.vhCDR3, CPA.7.006.vlCDR1, CPA.7.006.vlCDR2, and CPA.7.006.vlCDR3;

[0106] CPA.7.008, CPA.7.008.VH, CPA.7.008.VL, CPA.7.008.HC, CPA.7.008.LC, CPA.7.008.H1, CPA.7.008.H2, CPA.7.008.H3 CPA.7.008.H4; CPA.7.008.vhCDR1,

CPA.7.008.vhCDR2, CPA.7.008.vhCDR3, CPA.7.008.vlCDR1, CPA.7.008.vlCDR2, and CPA.7.008.vlCDR3;

[0107] CPA.7.009, CPA.7.009.VH, CPA.7.009.VL, CPA.7.009.HC, CPA.7.009.LC, CPA.7.009.H1, CPA.7.009.H2, CPA.7.009.H3 CPA.7.009.H4; CPA.7.009.vhCDR1, CPA.7.009.vhCDR2, CPA.7.009.vhCDR3, CPA.7.009.vlCDR1, CPA.7.009.vlCDR2, and CPA.7.009.vlCDR3;

[0108] CPA.7.010, CPA.7.010.VH, CPA.7.010.VL, CPA.7.010.HC, CPA.7.010.LC, CPA.7.010.H1, CPA.7.010.H2, CPA.7.010.H3 CPA.7.010.H4; CPA.7.010.vhCDR1, CPA.7.010.vhCDR2, CPA.7.010.vhCDR3, CPA.7.010.vlCDR1, CPA.7.010.vlCDR2, and CPA.7.010.vlCDR3;

[0109] CPA.7.011, CPA.7.011.VH, CPA.7.011.VL, CPA.7.011.HC, CPA.7.011.LC, CPA.7.011.H1, CPA.7.011.H2, CPA.7.011.H3 CPA.7.011.H4; CPA.7.011.vhCDR1, CPA.7.011.vhCDR2, CPA.7.011.vhCDR3, CPA.7.011.vlCDR1, CPA.7.011.vlCDR2, and CPA.7.011.vlCDR3;

[0110] CPA.7.012, CPA.7.012.VH, CPA.7.012.VL, CPA.7.012.HC, CPA.7.012.LC, CPA.7.012.H1, CPA.7.012.H2, CPA.7.012.H3 CPA.7.012.H4; CPA.7.012.vhCDR1, CPA.7.012.vhCDR2, CPA.7.012.vhCDR3, CPA.7.012.vlCDR1, CPA.7.012.vlCDR2, and CPA.7.012.vlCDR3;

[0111] CPA.7.013, CPA.7.013.VH, CPA.7.013.VL, CPA.7.013.HC, CPA.7.013.LC, CPA.7.013.H1, CPA.7.013.H2, CPA.7.013.H3 CPA.7.013.H4; CPA.7.013.vhCDR1, CPA.7.013.vhCDR2, CPA.7.013.vhCDR3, CPA.7.013.vlCDR1, CPA.7.013.vlCDR2, and CPA.7.013.vlCDR3;

[0112] CPA.7.014, CPA.7.014.VH, CPA.7.014.VL, CPA.7.014.HC, CPA.7.014.LC, CPA.7.014.H1, CPA.7.014.H2, CPA.7.014.H3 CPA.7.014.H4; CPA.7.014.vhCDR1, CPA.7.014.vhCDR2, CPA.7.014.vhCDR3, CPA.7.014.vlCDR1, CPA.7.014.vlCDR2, and CPA.7.014.vlCDR3;

[0113] CPA.7.015, CPA.7.015.VH, CPA.7.015.VL, CPA.7.015.HC, CPA.7.015.LC, CPA.7.015.H1, CPA.7.015.H2, CPA.7.015.H3 CPA.7.015.H4; CPA.7.015.vhCDR1, CPA.7.015.vhCDR2, CPA.7.015.vhCDR3, CPA.7.015.vlCDR1, CPA.7.015.vlCDR2, and CPA.7.015.vlCDR3;

[0114] CPA.7.017, CPA.7.017.VH, CPA.7.017.VL, CPA.7.017.HC, CPA.7.017.LC, CPA.7.017H1, CPA.7.017.H2, CPA.7.017.H3 CPA.7.017.H4; CPA.7.017.vhCDR1, CPA.7.000171.vhCDR2, CPA.7.017.vhCDR3, CPA.7.017.vlCDR1, CPA.7.017.vlCDR2, and CPA.7.017.vlCDR3;

[0115] CPA.7.018, CPA.7.018.VH, CPA.7.018.VL, CPA.7.018.HC, CPA.7.018.LC, CPA.7.018.H1, CPA.7.018.H2, CPA.7.018.H3 CPA.7.018.H4; CPA.7.017.vhCDR1, CPA.7.017.vhCDR2, CPA.7.017.vhCDR3, CPA.7.017.vlCDR1, CPA.7.017.vlCDR2, and CPA.7.017.vlCDR3;

[0116] CPA.7.019, CPA.7.019.VH, CPA.7.019.VL, CPA.7.019.HC, CPA.7.019.LC, CPA.7.019.H1, CPA.7.019.H2, CPA.7.019.H3 CPA.7.019.H4; CPA.7.019.vhCDR1, CPA.7.019.vhCDR2, CPA.7.019.vhCDR3, CPA.7.019.vlCDR1, CPA.7.019.vlCDR2, and CPA.7.019.vlCDR3;

[0117] CPA.7.021, CPA.7.021.VH, CPA.7.021.VL, CPA.7.021.HC, CPA.7.021.LC, CPA.7.021.H1, CPA.7.021.H2, CPA.7.021.H3 CPA.7.021.H4; CPA.7.021.vhCDR1, CPA.7.021.vhCDR2, CPA.7.021.vhCDR3, CPA.7.021.vlCDR1, CPA.7.021.vlCDR2, and CPA.7.021.vlCDR3;

[0118] CPA.7.022, CPA.7.022.VH, CPA.7.022.VL, CPA.7.022.HC, CPA.7.022.LC, CPA.7.022.H1, CPA.7.022.H2, CPA.7.022.H3 CPA.7.022.H4; CPA.7.022.vhCDR1, CPA.7.022.vhCDR2, CPA.7.002201.vhCDR3, CPA.7.022.vlCDR1, CPA.7.022.vlCDR2, and CPA.7.022.vlCDR3;

[0119] CPA.7.023, CPA.7.023.VH, CPA.7.023.VL, CPA.7.023.HC, CPA.7.023.LC, CPA.7.023.H1, CPA.7.023.H2, CPA.7.023.H3 CPA.7.023.H4; CPA.7.023.vhCDR1, CPA.7.023.vhCDR2, CPA.7.023.vhCDR3, CPA.7.023.vlCDR1, CPA.7.023.vlCDR2, and CPA.7.023.vlCDR3;

[0120] CPA.7.024, CPA.7.024.VH, CPA.7.024.VL, CPA.7.024.HC, CPA.7.024.LC, CPA.7.024.H1, CPA.7.024.H2, CPA.7.024.H3 CPA.7.024.H4; CPA.7.024.vhCDR1, CPA.7.024.vhCDR2, CPA.7.024.vhCDR3, CPA.7.024.vlCDR1, CPA.7.024.vlCDR2, and CPA.7.024.vlCDR3;

[0121] CPA.7.033, CPA.7.033.VH, CPA.7.033.VL, CPA.7.033.HC, CPA.7.033.LC, CPA.7.033.H1, CPA.7.033.H2, CPA.7.033.H3 CPA.7.033.H4; CPA.7.033.vhCDR1,

CPA.7.033.vhCDR2, CPA.7.033.vhCDR3, CPA.7.033.vlCDR1, CPA.7.033.vlCDR2, and CPA.7.033.vlCDR3;

[0122] CPA.7.034, CPA.7.034.VH, CPA.7.034.VL, CPA.7.034.HC, CPA.7.034.LC, CPA.7.034.H1, CPA.7.034.H2, CPA.7.034.H3 CPA.7.034.H4; CPA.7.034.vhCDR1, CPA.7.034.vhCDR2, CPA.7.034.vhCDR3, CPA.7.034.vlCDR1, CPA.7.034.vlCDR2, and CPA.7.034.vlCDR3;

[0123] CPA.7.036, CPA.7.036.VH, CPA.7.036.VL, CPA.7.036.HC, CPA.7.036.LC, CPA.7.036.H1, CPA.7.036.H2, CPA.7.036.H3 CPA.7.036.H4; CPA.7.036.vhCDR1, CPA.7.036.vhCDR2, CPA.7.036.vhCDR3, CPA.7.036.vlCDR1, CPA.7.036.vlCDR2, and CPA.7.036.vlCDR3;

[0124] CPA.7.040, CPA.7.040.VH, CPA.7.040.VL, CPA.7.040.HC, CPA.7.040.LC, CPA.7.040.H1, CPA.7.040.H2, CPA.7.040.H3 and CPA.7.040.H4; CPA.7.040.vhCDR1, CPA.7.040.vhCDR2, CPA.7.040.vhCDR3, CPA.7.040.vlCDR1, CPA.7.040.vlCDR2, and CPA.7.040.vlCDR3;

[0125] CPA.7.046, CPA.7.046.VH, CPA.7.046.VL, CPA.7.046.HC, CPA.7.046.LC, CPA.7.046.H1, CPA.7.046.H2, CPA.7.046.H3 CPA.7.046.H4; CPA.7.046.vhCDR1, CPA.7.046.vhCDR2, CPA.7.046.vhCDR3, CPA.7.046.vlCDR1, CPA.7.046.vlCDR2, and CPA.7.046.vlCDR3;

[0126] CPA.7.047, CPA.7.047.VH, CPA.7.047.VL, CPA.7.047.HC, CPA.7.047.LC, CPA.7.047.H1, CPA.7.047.H2, CPA.7.047.H3 CPA.7.047.H4; CPA.7.047.vhCDR1, CPA.7.047.vhCDR2, CPA.7.047.vhCDR3, CPA.7.047.vlCDR1, CPA.7.004701.vlCDR2, and CPA.7.047.vlCDR3;

[0127] CPA.7.049, CPA.7.049.VH, CPA.7.049.VL, CPA.7.049.HC, CPA.7.049.LC, CPA.7.049.H1, CPA.7.049.H2, CPA.7.049.H3 CPA.7.049.H4; CPA.7.049.vhCDR1, CPA.7.049.vhCDR2, CPA.7.049.vhCDR3, CPA.7.049.vlCDR1, CPA.7.049.vlCDR2, and CPA.7.049.vlCDR3; and

[0128] CPA.7.050, CPA.7.050.VH, CPA.7.050.VL, CPA.7.050.HC, CPA.7.050.LC, CPA.7.050.H1, CPA.7.050.H2, CPA.7.050.H3 CPA.7.050.H4, CPA.7.050.vhCDR1, CPA.7.050.vhCDR2, CPA.7.050.vhCDR3, CPA.7.050.vlCDR1, CPA.7.050.vlCDR2, and CPA.7.050.vlCDR3.

[0129] In addition, there are a number of CPA antibodies generated herein that bound to PVRIG but did not block the interaction of PVRIG and PVLR2. The anti-PVRIG antibodies for use in the present invention can comprise a PVRIG antibody and/or antigen binding domain sequence capable of binding but not blocking the receptor-ligand interaction. The anti-PVRIG for use in the present invention can comprise the CDRs from a PVRIG antibody sequence capable of sequence capable of binding but not blocking the receptor-ligand interaction. The CPA antibodies, as well as the CDR sequences, that bind but do not block the receptor-ligand interaction are as below, with their components outlined as well, the sequences for which are shown in Figure 63:

[0130] CPA.7.028, CPA.7.028.VH, CPA.7.028.VL, CPA.7.028.HC, CPA.7.028.LC, CPA.7.028.H1, CPA.7.028.H2, CPA.7.028.H3 and CPA.7.028.H4; CPA.7.028.vhCDR1, CPA.7.028.vhCDR2, CPA.7.028.vhCDR3, CPA.7.028.vlCDR1, CPA.7.028.vlCDR2, and CPA.7.028.vlCDR3.

[0131] CPA.7.030, CPA.7.030.VH, CPA.7.030.VL, CPA.7.030.HC, CPA.7.030.LC, CPA.7.030.H1, CPA.7.030.H2, CPA.7.030.H3 and CPA.7.030.H4; CPA.7.030.vhCDR1, CPA.7.030.vhCDR2, CPA.7.030.vhCDR3, CPA.7.030.vlCDR1, CPA.7.030.vlCDR2, and CPA.7.030.vlCDR3.

[0132] CPA.7.041, CPA.7.041.VH, CPA.7.041.VL, CPA.7.041.HC, CPA.7.041.LC, CPA.7.041.H1, CPA.7.041.H2, CPA.7.041.H3 and CPA.7.041.H4; CPA.7.041.vhCDR1, CPA.7.041.vhCDR2, CPA.7.041.vhCDR3, CPA.7.041.vlCDR1, CPA.7.041.vlCDR2, and CPA.7.041.vlCDR3.

[0133] CPA.7.016, CPA.7.016.VH, CPA.7.016.VL, CPA.7.016.HC, CPA.7.016.LC, CPA.7.016.H1, CPA.7.016.H2, CPA.7.016.H3 and CPA.7.016.H4; CPA.7.016.vhCDR1, CPA.7.016.vhCDR2, CPA.7.016.vhCDR3, CPA.7.016.vlCDR1, CPA.7.016.vlCDR2, and CPA.7.016.vlCDR3.

[0134] CPA.7.020, CPA.7.020.VH, CPA.7.020.VL, CPA.7.020.HC, CPA.7.020.LC, CPA.7.020.H1, CPA.7.020.H2, CPA.7.020.H3 and CPA.7.020.H4; CPA.7.020.vhCDR1, CPA.7.020.vhCDR2, CPA.7.020.vhCDR3, CPA.7.020.vlCDR1, CPA.7.020.vlCDR2, and CPA.7.020.vlCDR3.

[0135] CPA.7.038, CPA.7.038.VH, CPA.7.038.VL, CPA.7.038.HC, CPA.7.038.LC, CPA.7.038.H1, CPA.7.038.H2, CPA.7.038.H3 and CPA.7.038.H4; CPA.7.038.vhCDR1,

CPA.7.038.vhCDR2, CPA.7.038.vhCDR3, CPA.7.038.vlCDR1, CPA.7.038.vlCDR2, and CPA.7.038.vlCDR3.

[0136] CPA.7.044, CPA.7.044.VH, CPA.7.044.VL, CPA.7.044.HC, CPA.7.044.LC, CPA.7.044.H1, CPA.7.044.H2, CPA.7.044.H3 and CPA.7.044.H4; CPA.7.044.vhCDR1, CPA.7.044.vhCDR2, CPA.7.044.vhCDR3, CPA.7.044.vlCDR1, CPA.7.044.vlCDR2, and CPA.7.044.vlCDR3.

[0137] CPA.7.045, CPA.7.045.VH, CPA.7.045.VL, CPA.7.045.HC, CPA.7.045.LC, CPA.7.045.H1, CPA.7.045.H2, CPA.7.045.H3 and CPA.7.045.H4; CPA.7.045.vhCDR1, CPA.7.045.vhCDR2, CPA.7.045.vhCDR3, CPA.7.045.vlCDR1, CPA.7.045.vlCDR2, and CPA.7.045.vlCDR3.

[0138] As discussed herein, the invention further provides variants of the above components, including variants in the CDRs, as outlined above. In addition, variable heavy chains can be 80%, 90%, 95%, 98% or 99% identical to the "VH" sequences herein, and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. Variable light chains are provided that can be 80%, 90%, 95%, 98% or 99% identical to the "VL" sequences herein, and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. Similarly, heavy and light chains are provided that are 80%, 90%, 95%, 98% or 99% identical to the "HC" and "LC" sequences herein, and/or contain from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 amino acid changes, or more, when Fc variants are used. The anti-PVRIG for use in the present invention can comprise any of these PVRIG antibody and/or antigen bindgin domain sequences.

[0139] Furthermore, the present invention provides a number of CHA antibodies, which are murine antibodies generated from hybridomas. As is well known the art, the six CDRs are useful when put into either human framework variable heavy and variable light regions or when the variable heavy and light domains are humanized. See, for example, Figures 5 and 63.

[0140] The anti-PVRIG for use in the present the invention can comprise any of the following CHA sets of CDRs from PVRIG antibody sequences. Accordingly, the present invention provides for the use of anti-PVRIG that comprise the following CHA sets of CDRs, the sequences of which are shown in Figure 5 and/or Figure 63:

[0141] CHA.7.502.vhCDR1, CHA.7.502.vhCDR2, CHA.7.502.vhCDR3, CHA.7.502.vlCDR1, CHA.7.502.vlCDR2, and CHA.7.502.vlCDR3.

[0142] CHA.7.503.vhCDR1, CHA.7.503.vhCDR2, CHA.7.503.vhCDR3, CHA.7.503.vlCDR1, CHA.7.503.vlCDR2, and CHA.7.503.vlCDR3.

[0143] CHA.7.506.vhCDR1, CHA.7.506.vhCDR2, CHA.7.506.vhCDR3, CHA.7.506.vlCDR1, CHA.7.506.vlCDR2, and CHA.7.506.vlCDR3.

[0144] CHA.7.508.vhCDR1, CHA.7.508.vhCDR2, CHA.7.508.vhCDR3, CHA.7.508.vlCDR1, CHA.7.508.vlCDR2, and CHA.7.508.vlCDR3.

[0145] CHA.7.510.vhCDR1, CHA.7.510.vhCDR2, CHA.7.510.vhCDR3, CHA.7.510.vlCDR1, CHA.7.510.vlCDR2, and CHA.7.510.vlCDR3.

[0146] CHA.7.512.vhCDR1, CHA.7.512.vhCDR2, CHA.7.512.vhCDR3, CHA.7.512.vlCDR1, CHA.7.512.vlCDR2, and CHA.7.512.vlCDR3.

[0147] CHA.7.514.vhCDR1, CHA.7.514.vhCDR2, CHA.7.514.vhCDR3, CHA.7.514.vlCDR1, CHA.7.514.vlCDR2, and CHA.7.514.vlCDR3.

[0148] CHA.7.516.vhCDR1, CHA.7.516.vhCDR2, CHA.7.516.vhCDR3, CHA.7.516.vlCDR1, CHA.7.516.vlCDR2, and CHA.7.516.vlCDR3.

[0149] CHA.7.518.vhCDR1, CHA.7.518.vhCDR2, CHA.7.518.vhCDR3, CHA.7.518.vlCDR1, CHA.7.518.vlCDR2, and CHA.7.518.vlCDR3.

[0150] CHA.7.520_1.vhCDR1, CHA.7.520_1.vhCDR2, CHA.7.520_1.vhCDR3, CHA.7.520_1.vlCDR1, CHA.7.520_1.vlCDR2, and CHA.7.520_1.vlCDR3.

[0151] CHA.7.520_2.vhCDR1, CHA.7.520_2.vhCDR2, CHA.7.520_2.vhCDR3, CHA.7.520_2.vlCDR1, CHA.7.520_2.vlCDR2, and CHA.7.520_2.vlCDR3.

[0152] CHA.7.522.vhCDR1, CHA.7.522.vhCDR2, CHA.7.522.vhCDR3, CHA.7.522.vlCDR1, CHA.7.522.vlCDR2, and CHA.7.522.vlCDR3.

[0153] CHA.7.524.vhCDR1, CHA.7.524.vhCDR2, CHA.7.524.vhCDR3, CHA.7.524.vlCDR1, CHA.7.524.vlCDR2, and CHA.7.524.vlCDR3.

[0154] CHA.7.526.vhCDR1, CHA.7.526.vhCDR2, CHA.7.526.vhCDR3, CHA.7.526.vlCDR1, CHA.7.526.vlCDR2, and CHA.7.526.vlCDR3.

[0155] CHA.7.527.vhCDR1, CHA.7.527.vhCDR2, CHA.7.527.vhCDR3, CHA.7.527.vlCDR1, CHA.7.527.vlCDR2, and CHA.7.527.vlCDR3.

[0156] CHA.7.528.vhCDR1, CHA.7.528.vhCDR2, CHA.7.528.vhCDR3, CHA.7.528.vlCDR1, CHA.7.528.vlCDR2, and CHA.7.528.vlCDR3.

[0157] CHA.7.530.vhCDR1, CHA.7.530.vhCDR2, CHA.7.530.vhCDR3, CHA.7.530.vlCDR1, CHA.7.530.vlCDR2, and CHA.7.530.vlCDR3.

[0158] CHA.7.534.vhCDR1, CHA.7.534.vhCDR2, CHA.7.534.vhCDR3, CHA.7.534.vlCDR1, CHA.7.534.vlCDR2, and CHA.7.534.vlCDR3.

[0159] CHA.7.535.vhCDR1, CHA.7.535.vhCDR2, CHA.7.535.vhCDR3, CHA.7.535.vlCDR1, CHA.7.535.vlCDR2, and CHA.7.535.vlCDR3.

[0160] CHA.7.537.vhCDR1, CHA.7.537.vhCDR2, CHA.7.537.vhCDR3, CHA.7.537.vlCDR1, CHA.7.537.vlCDR2, and CHA.7.537.vlCDR3.

[0161] CHA.7.538_1.vhCDR1, CHA.7.538_1.vhCDR2, CHA.7.538_1.vhCDR3, CHA.7.538_1.vlCDR1, CHA.7.538_1.vlCDR2, and CHA.7.538_1.vlCDR3.

[0162] CHA.7.538_2.vhCDR1, CHA.7.538_2.vhCDR2, CHA.7.538_2.vhCDR3, CHA.7.538_2.vlCDR1, CHA.7.538_2.vlCDR2, and CHA.7.538_2.vlCDR3.

[0163] CHA.7.543.vhCDR1, CHA.7.543.vhCDR2, CHA.7.543.vhCDR3, CHA.7.543.vlCDR1, CHA.7.543.vlCDR2, and CHA.7.543.vlCDR3.

[0164] CHA.7.544.vhCDR1, CHA.7.544.vhCDR2, CHA.7.544.vhCDR3, CHA.7.544.vlCDR1, CHA.7.544.vlCDR2, and CHA.7.544.vlCDR3.

[0165] CHA.7.545.vhCDR1, CHA.7.545.vhCDR2, CHA.7.545.vhCDR3, CHA.7.545.vlCDR1, CHA.7.545.vlCDR2, and CHA.7.545.vlCDR3.

[0166] CHA.7.546.vhCDR1, CHA.7.546.vhCDR2, CHA.7.546.vhCDR3, CHA.7.546.vlCDR1, CHA.7.546.vlCDR2, and CHA.7.546.vlCDR3.

[0167] CHA.7.547.vhCDR1, CHA.7.547.vhCDR2, CHA.7.547.vhCDR3, CHA.7.547.vlCDR1, CHA.7.547.vlCDR2, and CHA.7.547.vlCDR3.

[0168] CHA.7.548.vhCDR1, CHA.7.548.vhCDR2, CHA.7.548.vhCDR3, CHA.7.548.vlCDR1, CHA.7.548.vlCDR2, and CHA.7.548.vlCDR3.

[0169] CHA.7.549.vhCDR1, CHA.7.549.vhCDR2, CHA.7.549.vhCDR3, CHA.7.549.vlCDR1, CHA.7.549.vlCDR2, and CHA.7.549.vlCDR3.

[0170] CHA.7.550.vhCDR1, CHA.7.550.vhCDR2, CHA.7.550.vhCDR3, CHA.7.550.vlCDR1, CHA.7.550.vlCDR2, and CHA.7.550.vlCDR3.

[0171] As above, these sets of CDRs may also be amino acid variants as described above.

[0172] In addition, the framework regions of the variable heavy and variable light chains can be humanized as is known in the art (with occasional variants generated in the CDRs as needed), and thus humanized variants of the VH and VL chains of Figure 63 can be generated. Furthermore, the humanized variable heavy and light domains can then be fused with human constant regions, such as the constant regions from IgG1, IgG2, IgG3 and IgG4.

[0173] In particular, as is known in the art, murine VH and VL chains can be humanized as is known in the art, for example, using the IgBLAST program of the NCBI website, as outlined in Ye et al. Nucleic Acids Res. 41:W34-W40 (2013), herein incorporated by reference in its entirety for the humanization methods. IgBLAST takes a murine VH and/or VL sequence and compares it to a library of known human germline sequences. As shown herein, for the humanized sequences generated herein, the databases used were IMGT human VH genes (F+ORF, 273 germline sequences) and IMGT human VL kappa genes (F+ORF, 74 germline sequences). An exemplary five CHA sequences were chosen: CHA.7.518, CHA.7.530, CHA.7.538_1, CHA.7.538_2 and CHA.7.524 (see Figures 5 and 63 for the VH and VL sequences). For this embodiment of the humanization, human germline IGHV1-46(allele1) was chosen for all 5 as the acceptor sequence and the human heavy chain IGHJ4(allele1) joining region (J gene). For three of four (CHA.7.518, CHA.7.530, CHA.7.538_1 and CHA.7.538_2), human germline IGKV1-39(allele 1) was chosen as the acceptor sequence and human light chain IGKJ2(allele1) (J gene) was chosen. The J gene was chosen from human joining region sequences compiled at IMGT® the international ImMunoGeneTics information system as www.imgt.org. CDRs were defined according to the AbM definition (see www.bioinfo.org.uk/abs/). Figure 63 also depicts humanized sequences as well as some potential changes to optimize binding to PVRIG. The anti-PVRIG antibodies for use in the present invention can comprise any of these humanized PVRIG antibody or antigen bindgin domain sequences.

[0174] Specific humanized antibodies of CHA antibodies include those shown in Figures 5 and 63, for example. The anti-PVRIG for use in the present invention can comprise CHA

PVRIG antibody sequences as shown in Figures 5 or 63. As will be appreciated by those in the art, each humanized variable heavy (**H**umanized **H**eavy; HH) and variable light (**H**umanized **L**ight, HL) sequence can be combined with the constant regions of human IgG1, IgG2, IgG3 and IgG4. That is, CHA.7.518.HH1 is the first humanized variable heavy chain, and CHA.7.518.HH1.**1** is the full length heavy chain, comprising the "HH1" humanized sequence with a IgG**1** constant region (CHA.7.518.HH1.**2** is CHA.7.518.HH1 with IgG**2**, etc.).

[0175] In some embodiments, the anti-PVRIG antibodies for use in the present invention include anti-PVRIG antibodies wherein the V_H and V_L sequences of different anti-PVRIG antibodies can be "mixed and matched" to create other anti-PVRIG antibodies. PVRIG binding of such "mixed and matched" antibodies can be tested using the binding assays described above. e.g., ELISAs). In some embodiments, when V_H and V_L chains are mixed and matched, a V_H sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_H sequence. Likewise, in some embodiments, a V_L sequence from a particular V_H/V_L pairing is replaced with a structurally similar V_L sequence. For example, the V_H and V_L sequences of homologous antibodies are particularly amenable for mixing and matching. The anti-PVRIG for use in the present invention can comprise PVRIG V_H and V_L sequences from different anti-PVRIG antibodies that have been "mixed and matched".

[0176] Accordingly, the antibodies of the invention comprise CDR amino acid sequences selected from the group consisting of (a) sequences as listed herein; (b) sequences that differ from those CDR amino acid sequences specified in (a) by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acid substitutions; (c) amino acid sequences having 90% or greater, 95% or greater, 98% or greater, or 99% or greater sequence identity to the sequences specified in (a) or (b); (d) a polypeptide having an amino acid sequence encoded by a polynucleotide having a nucleic acid sequence encoding the amino acids as listed herein. The anti-PVRIG for use in the present invention can comprise PVRIG variant CDR sequences.

[0177] Additionally included in the definition of PVRIG antibodies are antibodies that share identity to the anti-PVRIG antibodies enumerated herein. That is, in certain embodiments, an anti-PVRIG antibody according to the invention comprises heavy and light chain variable regions comprising amino acid sequences that are homologous to isolated anti-PVRIG amino acid sequences of preferred anti-PVRIG immune molecules, respectively, wherein the antibodies retain the desired functional properties of the parent anti-PVRIG antibodies. The

percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*e.g.*, % homology=# of identical positions/total # of positions X 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below. The anti-PVRIG antibodies for use in the present the invention can comprise heavy and light chain variable regions comprising amino acid sequences that are homologous to isolated anti-PVRIG amino acid sequences as described herein.

[0178] The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.*, 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available commercially), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0179] In general, the percentage identity for comparison between PVRIG antibodies is at least 75%, at least 80%, at least 90%, with at least about 95%, 96%, 97%, 98%, or 99% percent identity being preferred. The percentage identity may be along the whole amino acid sequence, for example the entire heavy or light chain or along a portion of the chains. For example, included within the definition of the anti-PVRIG antibodies of the invention are those that share identity along the entire variable region (for example, where the identity is 95% or 98% identical along the variable regions), or along the entire constant region, or along just the Fc domain.

G. TIGIT Antibodies with Anti-Tumor Antibodies

[00321] In some embodiments, the anti-TIGIT antibodies of the invention are co-administered with antibodies that, unlike immuno-oncology/checkpoint inhibitors that generally act on the immune system to increase a patient's native immune response, instead

are directed against a specific tumor target antigen (TTA). There are a wide number of anti-TTA antibodies either approved or in development that can be combined with the present TIGIT antibodies. Currently approved antibodies, include, but are not limited to, cetuximab, panitumumab, nimotuzumab (all to EGFR), rituximab (CD20), trastuzumab and pertuzumab (HER2), alemtuzumab (CD52), bevacizumab (VEGF), ofatumumab (CD20), denosumab (RANK ligand), brentuximab (CD30), daratumumab (CD38), ibritumomab (CD20) and ipilimumab (CTLA-4). Specific target oncology antibodies in clinical trials that can be combined with the anti-TIGIT antibodies herein include, but are not limited to, anti-CTLA4 mAbs, such as ipilimumab, tremelimumab (see, for Example U.S. Patent Publication No. 2017/0306025); anti-PD-1 such as nivolumab BMS-936558/ MDX-1106/ONO-4538, AMP224, CT-011, MK-3475, anti-PD-L1 antagonists such as Atezolizumab (IMpower133), BMS-936559/ MDX-1105, MEDI4736, RG-7446/MPDL3280A, as well as those described in U.S. Patent Publicaiton No. 2017/0281764); anti-LAG-3 such as IMP-321, anti-TIM-3, anti-BTLA, anti-B7-H4, anti-B7-H3, Anti-VISTA; agonistic antibodies targeting immunostimulatory proteins, including anti-CD40 mAbs such as CP-870,893, lucatumumab, dacetuzumab; anti-CD137 mAbs such as BMS-663513 urelumab (anti-4-1BB; *see*, for example, US Patent Nos. 7,288,638 and 8,962,804, incorporated by reference herein in their entireties); PF-05082566 utomilumab (*see*, for example, US Patent Nos. 8,821,867; 8,337,850; and 9,468,678, as well as International Patent Application Publication No. WO 2012/032433, incorporated by reference herein in their entireties); anti-OX40 mAbs, such as anti-OX40 (*see*, for example, WO2006/029879 or WO2010096418, incorporated by reference herein in their entireties); anti-GITR mAbs such as TRX518 (*see*, for example, US Patent No. 7,812,135, incorporated by reference herein in its entirety); anti-CD27 mAbs, such as varlilumab CDX-1127 (*see*, for example, WO 2016/145085 and U.S. Patent Publication Nos. US 2011/0274685 and US 2012/0213771, incorporated by reference herein in their entireties) anti-ICOS mAbs (for example, MEDI-570, JTX-2011, and anti-TIM3 antibodies (*see*, for example, WO 2013/006490 or U.S. Patent Publication No. US 2016/0257758, incorporated by reference herein in their entireties), as well as monoclonal antibodies to prostate cancer, ovarian cancer, breast cancer, endometrial cancer, multiple myeloma, melanoma, lymphomas, lung cancers including small cell lung cancer, kidney cancer, colorectal cancer, pancreatic cancer, gastric cancer, brain cancer, (see generally www.clinicaltrials.gov).

H. Specific anti-PD-1 antibodies

[00322] In another embodiment, the invention provides combinations of the anti-TIGIT antibodies of the invention and anti-PD-1 antibodies. There are two approved anti-PD-1 antibodies, pembrolizumab (Keytruda®; MK-3475-033), cemiplimab (REGN2810; see US20170174779), and nivolumab (Opdivo®; CheckMate078) and many more in development which can be used in combination with the anti-TIGIT antibodies of the invention. In other embodiments, the anti-PD-1 antibody can include, for example, SHR-1210 (CTR20160175 and CTR20170090), SHR-1210 (CTR20170299 and CTR20170322), JS-001 (CTR20160274), IBI308 (CTR20160735), BGB-A317 (CTR20160872) and/or a PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409. Exemplary anti-PD-1 anitbody sequences are shown in Figure 7 and any of these can be used with the combination therapy methods described herein.

[00323] In some embodiments, the anti-TIGIT antibodies of the invention are combined with anti-PVRIG antibodies as described herein as well as anti-PD-1 antibodies, as described herein or other anti-PD-1 antibodies known in the art, as a triple combination therapy.

I. Specific anti-PD-L1 antibodies

[00324] In another embodiment, the invention provides combinations of the anti-TIGIT antibodies of the invention and anti-PD-L1 antibodies. There are three approved anti-PD-L1 antibodies, atezolizumab (TECENTRIQ®; MPDL3280A), avelumab (BAVENCIO®; MSB001071 8C), and Durvalumab (MEDI4736), as well as other anti-PD-L1 antibodies in development. Numerous anti-PD-L1 antibodies are available and many more in development which can be used in combination with the anti-TIGIT antibodies of the invention. In embodiments, the PD-L1 antibody is one described in U.S. Patent Publication No. 2017/0281764 as well as International Patent Publication No. WO 2013/079174 (avelumab) and WO 2010/077634 (or U.S. Patent Application No. 20160222117 or U.S. Patent No. 8,217,149; atezolizumab). In some embodiments, the PD-L1 antibody comprises a heavy chain sequence of SEQ ID NO: 34 and a light chain sequence of SEQ ID NO: 36 (from US 2017/281764). In some embodiments, the PD-L1

antibody is atezolizumab (TECENTRIQ®; MPDL3280A; IMpower110). In some embodiments, the PD-L1 antibody is avelumab (BAVENCIO®; MSB001071 8C). In some embodiments, the PD-L1 antibody is durvalumab (MEDI4736). In some embodiments, the PD-L1 antibody includes, for example, Atezolizumab (IMpower133), BMS-936559/MDX-1105, and/or RG-7446/MPDL3280A, and/or YW243.55.S70, as well as any of those provided herein in Figure 62.

[00325] In some embodiments, the anti-TIGIT antibodies of the invention are combined with anti-PVRIG antibodies as described herein as well as anti-PD-L1 antibodies, as described herein or other anti-PD-L1 antibodies known in the art, as a triple combination therapy.

J. Optional Antibody Engineering

[00326] The antibodies of the invention can be modified, or engineered, to alter the amino acid sequences by amino acid substitutions. As discussed herein, amino acid substitutions can be made to alter the affinity of the CDRs for the antigen (including both increasing and decreasing binding), as well as to alter additional functional properties of the antibodies. For example, the antibodies may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody according to at least some embodiments of the invention may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Such embodiments are described further below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[00327] In one embodiment, the hinge region of C_{H1} is modified such that the number of cysteine residues in the hinge region is altered, e.g., increased or decreased. This approach is described further in U.S. Pat. No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[00328] In still another embodiment, the antibody can be modified to abrogate *in vivo* Fab arm exchange, in particular when IgG4 constant domains are used. Specifically, this

process involves the exchange of IgG4 half-molecules (one heavy chain plus one light chain) between other IgG4 antibodies that effectively results in antibodies which are functionally monovalent. Mutations to the hinge region and constant domains of the heavy chain can abrogate this exchange (see Aalberse, RC, Schuurman J., 2002, *Immunology* 105:9-19). As outlined herein, a mutation that finds particular use in the present invention is the S241P in the context of an IgG4 constant domain. IgG4 finds use in the present invention as it has no significant effector function, and is thus used to block the receptor-ligand binding without cell depletion.

[00329] In some embodiments, amino acid substitutions can be made in the Fc region, in general for altering binding to FcγR receptors. By "Fc gamma receptor", "FcγR" or "FcgammaR" as used herein is meant any member of the family of proteins that bind the IgG antibody Fc region and is encoded by an FcγR gene. In humans this family includes but is not limited to FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis et al., 2002, Immunol Lett 82:57-65, entirely incorporated by reference), as well as any undiscovered human FcγRs or FcγR isoforms or allotypes. An FcγR may be from any organism, including but not limited to humans, mice, rats, rabbits, and monkeys. Mouse FcγRs include but are not limited to FcγRI (CD64), FcγRII (CD32), FcγRIII-1 (CD16), and FcγRIII-2 (CD16-2), as well as any undiscovered mouse FcγRs or FcγR isoforms or allotypes.

[00330] There are a number of useful Fc substitutions that can be made to alter binding to one or more of the FcγR receptors. Substitutions that result in increased binding as well as decreased binding can be useful. For example, it is known that increased binding to FcγRIIIa generally results in increased ADCC (antibody dependent cell-mediated cytotoxicity; the cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell. Similarly, decreased binding to FcγRIIb (an inhibitory receptor) can be beneficial as well in some circumstances. Amino acid substitutions that find use in the present invention

include those listed in U.S. Ser. Nos. 11/124,620 (particularly FIG. 41) and U.S. Patent No. 6,737,056, both of which are expressly incorporated herein by reference in their entirety and specifically for the variants disclosed therein.

[00331] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260, both by Winter et al.

[00332] In another example, one or more amino acids selected from amino acid residues 329, 331 and 322 can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. Nos. 6,194,551 by Idusogie et al.

[00333] In another example, one or more amino acid residues within amino acid positions 231 and 239 are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

[00334] In yet another example, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields, R. L. et al. (2001) *J. Biol. Chem.* 276:6591-6604). Specific

mutations at positions 256, 290, 298, 333, 334 and 339 are shown to improve binding to FcγRIII. Additionally, the following combination mutants are shown to improve FcγRIII binding: T256A/S298A, S298A/E333A, S298A/K224A and S298A/E333A/K334A. Furthermore, mutations such as M252Y/S254T/T256E or M428L/N434S improve binding to FcRn and increase antibody circulation half-life (see Chan CA and Carter PJ (2010) *Nature Rev Immunol* 10:301-316).

[00335] In addition, the antibodies of the invention are modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Pat. No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the C_{H1} or C_L region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022 by Presta et al. Additional mutations to increase serum half-life are disclosed in U.S. Patent Nos. 8,883,973, 6,737,056 and 7,371,826 and include 428L, 434A, 434S, and 428L/434S.

[00336] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen or reduce effector function such as ADCC. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence, for example N297. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site, with an alanine replacement finding use in some embodiments.

[00337] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered

glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies according to at least some embodiments of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (α (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8 cell lines are created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see U.S. Patent Publication No. 20040110704 by Yamane et al. and Yamane-Ohnuki et al. (2004) *Biotechnol Bioeng* 87:614-22). As another example, EP 1,176,195 by Hanai et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the α 1,6 bond-related enzyme. Hanai et al. also describe cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R. L. et al. (2002) *J. Biol. Chem.* 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., β(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al. (1999) *Nat. Biotech.* 17:176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase α-L-fucosidase removes fucosyl residues from antibodies (Tarentino, A. L. et al. (1975) *Biochem.* 14:5516-23).

[00338] Another modification of the antibodies herein that is contemplated by the invention is PEGylation or the addition of other water soluble moieties, typically polymers, e.g., in order to enhance half-life. An antibody can be PEGylated to, for example, increase the biological (e.g., serum) half-life of the antibody. To PEGylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive

ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Preferably, the PEGylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C_1-C_{10}) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be PEGylated is an aglycosylated antibody. Methods for PEGylating proteins are known in the art and can be applied to the antibodies according to at least some embodiments of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

[00339] In addition to substitutions made to alter binding affinity to FcγRs and/or FcRn and/or increase in vivo serum half-life, additional antibody modifications can be made, as described in further detail below.

[00340] In some cases, affinity maturation is done. Amino acid modifications in the CDRs are sometimes referred to as "affinity maturation". An "affinity matured" antibody is one having one or more alteration(s) in one or more CDRs which results in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). In some cases, it may be desirable to decrease the affinity of an antibody to its antigen.

[00341] In some embodiments, one or more amino acid modifications are made in one or more of the CDRs of the antibodies of the invention. In general, only 1 or 2 or 3-amino acids are substituted in any single CDR, and generally no more than from 1, 2, 3. 4, 5, 6, 7, 8 9 or 10 changes are made within a set of CDRs. However, it should be appreciated that any combination of no substitutions, 1, 2 or 3 substitutions in any CDR can be independently and optionally combined with any other substitution.

[00342] Affinity maturation can be done to increase the binding affinity of the antibody for the antigen by at least about 10% to 50-100-150% or more, or from 1 to 5 fold as compared to the "parent" antibody. Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the antigen. Affinity matured antibodies are produced by known procedures. See, for example, Marks et al., 1992, Biotechnology 10:779-

783 that describes affinity maturation by variable heavy chain (VH) and variable light chain (VL) domain shuffling. Random mutagenesis of CDR and/or framework residues is described in: Barbas, et al. 1994, Proc. Nat. Acad. Sci, USA 91:3809-3813; Shier et al., 1995, Gene 169:147-155; Yelton et al., 1995, J. Immunol. 155:1994-2004; Jackson et al., 1995, J. Immunol. 154(7):3310-9; and Hawkins et al, 1992, J. Mol. Biol. 226:889-896, for example.

[00343] Alternatively, amino acid modifications can be made in one or more of the CDRs of the antibodies of the invention that are "silent", e.g. that do not significantly alter the affinity of the antibody for the antigen. These can be made for a number of reasons, including optimizing expression (as can be done for the nucleic acids encoding the antibodies of the invention).

[00344] Thus, included within the definition of the CDRs and antibodies of the invention are variant CDRs and antibodies; that is, the antibodies of the invention can include amino acid modifications in one or more of the CDRs of the enumerated antibodies of the invention. In addition, as outlined below, amino acid modifications can also independently and optionally be made in any region outside the CDRs, including framework and constant regions.

VI. Anti-TIGIT Antibodies in Combination Therapy

[00345] The TIGIT and PVRIG antibodies of the invention find particular use in the treatment of cancer when used in combination and for example with a checkpoint inhibitor such as an anti-PD-1 antibody, as described herein. In general, the antibodies of the invention are immunomodulatory, in that rather than directly attack cancerous cells, the anti-TIGIT and anti-PVRIG antibodies of the invention stimulate the immune system, generally by inhibiting the action of TIGIT and PVRIG, respectively. Thus, unlike tumor-targeted therapies, which are aimed at inhibiting molecular pathways that are crucial for tumor growth and development, and/or depleting tumor cells, cancer immunotherapy is aimed to stimulate the patient's own immune system to eliminate cancer cells, providing long-lived tumor destruction. Various approaches can be used in cancer immunotherapy, among them are therapeutic cancer vaccines to induce tumor-specific T cell responses, and immunostimulatory antibodies (i.e. antagonists of inhibitory receptors = immune checkpoints) to remove immunosuppressive pathways.

[00346] Clinical responses with targeted therapy or conventional anti-cancer therapies tend to be transient as cancer cells develop resistance, and tumor recurrence takes place. However, the clinical use of cancer immunotherapy in the past few years has shown that this type of therapy can have durable clinical responses, showing dramatic impact on long term survival. However, although responses are long term, only a small number of patients respond (as opposed to conventional or targeted therapy, where a large number of patients respond, but responses are transient).

[00347] By the time a tumor is detected clinically, it has already evaded the immune-defense system by acquiring immunoresistant and immunosuppressive properties and creating an immunosuppressive tumor microenvironment through various mechanisms and a variety of immune cells.

[00348] Accordingly, the anti-TIGIT and anti-PVRIG combinations of the invention are useful in treating cancer. Due to the nature of an immuno-oncology mechanism of action, TIGIT and or PVRIG do not necessarily need to be overexpressed on or correlated with a particular cancer type; that is, the goal is to have the anti-TIGIT antibodies de-suppress T cell and NK cell activation, such that the immune system will go after the cancers.

VII. Nucleic Acid Compositions

[00349] Nucleic acid compositions encoding the anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies of the invention are also provided, as well as expression vectors containing the nucleic acids and host cells transformed with the nucleic acid and/or expression vector compositions. As will be appreciated by those in the art, the protein sequences depicted herein can be encoded by any number of possible nucleic acid sequences, due to the degeneracy of the genetic code.

[00350] The nucleic acid compositions that encode the antibodies will depend on the format of the antibody. For traditional, tetrameric antibodies containing two heavy chains and two light chains are encoded by two different nucleic acids, one encoding the heavy chain and one encoding the light chain. These can be put into a single expression vector or two expression vectors, as is known in the art, transformed into host cells, where they are

expressed to form the antibodies of the invention. In some embodiments, for example when scFv constructs are used, a single nucleic acid encoding the variable heavy chain-linker-variable light chain is generally used, which can be inserted into an expression vector for transformation into host cells. The nucleic acids can be put into expression vectors that contain the appropriate transcriptional and translational control sequences, including, but not limited to, signal and secretion sequences, regulatory sequences, promoters, origins of replication, selection genes, etc.

[00351] Preferred mammalian host cells for expressing the recombinant antibodies according to at least some embodiments of the invention include Chinese Hamster Ovary (CHO cells), PER.C6, HEK293 and others as is known in the art.

[00352] The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art.

[00353] To create a scFv gene, the V_H- and V_L-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence (Gly4-Ser)3, such that the V_H and V_L sequences can be expressed as a contiguous single-chain protein, with the V_L and V_H regions joined by the flexible linker (see e.g., Bird et al. (1988) *Science* 242:423-426; Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883; McCafferty et al., (1990) *Nature* 348:552-554).

VIII. Formulations of the Antibodies of the Invention

[00354] The therapeutic compositions used in the practice of the foregoing methods can be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material that when combined with the therapeutic composition retains the anti-tumor function of the therapeutic composition and is generally non-reactive with the patient's immune system. Examples include, but are not limited to, any of a number of standard pharmaceutical carriers such as sterile

phosphate buffered saline solutions, bacteriostatic water, and the like (see, generally, Remington's Pharmaceutical Sciences 16th Edition, A. Osal., Ed., 1980). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed and may include buffers.

[00355] In a preferred embodiment, the pharmaceutical composition that comprises the antibodies of the invention may be in a water-soluble form, such as being present as pharmaceutically acceptable salts, which is meant to include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids and the like. "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases and the like.

[00356] Administration of the pharmaceutical composition comprising antibodies of the present invention, preferably in the form of a sterile aqueous solution, may be done in a variety of ways, including, but not limited to subcutaneously and intravenously.

[00357] The dosing amounts and frequencies of administration are, in a preferred embodiment, selected to be therapeutically or prophylactically effective. As is known in the art, adjustments for protein degradation, systemic versus localized delivery, and rate of new protease synthesis, as well as the age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

[00358] In order to treat a patient, a therapeutically effective dose of the Fc variant of the present invention may be administered. By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques.

A. Combination formulations

[00359] The antibodies of the invention (either as a triple combination of anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies or as a double combination of anti-TIGIT and anti-PVRIG antibodies) can be done in a variety of ways as those in the art will appreciate. In

some cases, the antibodies are administered simultaneously, either as separate infusions (e.g. each IV bag holds a single antibody), for example, or as one infusion of a mixture of the antibodies. Alternatively, the antibodies can be administered sequentially, for example over a period of hours or days.

[00360] In some cases, the antibodies are provided in an administration kit, with dosage units of each antibody, again either packaged separately in individual dosage units, or together, as a mixture of antibodies as a single dosage unit.

IX. Combination Therapies and Uses

A. Cancer Therapies

[00361] "Cancer," as used herein, refers broadly to any neoplastic disease (whether invasive or metastatic) characterized by abnormal and uncontrolled cell division causing malignant growth or tumor (e.g., unregulated cell growth.) The term "cancer" or "cancerous" as used herein should be understood to encompass any neoplastic disease (whether invasive, non-invasive or metastatic) which is characterized by abnormal and uncontrolled cell division causing malignant growth or tumor, non-limiting examples of which are described herein. This includes any physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer are exemplified in the working examples and also are described within the specification.

[00362] Non-limiting examples of cancer that can be treated using anti-TIGIT antibodies, anit-PVRIG antibodies, as well as combinations of anti-TIGIT antibodies and other antibodies, such as any of the anti-TIGIT, anit-PVRIG, anti-PD-1 and/or anti-PD-L1 antibodies as provided herein. Such cancers include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), esophageal cancer, melanoma, mesothelioma, merkel cell cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic

carcinoma and various types of head and neck cancer, larynx cancer, oral cavity cancer, urothelial cancer, KRAS mutant tumors, Myelodysplastic syndromes (MDS), as well as B-cell malignancies, B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenström's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; adult T-cell leukemia/lymphoma; myeloma; multiple myeloma and post-transplant lymphoproliferative disorder (PTLD), lymphoid malignancies, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome, rectal cancer, renal cell cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, ovarian early or advanced (including metastatic). The cancerous conditions amenable for treatment of the invention include cancers that express or do not express TIGIT, PVRIG, PVRL, PD-1, and/or PD-L1, and further include non-metastatic or non-invasive as well as invasive or metastatic cancers wherein TIGIT, PVRIG, PVRL, PD-1, and/or PD-L1, expression by immune, stromal or diseased cells suppress antitumor responses and anti-invasive immune responses. The method of the present invention is particularly suitable for the treatment of vascularized tumors. In some embodiments, the cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).. In some embodiments of the method, the cancer is selected from the group consisting of cancer triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high

cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

[00363] "Cancer therapy" herein refers to any method which prevents or treats cancer or ameliorates one or more of the symptoms of cancer. Typically, such therapies will comprises administration of immunostimulatory anti-TIGIT and anti-PVRIG antibodies (including antigen-binding fragments) in combination with chemotherapy or radiotherapy or other biologics and for enhancing the activity thereof, i.e., in individuals wherein expression of TIGIT and or PVRIG suppresses antitumor responses and the efficacy of chemotherapy or radiotherapy or biologic efficacy.

[00364] The present invention provides combination therapies and uses of anti-TIGIT antibodies and anti-PVRIG antibodies, sometimes with the addition of anti-PD-1 antibodies, for a triple combination therapy. The present invention provides combination therapies and uses of anti-TIGIT antibodies and anti-PVRIG antibodies, sometimes with the addition of anti-PD-L1 antibodies. Any of the PVRIG antibodies listed above or in the figures can employed for a triple combination therapy. Any of the TIGIT antibodies listed above or in the figures can be employed for a triple combination therapy. Any of the PD-1 antibodies listed above or in the figures can employed for a triple combination therapy. Any of the PD-L1 antibodies listed above or in the figures can employed for a triple combination therapy. In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3. In some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63. In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[00365] In some embodiments, the anti-PD-1 antibody is selected from pembrolizumab (Keytruda®; MK-3475-033), nivolumab (Opdivo®; CheckMate078), cemplimab (REGN2810), SHR-1210 (CTR20160175 and CTR20170090), SHR-1210 (CTR20170299 and CTR20170322), JS-001 (CTR20160274), IBI308 (CTR20160735), BGB-A317 (CTR20160872) and/or a PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00366] In some embodiments, the anti-PD-L1 antibody is selected from antibody is one described in U.S. Patent Publication No. 2017/0281764 as well as International Patent Publication No. WO 2013/079174 (avelumab) and WO 2010/077634 (or U.S. Patent Application No. 20160222117 or U.S. Patent No. 8,217,149; atezolizumab). In some embodiments, the PD-L1 antibody comprises a heavy chain sequence of SEQ ID NO: 34 and a light chain sequence of SEQ ID NO: 36 (from US 2017/281764). In some embodiments, the PD-L1 antibody is atezolizumab (TECENTRIQ®; MPDL3280A; IMpower110). In some embodiments, the PD-L1 antibody is avelumab (BAVENCIO®; MSB001071 8C). In some embodiments, the PD-L1 antibody is durvalumab (MEDI4736). In some embodiments, the PD-L1 antibody includes, for example, Atezolizumab (IMpower133), BMS-936559/MDX-1105, and/or RG-7446/MPDL3280A, and/or YW243.55.S70, as well as any of those provided herein in Figure 62.

[00367] In some embodiments, the anti-PVRIG antibody is selected from an antibody the sequences for which are shown in Figures 5 and/or 63:

CPA.7.001, CPA.7.001.VH, CPA.7.001.VL, CPA.7.001.HC, CPA.7.001.LC and CPA.7.001.H1, CPA.7.001.H2, CPA.7.001.H3, CPA.7.001.H4; CPA.7.001.vhCDR1, CPA.7.001.vhCDR2, CPA.7.001.vhCDR3, CPA.7.001.vlCDR1, CPA.7.001.vlCDR2, and CPA.7.001.vlCDR3;

CPA.7.003, CPA.7.003.VH, CPA.7.003.VL, CPA.7.003.HC, CPA.7.003.LC, CPA.7.003.H1, CPA.7.003.H2, CPA.7.003.H3, CPA.7.003.H4; CPA.7.003.vhCDR1, CPA.7.003.vhCDR2, CPA.7.003.vhCDR3, CPA.7.003.vlCDR1, CPA.7.003.vlCDR2, and CPA.7.003.vlCDR3;

CPA.7.004, CPA.7.004.VH, CPA.7.004.VL, CPA.7.004.HC, CPA.7.004.LC, CPA.7.004.H1, CPA.7.004.H2, CPA.7.004.H3 CPA.7.004.H4; CPA.7.004.vhCDR1, CPA.7.004.vhCDR2, CPA.7.004.vhCDR3, CPA.7.004.vlCDR1, CPA.7.004.vlCDR2, and CPA.7.004.vlCDR3;

CPA.7.006, CPA.7.006.VH, CPA.7.006.VL, CPA.7.006.HC, CPA.7.006.LC, CPA.7.006.H1, CPA.7.006.H2, CPA.7.006.H3 CPA.7.006.H4; CPA.7.006.vhCDR1, CPA.7.006.vhCDR2, CPA.7.006.vhCDR3, CPA.7.006.vlCDR1, CPA.7.006.vlCDR2, and CPA.7.006.vlCDR3;

CPA.7.008, CPA.7.008.VH, CPA.7.008.VL, CPA.7.008.HC, CPA.7.008.LC, CPA.7.008.H1, CPA.7.008.H2, CPA.7.008.H3 CPA.7.008.H4; CPA.7.008.vhCDR1, CPA.7.008.vhCDR2, CPA.7.008.vhCDR3, CPA.7.008.vlCDR1, CPA.7.008.vlCDR2, and CPA.7.008.vlCDR3;

CPA.7.009, CPA.7.009.VH, CPA.7.009.VL, CPA.7.009.HC, CPA.7.009.LC, CPA.7.009.H1, CPA.7.009.H2, CPA.7.009.H3 CPA.7.009.H4; CPA.7.009.vhCDR1, CPA.7.009.vhCDR2, CPA.7.009.vhCDR3, CPA.7.009.vlCDR1, CPA.7.009.vlCDR2, and CPA.7.009.vlCDR3;

CPA.7.010, CPA.7.010.VH, CPA.7.010.VL, CPA.7.010.HC, CPA.7.010.LC, CPA.7.010.H1, CPA.7.010.H2, CPA.7.010.H3 CPA.7.010.H4; CPA.7.010.vhCDR1, CPA.7.010.vhCDR2, CPA.7.010.vhCDR3, CPA.7.010.vlCDR1, CPA.7.010.vlCDR2, and CPA.7.010.vlCDR3;

CPA.7.011, CPA.7.011.VH, CPA.7.011.VL, CPA.7.011.HC, CPA.7.011.LC, CPA.7.011.H1, CPA.7.011.H2, CPA.7.011.H3 CPA.7.011.H4; CPA.7.011.vhCDR1, CPA.7.011.vhCDR2, CPA.7.011.vhCDR3, CPA.7.011.vlCDR1, CPA.7.011.vlCDR2, and CPA.7.011.vlCDR3;

CPA.7.012, CPA.7.012.VH, CPA.7.012.VL, CPA.7.012.HC, CPA.7.012.LC, CPA.7.012.H1, CPA.7.012.H2, CPA.7.012.H3 CPA.7.012.H4; CPA.7.012.vhCDR1, CPA.7.012.vhCDR2, CPA.7.012.vhCDR3, CPA.7.012.vlCDR1, CPA.7.012.vlCDR2, and CPA.7.012.vlCDR3;

CPA.7.013, CPA.7.013.VH, CPA.7.013.VL, CPA.7.013.HC, CPA.7.013.LC, CPA.7.013.H1, CPA.7.013.H2, CPA.7.013.H3 CPA.7.013.H4; CPA.7.013.vhCDR1, CPA.7.013.vhCDR2, CPA.7.013.vhCDR3, CPA.7.013.vlCDR1, CPA.7.013.vlCDR2, and CPA.7.013.vlCDR3;

CPA.7.014, CPA.7.014.VH, CPA.7.014.VL, CPA.7.014.HC, CPA.7.014.LC, CPA.7.014.H1, CPA.7.014.H2, CPA.7.014.H3 CPA.7.014.H4; CPA.7.014.vhCDR1, CPA.7.014.vhCDR2, CPA.7.014.vhCDR3, CPA.7.014.vlCDR1, CPA.7.014.vlCDR2, and CPA.7.014.vlCDR3;

CPA.7.015, CPA.7.015.VH, CPA.7.015.VL, CPA.7.015.HC, CPA.7.015.LC, CPA.7.015.H1, CPA.7.015.H2, CPA.7.015.H3 CPA.7.015.H4; CPA.7.015.vhCDR1, CPA.7.015.vhCDR2, CPA.7.015.vhCDR3, CPA.7.015.vlCDR1, CPA.7.015.vlCDR2, and CPA.7.015.vlCDR3;

CPA.7.017, CPA.7.017.VH, CPA.7.017.VL, CPA.7.017.HC, CPA.7.017.LC, CPA.7.017H1, CPA.7.017.H2, CPA.7.017.H3 CPA.7.017.H4; CPA.7.017.vhCDR1, CPA.7.000171.vhCDR2, CPA.7.017.vhCDR3, CPA.7.017.vlCDR1, CPA.7.017.vlCDR2, and CPA.7.017.vlCDR3;

CPA.7.018, CPA.7.018.VH, CPA.7.018.VL, CPA.7.018.HC, CPA.7.018.LC, CPA.7.018.H1, CPA.7.018.H2, CPA.7.018.H3 CPA.7.018.H4; CPA.7.017.vhCDR1, CPA.7.017.vhCDR2, CPA.7.017.vhCDR3, CPA.7.017.vlCDR1, CPA.7.017.vlCDR2, and CPA.7.017.vlCDR3;

CPA.7.019, CPA.7.019.VH, CPA.7.019.VL, CPA.7.019.HC, CPA.7.019.LC, CPA.7.019.H1, CPA.7.019.H2, CPA.7.019.H3 CPA.7.019.H4; CPA.7.019.vhCDR1, CPA.7.019.vhCDR2, CPA.7.019.vhCDR3, CPA.7.019.vlCDR1, CPA.7.019.vlCDR2, and CPA.7.019.vlCDR3;

CPA.7.021, CPA.7.021.VH, CPA.7.021.VL, CPA.7.021.HC, CPA.7.021.LC, CPA.7.021.H1, CPA.7.021.H2, CPA.7.021.H3 CPA.7.021.H4; CPA.7.021.vhCDR1, CPA.7.021.vhCDR2, CPA.7.021.vhCDR3, CPA.7.021.vlCDR1, CPA.7.021.vlCDR2, and CPA.7.021.vlCDR3;

CPA.7.022, CPA.7.022.VH, CPA.7.022.VL, CPA.7.022.HC, CPA.7.022.LC, CPA.7.022.H1, CPA.7.022.H2, CPA.7.022.H3 CPA.7.022.H4; CPA.7.022.vhCDR1, CPA.7.022.vhCDR2, CPA.7.002201.vhCDR3, CPA.7.022.vlCDR1, CPA.7.022.vlCDR2, and CPA.7.022.vlCDR3;

CPA.7.023, CPA.7.023.VH, CPA.7.023.VL, CPA.7.023.HC, CPA.7.023.LC, CPA.7.023.H1, CPA.7.023.H2, CPA.7.023.H3 CPA.7.023.H4; CPA.7.023.vhCDR1, CPA.7.023.vhCDR2, CPA.7.023.vhCDR3, CPA.7.023.vlCDR1, CPA.7.023.vlCDR2, and CPA.7.023.vlCDR3;

CPA.7.024, CPA.7.024.VH, CPA.7.024.VL, CPA.7.024.HC, CPA.7.024.LC, CPA.7.024.H1, CPA.7.024.H2, CPA.7.024.H3 CPA.7.024.H4; CPA.7.024.vhCDR1, CPA.7.024.vhCDR2, CPA.7.024.vhCDR3, CPA.7.024.vlCDR1, CPA.7.024.vlCDR2, and CPA.7.024.vlCDR3;

CPA.7.033, CPA.7.033.VH, CPA.7.033.VL, CPA.7.033.HC, CPA.7.033.LC, CPA.7.033.H1, CPA.7.033.H2, CPA.7.033.H3 CPA.7.033.H4; CPA.7.033.vhCDR1, CPA.7.033.vhCDR2, CPA.7.033.vhCDR3, CPA.7.033.vlCDR1, CPA.7.033.vlCDR2, and CPA.7.033.vlCDR3;

CPA.7.034, CPA.7.034.VH, CPA.7.034.VL, CPA.7.034.HC, CPA.7.034.LC, CPA.7.034.H1, CPA.7.034.H2, CPA.7.034.H3 CPA.7.034.H4; CPA.7.034.vhCDR1, CPA.7.034.vhCDR2, CPA.7.034.vhCDR3, CPA.7.034.vlCDR1, CPA.7.034.vlCDR2, and CPA.7.034.vlCDR3;

CPA.7.036, CPA.7.036.VH, CPA.7.036.VL, CPA.7.036.HC, CPA.7.036.LC, CPA.7.036.H1, CPA.7.036.H2, CPA.7.036.H3 CPA.7.036.H4; CPA.7.036.vhCDR1, CPA.7.036.vhCDR2, CPA.7.036.vhCDR3, CPA.7.036.vlCDR1, CPA.7.036.vlCDR2, and CPA.7.036.vlCDR3;

CPA.7.040, CPA.7.040.VH, CPA.7.040.VL, CPA.7.040.HC, CPA.7.040.LC, CPA.7.040.H1, CPA.7.040.H2, CPA.7.040.H3 and CPA.7.040.H4; CPA.7.040.vhCDR1, CPA.7.040.vhCDR2, CPA.7.040.vhCDR3, CPA.7.040.vlCDR1, CPA.7.040.vlCDR2, and CPA.7.040.vlCDR3;

CPA.7.046, CPA.7.046.VH, CPA.7.046.VL, CPA.7.046.HC, CPA.7.046.LC, CPA.7.046.H1, CPA.7.046.H2, CPA.7.046.H3 CPA.7.046.H4; CPA.7.046.vhCDR1, CPA.7.046.vhCDR2, CPA.7.046.vhCDR3, CPA.7.046.vlCDR1, CPA.7.046.vlCDR2, and CPA.7.046.vlCDR3;

CPA.7.047, CPA.7.047.VH, CPA.7.047.VL, CPA.7.047.HC, CPA.7.047.LC, CPA.7.047.H1, CPA.7.047.H2, CPA.7.047.H3 CPA.7.047.H4; CPA.7.047.vhCDR1, CPA.7.047.vhCDR2, CPA.7.047.vhCDR3, CPA.7.047.vlCDR1, CPA.7.004701.vlCDR2, and CPA.7.047.vlCDR3;

CPA.7.049, CPA.7.049.VH, CPA.7.049.VL, CPA.7.049.HC, CPA.7.049.LC, CPA.7.049.H1, CPA.7.049.H2, CPA.7.049.H3 CPA.7.049.H4; CPA.7.049.vhCDR1, CPA.7.049.vhCDR2, CPA.7.049.vhCDR3, CPA.7.049.vlCDR1, CPA.7.049.vlCDR2, and CPA.7.049.vlCDR3; and

CPA.7.050, CPA.7.050.VH, CPA.7.050.VL, CPA.7.050.HC, CPA.7.050.LC, CPA.7.050.H1, CPA.7.050.H2, CPA.7.050.H3 CPA.7.050.H4, CPA.7.050.vhCDR1, CPA.7.050.vhCDR2, CPA.7.050.vhCDR3, CPA.7.050.vlCDR1, CPA.7.050.vlCDR2, and CPA.7.050.vlCDR3.

CPA.7.028, CPA.7.028.VH, CPA.7.028.VL, CPA.7.028.HC, CPA.7.028.LC, CPA.7.028.H1, CPA.7.028.H2, CPA.7.028.H3 and CPA.7.028.H4; CPA.7.028.vhCDR1, CPA.7.028.vhCDR2, CPA.7.028.vhCDR3, CPA.7.028.vlCDR1, CPA.7.028.vlCDR2, and CPA.7.028.vlCDR3.

CPA.7.030, CPA.7.030.VH, CPA.7.030.VL, CPA.7.030.HC, CPA.7.030.LC, CPA.7.030.H1, CPA.7.030.H2, CPA.7.030.H3 and CPA.7.030.H4; CPA.7.030.vhCDR1, CPA.7.030.vhCDR2, CPA.7.030.vhCDR3, CPA.7.030.vlCDR1, CPA.7.030.vlCDR2, and CPA.7.030.vlCDR3.

CPA.7.041, CPA.7.041.VH, CPA.7.041.VL, CPA.7.041.HC, CPA.7.041.LC, CPA.7.041.H1, CPA.7.041.H2, CPA.7.041.H3 and CPA.7.041.H4; CPA.7.041.vhCDR1, CPA.7.041.vhCDR2, CPA.7.041.vhCDR3, CPA.7.041.vlCDR1, CPA.7.041.vlCDR2, and CPA.7.041.vlCDR3.

CPA.7.016, CPA.7.016.VH, CPA.7.016.VL, CPA.7.016.HC, CPA.7.016.LC, CPA.7.016.H1, CPA.7.016.H2, CPA.7.016.H3 and CPA.7.016.H4; CPA.7.016.vhCDR1, CPA.7.016.vhCDR2, CPA.7.016.vhCDR3, CPA.7.016.vlCDR1, CPA.7.016.vlCDR2, and CPA.7.016.vlCDR3.

CPA.7.020, CPA.7.020.VH, CPA.7.020.VL, CPA.7.020.HC, CPA.7.020.LC, CPA.7.020.H1, CPA.7.020.H2, CPA.7.020.H3 and CPA.7.020.H4; CPA.7.020.vhCDR1, CPA.7.020.vhCDR2, CPA.7.020.vhCDR3, CPA.7.020.vlCDR1, CPA.7.020.vlCDR2, and CPA.7.020.vlCDR3.

CPA.7.038, CPA.7.038.VH, CPA.7.038.VL, CPA.7.038.HC, CPA.7.038.LC, CPA.7.038.H1, CPA.7.038.H2, CPA.7.038.H3 and CPA.7.038.H4; CPA.7.038.vhCDR1, CPA.7.038.vhCDR2, CPA.7.038.vhCDR3, CPA.7.038.vlCDR1, CPA.7.038.vlCDR2, and CPA.7.038.vlCDR3.

CPA.7.044, CPA.7.044.VH, CPA.7.044.VL, CPA.7.044.HC, CPA.7.044.LC, CPA.7.044.H1, CPA.7.044.H2, CPA.7.044.H3 and CPA.7.044.H4; CPA.7.044.vhCDR1, CPA.7.044.vhCDR2, CPA.7.044.vhCDR3, CPA.7.044.vlCDR1, CPA.7.044.vlCDR2, and CPA.7.044.vlCDR3.

CPA.7.045, CPA.7.045.VH, CPA.7.045.VL, CPA.7.045.HC, CPA.7.045.LC, CPA.7.045.H1, CPA.7.045.H2, CPA.7.045.H3 and CPA.7.045.H4; CPA.7.045.vhCDR1, CPA.7.045.vhCDR2, CPA.7.045.vhCDR3, CPA.7.045.vlCDR1, CPA.7.045.vlCDR2, and CPA.7.045.vlCDR3.

[00368] In some embodiments, the anti-TIGIT antibody is selected from an antibody the sequences for which are shown in Figure 3:

CPA.9.018, CPA.9.018.VH, CPA.9.018.VL, CPA.9.018.HC, CPA.9.018.LC, CPA.9.018.H1, CPA.9.018.H2, CPA.9.018.H3, CPA.9.018.H4; CPA.9.018.H4(S241P); CPA.9.018.vhCDR1, CPA.9.018.vhCDR2, CPA.9.018.vhCDR3, CPA.9.018.vlCDR1, CPA.9.018.vlCDR2, CPA.9.018.vlCDR3 and scFv-CPA.9.018;

CPA.9.027, CPA.9.027.VH, CPA.9.027.VL, CPA.9.027.HC, CPA.9.027.LC, CPA.9.027.H1, CPA.9.027.H2, CPA.9.027.H3, CPA.9.027.H4; CPA.9.018.H4(S241P); CPA.9.027.vhCDR1, CPA.9.027.vhCDR2, CPA.9.027.vhCDR3, CPA.9.027.vlCDR1, CPA.9.027.vlCDR2, CPA.9.027.vlCDR3 and scFv-CPA.9.027;

CPA.9.049, CPA.9.049.VH, CPA.9.049.VL, CPA.9.049.HC, CPA.9.049.LC, CPA.9.049.H1, CPA.9.049.H2, CPA.9.049.H3; CPA.9.049.H4; CPA.9.049.H4(S241P); CPA.9.049.vhCDR1, CPA.9.049.vhCDR2, CPA.9.049.vhCDR3, CPA.9.049.vlCDR1, CPA.9.049.vlCDR2, CPA.9.049.vlCDR3 and scFv-CPA.9.049;

CPA.9.057, CPA.9.057.VH, CPA.9.057.VL, CPA.9.057.HC, CPA.9.057.LC, CPA.9.057.H1, CPA.9.057.H2, CPA.9.057.H3; CPA.9.057.H4; CPA.9.057.H4(S241P); CPA.9.057.vhCDR1, CPA.9.057.vhCDR2, CPA.9.057.vhCDR3, CPA.9.057.vlCDR1, CPA.9.057.vlCDR2, CPA.9.057.vlCDR3 and scFv-CPA.9.057;

CPA.9.059, CPA.9.059.VH, CPA.9.059.VL, CPA.9.059.HC, CPA.9.059.LC, CPA.9.059.H1, CPA.9.059.H2, CPA.9.059.H3; CPA.9.059.H4; CPA.9.059.H4(S241P); CPA.9.059.vhCDR1,

CPA.9.059.vhCDR2, CPA.9.059.vhCDR3, CPA.9.059.vlCDR1, CPA.9.059.vlCDR2, CPA.9.059.vlCDR3 and scFv-CPA.9.059;

CPA.9.083, CPA.9.083.VH, CPA.9.083.VL, CPA.9.083.HC, CPA.9.083.LC, CPA.9.083.H1, CPA.9.083.H2, CPA.9.083.H3; CPA.9.083.H4; CPA.9.083.H4(S241P); CPA.9.083.vhCDR1, CPA.9.083.vhCDR2, CPA.9.083.vhCDR3, CPA.9.083.vlCDR1, CPA.9.083.vlCDR2, CPA.9.083.vlCDR3 and scFv-CPA.9.083;

CPA.9.086, CPA.9.086.VH, CPA.9.086.VL, CPA.9.086.HC, CPA.9.086.LC, CPA.9.086.H1, CPA.9.086.H2, CPA.9.086.H3; CPA.9.086.H4; CPA.9.086.H4(S241P); CPA.9.086.vhCDR1, CPA.9.086.vhCDR2, CPA.9.086.vhCDR3, CPA.9.086.vlCDR1, CPA.9.086.vlCDR2, CPA.9.086.vlCDR3 and scFv-CPA.9.086;

CPA.9.089, CPA.9.089.VH, CPA.9.089.VL, CPA.9.089.HC, CPA.9.089.LC, CPA.9.089.H1, CPA.9.089.H2, CPA.9.089.H3; CPA.9.089.H4; CPA.9.089.H4(S241P); CPA.9.089.vhCDR1, CPA.9.089.vhCDR2, CPA.9.089.vhCDR3, CPA.9.089.vlCDR1, CPA.9.089.vlCDR2, CPA.9.089.vlCDR3 and scFv-CPA.9.089;

CPA.9.093, CPA.9.093.VH, CPA.9.093.VL, CPA.9.093.HC, CPA.9.093.LC, CPA.9.093.H1, CPA.9.093.H2, CPA.9.093.H3; CPA.9.093.H4; CPA.9.093.H4(S241P); CPA.9.093.vhCDR1, CPA.9.093.vhCDR2, CPA.9.093.vhCDR3, CPA.9.093.vlCDR1, CPA.9.093.vlCDR2, CPA.9.093.vlCDR3 and scFv-CPA.9.093;

CPA.9.101, CPA.9.101.VH, CPA.9.101.VL, CPA.9.101.HC, CPA.9.101.LC, CPA.9.101.H1, CPA.9.101.H2, CPA.9.101.H3; CPA.9.101.H4; CPA.9.101.H4(S241P); CPA.9.101.vhCDR1, CPA.9.101.vhCDR2, CPA.9.101.vhCDR3, CPA.9.101.vlCDR1, CPA.9.101.vlCDR2, CPA.9.101.vlCDR3 and scFv-CPA.9.101; and

CPA.9.103, CPA.9.103.VH, CPA.9.103.VL, CPA.9.103.HC, CPA.9.103.LC, CPA.9.103.H1, CPA.9.103.H2, CPA.9.103.H3; CPA.9.103.H4; CPA.9.103.H4(S241P); CPA.9.103.vhCDR1, CPA.9.103.vhCDR2, CPA.9.103.vhCDR3, CPA.9.103.vlCDR1, CPA.9.103.vlCDR2, CPA.9.103.vlCDR3 and scFv-CPA.9.103.

CHA.9.536.1, CHA.9.536.1.VH, CHA.9.536.1.VL, CHA.9.536.1.HC, CHA.9.536.1.LC, CHA.9.536.1.H1, CHA.9.536.1.H2, CHA.9.536.1.H3; CHA.9.536.1.H4, CHA.9.536.1.H4(S241P), CHA.9.536.1.vhCDR1, CHA.9.536.1.vhCDR2,

CHA.9.536.1.vhCDR3, CHA.9.536.1.vlCDR1, CHA.9.536.1.vlCDR2 and CHA.9.536.1.vhCDR3;

CHA.9.536.3, CHA.9.536.3.VH, CHA.9.536.3.VL, CHA.9.536.3.HC, CHA.9.536.3.LC, CHA.9.536.3.H1, CHA.9.536.3.H2, CHA.9.536.3.H3; CHA.9.536.3.H4, CHA.9.536.3.H4(S241P); CHA.9.536.3.vhCDR1, CHA.9.536.3.vhCDR2, CHA.9.536.3.vhCDR3, CHA.9.536.3.vlCDR1, CHA.9.536.3.vlCDR2 and CHA.9.536.3.vhCDR3;

CHA.9.536.4, CHA.9.536.4.VH, CHA.9.536.4.VL, CHA.9.536.4.HC, CHA.9.536.4.LC, CHA.9.536.4.H1, CHA.9.536.4.H2, CHA.9.536.4.H3; CHA.9.536.4.H4, CHA.9.536.4.H4(S241P), CHA.9.536.4.vhCDR1, CHA.9.536.4.vhCDR2, CHA.9.536.4.vhCDR3, CHA.9.536.4.vlCDR1, CHA.9.536.4.vlCDR2 and CHA.9.536.4.vhCDR3;

CHA.9.536.5, CHA.9.536.5.VH, CHA.9.536.5.VL, CHA.9.536.5.HC, CHA.9.536.5.LC, CHA.9.536.5.H1, CHA.9.536.5.H2, CHA.9.536.5.H3; CHA.9.536.5.H4, CHA.9.536.5.H4(S241P), CHA.9.536.5.vhCDR1, CHA.9.536.5.vhCDR2, CHA.9.536.5.vhCDR3, CHA.9.536.5.vlCDR1, CHA.9.536.5.vlCDR2 and CHA.9.536.5.vhCDR3;

CHA.9.536.6, CHA.9.536.6.VH, CHA.9.536.6.VL, CHA.9.536.6.HC, CHA.9.536.6.LC, CHA.9.536.6.H1, CHA.9.536.6.H2, CHA.9.536.6.H3; CHA.9.536.6.H4, CHA.9.536.6.vhCDR1, CHA.9.536.6.vhCDR2, CHA.9.536.6.vhCDR3, CHA.9.536.6.vlCDR1, CHA.9.536.6.vlCDR2 and CHA.9.536.6.vhCDR3;

CHA.9.536.7, CHA.9.536.7.VH, CHA.9.536.7.VL, CHA.9.536.7.HC, CHA.9.536.7.LC, CHA.9.536.7.H1, CHA.9.536.7.H2, CHA.9.536.7.H3; CHA.9.536.7.H4, CHA.9.536.5.H4(S241P); CHA.9.536.7.vhCDR1, CHA.9.536.7.vhCDR2, CHA.9.536.7.vhCDR3, CHA.9.536.7.vlCDR1, CHA.9.536.7.vlCDR2 and CHA.9.536.7.vhCDR3;

CHA.9.536.8, CHA.9.536.8.VH, CHA.9.536.8.VL, CHA.9.536.8.HC, CHA.9.536.8.LC, CHA.9.536.8.H1, CHA.9.536.8.H2, CHA.9.536.8.H3; CHA.9.536.8.H4, CHA.9.536.8.H4(S241P), CHA.9.536.8.vhCDR1, CHA.9.536.8.vhCDR2,

CHA.9.536.8.vhCDR3, CHA.9.536.8.vlCDR1, CHA.9.536.8.vlCDR2 and CHA.9.536.8.vhCDR3;

CHA.9.560.1, CHA. 9.560.1VH, CHA. 9.560.1.VL, CHA. 9.560.1.HC, CHA. 9.560.1.LC, CHA. 9.560.1.H1, CHA. 9.560.1.H2, CHA. 9.560.1.H3; CHA. 9.560.1.H4, CHA. 9.560.1.H4(S241P), CHA. 9.560.1.vhCDR1, CHA. 9.560.1.vhCDR2, CHA. 9.560.1.vhCDR3, CHA. 9.560.1.vlCDR1, CHA. 9.560.1.vlCDR2 and CHA. 9.560.1.vhCDR3;

CHA.9.560.3, CHA. 9.560. 3VH, CHA. 9.560. 3.VL, CHA. 9.560. 3.HC, CHA. 9.560. 3.LC, CHA. 9.560. 3.H1, CHA. 9.560. 3.H2, CHA. 9.560. 3.H3; CHA.9.560.3.H4, CHA.9.560.3.H4(S241P); CHA. 9.560. 3.vhCDR1, CHA. 9.560. 3.vhCDR2, CHA. 9.560. 3.vhCDR3, CHA. 9.560. 3.vlCDR1, CHA. 9.560. 3.vlCDR2 and CHA. 9.560. 3.vhCDR3;

CHA.9.560.4, CHA. 9.560. 4VH, CHA. 9.560. 4.VL, CHA. 9.560. 4.HC, CHA. 9.560. 4.LC, CHA. 9.560. 4.H1, CHA. 9.560. 4.H2, CHA. 9.560. 4.H3; CHA.9.560.4.H4, CHA.9.560.4.H4(S241P), CHA. 9.560. 4.vhCDR1, CHA. 9.560. 4.vhCDR2, CHA. 9.560. 4.vhCDR3, CHA. 9.560. 4.vlCDR1, CHA. 9.560. 4.vlCDR2 and CHA. 9.560. 4.vhCDR3;

CHA.9.560.5, CHA. 9.560. 5VH, CHA. 9.560. 5.VL, CHA. 9.560. 5.HC, CHA. 9.560. 5.LC, CHA. 9.560. 5.H1, CHA. 9.560. 5.H2, CHA. 9.560. 5.H3; CHA. 9.560. 5.H4, CHA. 9.560. 5.vhCDR1, CHA. 9.560. 5.vhCDR2, CHA. 9.560. 5.vhCDR3, CHA. 9.560. 5.vlCDR1, CHA. 9.560. 5.vlCDR2 and CHA. 9.560. 5.vhCDR3;

CHA.9.560.6, CHA. 9.560. 6VH, CHA. 9.560. 6.VL, CHA. 9.560. 6.HC, CHA. 9.560. 6.LC, CHA. 9.560. 6.H1, CHA. 9.560. 6.H2, CHA. 9.560. 6.H3; CHA.9.560.6.H4, CHA.9.560.6.H4(S241P), CHA. 9.560. 6.vhCDR1, CHA. 9.560. 6.vhCDR2, CHA. 9.560. 6.vhCDR3, CHA. 9.560. 6.vlCDR1, CHA. 9.560. 6.vlCDR2 and CHA. 9.560. 6.vhCDR3;

CHA.9.560.7, CHA. 9.560. 7VH, CHA. 9.560. 7.VL, CHA. 9.560. 7.HC, CHA. 9.560. 7.LC, CHA. 9.560. 7.H1, CHA. 9.560. 7.H2, CHA. 9.560. 7.H3; CHA.9.560.7.H4; CHA.9.560.7.H4(S241P); CHA. 9.560. 7.vhCDR1, CHA. 9.560. 7.vhCDR2, CHA. 9.560. 7.vhCDR3, CHA. 9.560. 7.vlCDR1, CHA. 9.560. 7.vlCDR2 and CHA. 9.560. 7.vhCDR3;

CHA.9.560.8, CHA. 9.560. 8VH, CHA. 9.560. 8.VL, CHA. 9.560. 8.HC, CHA. 9.560. 8.LC, CHA. 9.560. 8.H1, CHA. 9.560. 8.H2, CHA. 9.560. 8.H3; CHA.9.560.8.H4,

CHA.9.560.8.H4(S241P); CHA. 9.560. 8.vhCDR1, CHA. 9.560. 8.vhCDR2, CHA. 9.560. 8.vhCDR3, CHA. 9.560. 8.vlCDR1, CHA. 9.560. 8.vlCDR2 and CHA. 9.560. 8.vhCDR3;

CHA.9.546.1, CHA. 9. 546.1VH, CHA. 9. 546.1.VL, CHA. 9. 546.1.HC, CHA. 9. 546.1.LC, CHA. 9. 546.1.H1, CHA. 9. 546.1.H2, CHA. 9. 546.1.H3; CHA.9.546.1.H4, CHA.9.546.1.H4(S241P), CHA. 9. 546.1.vhCDR1, CHA. 9. 546.1.vhCDR2, CHA. 9. 546.1.vhCDR3, CHA. 9. 546.1.vlCDR1, CHA. 9. 546.1.vlCDR2 and CHA. 9. 546.1.vhCDR3;

CHA.9.547.1, CHA. 9. 547.1VH, CHA. 9. 547.1.VL, CHA. 9. 547.1.HC, CHA. 9. 547.1.LC, CHA. 9. 547.1.H1, CHA. 9. 547.1.H2, CHA. 9. 547.1.H3; CHA.9.547.1.H4, CHA.9.547.1.H4(S241P), CHA. 9. 547.1.vhCDR1, CHA. 9. 547.1.vhCDR2, CHA. 9. 547.1.vhCDR3, CHA. 9. 547.1.vlCDR1, CHA. 9. 547.1.vlCDR2 and CHA. 9. 547.1.vhCDR3;

CHA.9.547.2, CHA. 9. 547. 2VH, CHA. 9. 547. 2.VL, CHA. 9. 547. 2.HC, CHA. 9. 547. 2.LC, CHA. 9. 547. 2.H1, CHA. 9. 547. 2.H2, CHA. 9. 547. 2.H3; CHA.9.547.2.H4, CHA.9.547.2.H4(S241P), CHA. 9. 547. 2.vhCDR1, CHA. 9. 547. 2.vhCDR2, CHA. 9. 547. 2.vhCDR3, CHA. 9. 547. 2.vlCDR1, CHA. 9. 547. 2.vlCDR2 and CHA. 9. 547. 2.vhCDR3;

CHA.9.547.3, CHA. 9. 547. 3VH, CHA. 9. 547. 3.VL, CHA. 9. 547. 3.HC, CHA. 9. 547. 3.LC, CHA. 9. 547. 3.H1, CHA. 9. 547. 3.H2, CHA. 9. 547. 3.H3; CHA.9.547.3.H4, CHA.9.547.3.H4(S241P), CHA. 9. 547. 3.vhCDR1, CHA. 9.547. 3.vhCDR2, CHA. 9. 547. 3.vhCDR3, CHA. 9. 547. 3.vlCDR1, CHA. 9. 547. 3.vlCDR2 and CHA. 9. 547. 3.vhCDR3;

CHA.9.547.4, CHA. 9. 547. 4VH, CHA. 9. 547. 4.VL, CHA. 9. 547. 4.HC, CHA. 9.547. 4.LC, CHA. 9. 547. 4.H1, CHA. 9. 547. 4.H2, CHA. 9. 547. 4.H3; CHA.9.547.4.H4, CHA.9.547.4.H4(S241P), CHA. 9. 547. 4.vhCDR1, CHA. 9. 547. 4.vhCDR2, CHA. 9. 547. 4.vhCDR3, CHA. 9. 547. 4.vlCDR1, CHA. 9. 547. 4.vlCDR2 and CHA. 9. 547. 4.vhCDR3;

CHA.9.547.6, CHA. 9. 547. 6 VH, CHA. 9. 547. 6.VL, CHA. 9. 547. 6.HC, CHA. 9. 547. 6.LC, CHA. 9. 547. 6.H1, CHA. 9. 547. 6.H2, CHA. 9. 547. 6.H3; CHA.9.547.6.H4, CHA.9.547.6.H4(S241P), CHA. 9. 547. 6.vhCDR1, CHA. 9. 547. 6.vhCDR2, CHA. 9. 547. 6.vhCDR3, CHA. 9. 547. 6.vlCDR1, CHA. 9. 547. 6.vlCDR2 and CHA. 9. 547. 6.vhCDR3;

CHA.9.547.7, CHA. 9. 547. 7VH, CHA. 9. 547. 7.VL, CHA. 9. 547. 7.HC, CHA. 9. 547. 7.LC, CHA. 9. 547. 7.H1, CHA. 9. 547. 7.H2, CHA. 9. 547. 7.H3; CHA.9.547.7.H4,

CHA.9.547.7.H4(S241P), CHA. 9. 547. 7.vhCDR1, CHA. 9. 547. 7.vhCDR2, CHA. 9. 547. 7.vhCDR3, CHA. 9. 547. 7.vlCDR1, CHA. 9. 547. 7.vlCDR2 and CHA. 9. 547. 7.vhCDR3;

CHA.9.547.8, CHA. 9. 547. 8VH, CHA. 9. 547. 8.VL, CHA. 9. 547. 8.HC, CHA.9.547.8.LC, CHA. 9. 547. 8.H1, CHA. 9. 547. 8.H2, CHA. 9. 547. 8.H3; CHA.9.547.8.H4, CHA.9.547.8.H4(S241P), CHA. 9. 547. 8.vhCDR1, CHA. 9. 547. 8.vhCDR2, CHA. 9. 547. 8.vhCDR3, CHA. 9. 547. 8.vlCDR1, CHA. 9. 547. 8.vlCDR2 and CHA. 9. 547. 8.vhCDR3;

CHA.9.547.9, CHA.9.547.9, CHA.9.547.9VH, CHA.9.547.9.VL, CHA.9. 547.9.HC, CHA.9.547.9.LC, CHA.9.547.9.H1, CHA.9.547.9.H2, CHA.9.547.9.H3; CHA.9.547.9.H4, CHA.9.547.9.H4, CHA.9.547.9.H4(S241P), CHA.9.547.9.H4(S241P), CHA.9.547.9.vhCDR1, CHA.9.547.9.vhCDR2, CHA.9.547.9.vhCDR3, CHA.9.547.9.vlCDR1, CHA.9.547.9.vlCDR2 and CHA.9.547.9.vhCDR3;

CHA.9.547.13, CHA.9.547.13, CHA.9.547. 13VH, CHA.9. 547.13.VL, CHA.9. 547.13.HC, CHA. 9.547.13.LC, CHA. 9.547.13.H1, CHA.9.547.13.H2, CHA.9. 547.13.H3; CHA.9.547.13.H4, CHA.9.547.13.H4, CHA.9.547.13.H4(S241P), CHA.9.547.13.H4(S241P), CHA. 9. 547.13.vhCDR1, CHA.9.547.13.vhCDR2, CHA.9.547. 13.vhCDR3, CHA. 9. 547.13.vlCDR1, CHA. 9. 547.13.vlCDR2 and CHA. 9. 547. 13.vhCDR3;

CHA.9.541.1, CHA. 9. 541.1.VH, CHA. 9. 541.1.VL, CHA. 9. 541.1.HC, CHA. 9. 541.1.LC, CHA. 9. 541.1.H1, CHA. 9. 541.1.H2, CHA. 9. 541.1.H3; CHA.9.541.1.H4, CHA.9.541.1.H4(S241P), CHA. 9. 541.1.vhCDR1, CHA. 9. 541.1.vhCDR2, CHA. 9. 541.1.vhCDR3, CHA. 9. 541.1.vlCDR1, CHA. 9. 541.1.vlCDR2 and CHA. 9.541.1.vhCDR3;

CHA.9.541.3, CHA. 9. 541. 3.VH, CHA. 9. 541. 3.VL, CHA. 9. 541. 3.HC, CHA. 9. 541. 3.LC, CHA. 9. 541. 3.H1, CHA. 9. 541. 3.H2, CHA. 9. 541. 3.H3; CHA.9.541.3.H4, CHA.9.541.3.H4(S241P), CHA. 9. 541. 3.vhCDR1, CHA. 9. 541. 3.vhCDR2, CHA. 9. 541. 3.vhCDR3, CHA. 9. 541. 3.vlCDR1, CHA. 9. 541. 3.vlCDR2 and CHA. 9.541. 3.vhCDR3;

CHA.9.541.4, CHA. 9. 541.4.VH, CHA. 9. 541. 4.VL, CHA. 9. 541. 4.HC, CHA. 9. 541. 4.LC, CHA. 9. 541. 4.H1, CHA. 9. 541. 4.H2, CHA. 9. 541. 4.H3; CHA.9.541.4.H4, CHA.9.541.4.H4(S241P), CHA. 9. 541. 4.vhCDR1, CHA. 9. 541. 4.vhCDR2, CHA. 9. 541. 4.vhCDR3, CHA. 9. 541. 4.vlCDR1, CHA. 9. 541. 4.vlCDR2 and CHA. 9.541. 4.vhCDR3;

CHA.9.541.5, CHA. 9. 541. 5.VH, CHA. 9. 541. 5.VL, CHA. 9. 541. 5.HC, CHA. 9. 541. 5.LC, CHA. 9. 541. 5.H1, CHA. 9. 541. 5.H2, CHA. 9. 541. 5.H3; CHA.9.541.5.H4, CHA.9.541.5.H4(S241P), CHA. 9. 541. 5.vhCDR1, CHA. 9. 541. 5.vhCDR2, CHA. 9. 541. 5.vhCDR3, CHA. 9. 541. 5.vlCDR1, CHA. 9. 541. 5.vlCDR2 and CHA. 9.541. 5.vhCDR3;

CHA.9.541.6, CHA. 9. 541. 6.VH, CHA. 9. 541. 6.VL, CHA. 9. 541. 6.HC, CHA. 9. 541. 6.LC, CHA. 9. 541. 6.H1, CHA. 9. 541. 6.H2, CHA. 9. 541.6.H3; CHA.9.541.6.H4, CHA.9.541.6.H4(S241P), CHA. 9. 541. 6.vhCDR1, CHA. 9. 541. 6.vhCDR2, CHA. 9. 541. 6.vhCDR3, CHA. 9. 541. 6.vlCDR1, CHA. 9. 541. 6.vlCDR2 and CHA. 9.541. 6.vhCDR3;

CHA.9.541.7, CHA. 9. 541. 7.VH, CHA. 9. 541. 7.VL, CHA. 9. 541. 7.HC, CHA. 9. 541. 7.LC, CHA. 9. 541. 7.H1, CHA. 9. 541. 7.H2, CHA. 9. 541. 7.H3; CHA.9.541.7.H4, CHA.9.541.7.H4(S241P), CHA. 9. 541. 7.vhCDR1, CHA. 9. 541. 7.vhCDR2, CHA. 9. 541. 7.vhCDR3, CHA. 9. 541. 7.vlCDR1, CHA. 9. 541. 7.vlCDR2 and CHA. 9.541. 7.vhCDR3; and

CHA.9.541.8, CHA. 9. 541. 8.VH, CHA. 9. 541. 8.VL, CHA. 9. 541. 8.HC, CHA. 9. 541. 8.LC, CHA. 9. 541. 8.H1, CHA. 9. 541. 8.H2, CHA. 9. 541. 8.H3; CHA.9.541.8.H4, CHA.9.541.8.H4(S241P); CHA. 9. 541. 8vhCDR1, CHA. 9. 541. 8.vhCDR2, CHA. 9. 541. 8.vhCDR3, CHA. 9. 541. 8.vlCDR1, CHA. 9. 541. 8.vlCDR2 and CHA. 9.541. 8.vhCDR3.

[00369] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00370] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00371] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00372] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00373] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-1 antibody is nivolumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00374] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PD-1 antibody is nivolumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00375] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-1 antibody is nivolumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00376] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the PD-1 antibody is nivolumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00377] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-1 antibody is cemiplimab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00378] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PD-1 antibody is cemiplimab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00379] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-1 antibody is cemiplimab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00380] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the PD-1 antibody is cemiplimab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00381] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00382] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-1 antibody is pembrolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00383] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-1 antibody is nivolumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00384] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-1 antibody is nivolumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00385] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-1 antibody is cemiplimab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00386] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-1 antibody is cemiplimab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00387] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00388] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00389] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00390] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00391] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00392] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00393] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00394] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is pembrolizumab.

[00395] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00396] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00397] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00398] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00399] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00400] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00401] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00402] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is SHR-1210.

[00403] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00404] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00405] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00406] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00407] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00408] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00409] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00410] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is IBI308.

[00411] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00412] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00413] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00414] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00415] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00416] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00417] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00418] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is BGB-A317.

[00419] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00420] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00421] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00422] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00423] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00424] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00425] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00426] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is an anti-PD-1 antibody as recited in U.S. Patent Publication No. 2017/0081409.

[00427] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00428] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00429] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00430] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00431] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00432] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00433] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00434] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-1 antibody is cemiplimab.

[00435] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00436] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P the anti-PD-L1 antibody is atezolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00437] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00438] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00439] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00440] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00441] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00442] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P the anti-PD-L1 antibody is avelumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00443] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00444] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P the anti-PD-L1 antibody is durvalumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00445] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00446] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-PVRIG antibody is one of the above and/or from Figure 5 or 63.

[00447] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00448] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00449] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00450] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is atezolizumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00451] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00452] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00453] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00454] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is avelumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00455] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00456] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00457] In some embodiments, the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00458] In some embodiments, the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), the anti-PD-L1 antibody is durvalumab, and the anti-TIGIT antibody one of the above and/or from Figure 3.

[00459] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00460] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00461] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00462] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00463] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00464] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00465] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00466] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is atezolizumab.

[00467] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00468] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00469] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00470] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00471] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00472] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00473] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00474] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is avelumab.

[00475] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00476] In some embodiments, the anti-TIGIT antibody is CPA.9.083.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00477] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00478] In some embodiments, the anti-TIGIT antibody is CPA.9.086.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00479] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00480] In some embodiments, the anti-TIGIT antibody is CHA.9.547.7.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00481] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.538.1.2.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

[00482] In some embodiments, the anti-TIGIT antibody is CHA.9.547.13.H4(S241P), the anti-PVRIG antibody is CHA.7.518.1.H4(S241P), and the anti-PD-L1 antibody is durvalumab.

B. Biomarker Analysis

[00483] As shown herein, the selection of the combination therapy to administer can be done using an evaluation of the expression of particular biomarkers from tumor biopsy. That is, by taking a biopsy from a tumor sample of a patient and testing for the presence and levels of certain proteins using protein staining and sorting, a suitable therapy can be chosen. As shown in Example 2, cells from tumors can be screened to identify immune and non-immune cell populations, and then the immune cell populations assessed for the levels of a number of biomarkers including PD-1, PD-L1, PVRIG, PVR, PVRL2 and TIGIT, including by examining both ligand and antigen levels.

[00484] Thus, for example, to identify immune cell populations, antibodies to one or more of CD45, CD3, CD8, CD33, CD25, CD127, CD14, CD4 and CD56 can be assessed to categorize the cell populations in the tumor sample as shown below in Table 1:

Cell Subset Name	Gating Markers
$CD4^+$ T cells	$CD45^+CD3^+CD14^-CD4^+$
$CD8^+$ T cells	$CD45^+CD3^+CD14^-CD8^+$
$CD4^-CD8^-$ T cells	$CD45^+CD3^+CD14^-CD4^-CD8^-$
NK cells	$CD45^+CD3^-CD14^-CD56^+$
Monocytes	$CD45^+CD3^-CD14^+$
mDCs	$CD45^+CD3^-CD14^-CD56^-CD33^{hi}$
pDCs	$CD45^+CD3^-CD14^-CD56^-CD33^{mid}$
$CD45^-$ cells	$CD45^-$

[00485] Several of these cell types are then assessed for expression of one or more of PD-1, PD-L1, PVRIG, PVR, PVRL2 and TIGIT, generally using labeled antibodies and

scored. If the percentage of PD-L1 positive tumor cells or immune cells is greater than 1% (>1%) compared to the same tumor cells stained with antibody relevant isotype control antibody for the antibodies used, then a triple combination of anti-TIGIT, anti-PVRIG and anti-PD1 antibodies should be administered. Whereas, patients with a frequency of PD-L1 positive tumor cells or immune cells below 1% (<1%) compared to the isotype control should be administered a double combination of anti-TIGIT and anti-PVRIG antibodies.

1. Combination Therapy of Anti-TIGIT, Anti-PVRIG and Anti-PD-1 Antibodies

[00486] In some embodiments, once the immune cells from the tumor have been optionally tested for expression of at least one cell surface marker selected from PD-1, PD-L1, PVRIG, PVR, PVRL2 and TIGIT, therapeutic decisions can be made. In the case where the expression of PD-L1 positive tumor cells or immune cells is >1%, the patient can be administered a triple combination of anti-TIGIT, anti-PVRIG and anti-PD-1 antibodies as outlined herein.

[00487] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab.

[00488] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab.

[00489] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P) and pembrolizumab.

[00490] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-

PVRIG antibody CHA.7.538.1.2 and pembrolizumab. In a particular embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab.

[00491] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab.

[00492] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab.

[00493] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab.

[00494] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab.

[00495] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab.

[00496] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab.

[00497] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-

PVRIG antibody CHA.7.518.1 and nivolumab. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P) and nivolumab.

[00498] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab. In a particular embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab.

[00499] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab.

[00500] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab.

[00501] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab.

[00502] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab.

[00503] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and cemiplimab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and cemiplimab.

[00504] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-

PVRIG antibody CHA.7.538.1.2 and cemiplimab. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and cemiplimab.

[00505] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and cemiplimab. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P) and cemiplimab.

[00506] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and cemiplimab. In a particular embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and cemiplimab.

[00507] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and cemiplimab. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P) and cemiplimab.

[00508] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and cemiplimab. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and cemiplimab.

[00509] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and cemiplimab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and cemiplimab.

[00510] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and cemiplimab. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and cemiplimab.

[00511]

2. Combination Therapy of Anti-TIGIT and Anti-PVRIG Antibodies

[00512] Similarly, once the once the immune cells from the tumor have been tested for expression of at least one cell surface marker selected from PD-1, PD-L1, PVRIG, PVR, PVRL2 and TIGIT, therapeutic decisions can be made. In the case where the expression of PD-L1 positive tumor cells or immune cells is <1%, the patient can be administered a double combination of anti-TIGIT and anti-PVRIG antibodies as outlined herein.

[00513] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P).

[00514] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P).

[00515] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P).

[00516] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2. In a particular embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P).

[00517] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P).

[00518] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P).

[00519] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P).

[00520] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P).

[00521] In one embodiment, the invention provides combinations of the anti-TIGIT antibodies of the invention and anti-PD-1 antibodies. In one embodiment, the invention provides combinations of the anti-TIGIT antibodies of the invention and anti-PD-L1 antibodies.

[00522] In one embodiment, a biopsy is taken from a tumor from a patient with cancer, and dissociated as is known in the art for FACS analysis. The cells are stained with labeled antibodies to (1) TIGIT (for example using any described herein or others in the art such as MBSA43); (2) PD-1 (for example using those known in the art including EH12.2H7, Keytruda®, Opdivo®, Cemiplimab, etc.); (3) PD-L1 (for example using those known in the art such as BM-1, atezolizumab, avelumab, and durvalumab, outlined herein) and (4) PVR (for example using those known in the art such as SKII.4); and (5) a relevant isotype control antibody for the antibodies used. FACS is done, and for each receptor, the percentage of the cells expressing the receptor relative to the control antibody is calculated. If the percentage of positive cells for TIGIT, PD-1, PD-1 and PVR is $\geq$ 1% for all 4 receptors, then the patient is treated with antibodies to TIGIT and PD-1 as outlined herein.

[00523] In one embodiment, a biopsy is taken from a tumor from a patient with cancer, and dissociated as is known in the art for FACS analysis. The cells are stained with labeled antibodies to (1) PVRIG (generally using CHA.7.518.1H4(S241P), for example, although any outlined in WO2016/134333 (specifically including any that bind, even if they don't block) or WO2017/041004) can be used); (2) PD-1 (for example using those known in the art including EH12.2H7, Keytruda®, Opdivo®, Cemiplimab, etc.); (3) PD-L1 (for example using those known in the art such as BM-1, atezolizumab, avelumab, and

durvalumab, outlined herein) and (4) PVRL2 (for example using those known in the art such as TX11); and (5) a relevant isotype control antibody for the antibodies used. FACS is done, and for each receptor, the percentage of the cells expressing the receptor relative to the control antibody is calculated. If the percentage of positive cells for PVRIG, PD-1, PD-1 and PVRL2 is $\geq$ 1% for all 4 receptors, then the patient is treated with antibodies to PVRIG and PD-1 as outlined herein.

[00524] In one embodiment, a biopsy is taken from a tumor from a patient with cancer, and dissociated as is known in the art for FACS analysis. The cells are stained with labeled antibodies to (1) PVRIG (generally using CHA.7.518.1H4(S241P), for example, although any outlined in WO2016/134333 (specifically including any that bind, even if they don't block) or WO2017/041004) can be used); (2) TIGIT (for example using any described herein or others in the art such as MBSA43); (3) PVR (for example using those known in the art such as SKII.4) and (4) PVRL2 (for example using those known in the art such as TX11); and (5) a relevant isotype control antibody for the antibodies used. FACS is done, and for each receptor, the percentage of the cells expressing the receptor relative to the control antibody is calculated. If the percentage of positive cells for PVRIG, TIGIT, PVR and PVRL2 is $\geq$ 1% for all 4 receptors, then the patient is treated with antibodies to PVRIG and TIGIT. Preferred combinations in this regard are CHA.7.518.1.H4(S241P) and CPA.9.086.

[00525] In one embodiment, a biopsy is taken from a tumor from a patient with cancer, and dissociated as is known in the art for FACS analysis. The cells are stained with labeled antibodies to (1) PVRIG (generally using CHA.7.518.1H4(S241P), for example, although any outlined in WO2016/134333 (specifically including any that bind, even if they don't block) or WO2017/041004) can be used); (2) TIGIT (for example using any described herein or others in the art such as MBSA43); (3) PVR (for example using those known in the art such as SKII.4) and (4) PVRL2 (for example using those known in the art such as TX11); (5) PD-1 (for example using those known in the art including EH12.2H7, Keytruda®, Opdivo®, Cemiplimab, etc.); and (6) a relevant isotype control antibody for the antibodies used. FACS is done, and for each receptor, the percentage of the cells expressing the receptor relative to the control antibody is calculated. If the percentage of positive cells for PVRIG, TIGIT, PVR, PVRL2 and PD-1 is $\geq$ 1% for all 5 receptors, then the patient is treated

with antibodies to PVRIG, TIGIT, and PD-1. Preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and EH12.2H7. Other preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and Keytruda®. Yet other preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and Opdivo®.

[00526] In one embodiment, a biopsy is taken from a tumor from a patient with cancer, and dissociated as is known in the art for FACS analysis. The cells are stained with labeled antibodies to (1) PVRIG (generally using CHA.7.518.1H4(S241P), for example, although any outlined in WO2016/134333 (specifically including any that bind, even if they don't block) or WO2017/041004) can be used); (2) TIGIT (for example using any described herein or others in the art such as MBSA43); ((3) PD-L1 (for example using those known in the art such as BM-1, atezolizumab, avelumab, and durvalumab, outlined herein) and (4) PVR (for example using those known in the art such as SKII.4); (5) PD-1 (for example using those known in the art including EH12.2H7, Keytruda®, Opdivo®, Cemiplimab, etc.); and (6) a relevant isotype control antibody for the antibodies used. FACS is done, and for each receptor, the percentage of the cells expressing the receptor relative to the control antibody is calculated. If the percentage of positive cells for PVRIG, TIGIT, PD-L1, PVR and PD-1 is $\geq$ 1% for all 5 receptors, then the patient is treated with antibodies to PVRIG, TIGIT, and PD-1. Preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and EH12.2H7. Other preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and Keytruda®. Yet other preferred combinations in this regard are CHA.7.518.1.H4(S241P), CPA.9.086, and Opdivo®.

3. Combination Therapy of Anti-TIGIT and Anti-PVRIG Antibodies with PD-1 antibodies for Refractory patients

[00527] In some embodiments, the treatment includes a combination of anti-TIGIT antibodies, anti-PVRIG antibodies, and anti-PD-1 antibodies for targeting tumor cells with high PD-L1 expression. In some embodiments, the treatment includes a combination of anti-TIGIT antibodies, anti-PVRIG antibodies, and anti-PD-1 antibodies for use in a patient whose tumors express PD-L1. In some embodiments, the treatment includes a combination

of anti-TIGIT antibodies, anti-PVRIG antibodies, and anti-PD-1 antibodies for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In some embodiments, the treatment includes a combination of anti-TIGIT antibodies, anti-PVRIG antibodies, and anti-PD-1 antibodies for use in a cancer patient whose tumor expresses PD-L1 and who is refractory to anti-PD-1 therapeutics.

[00528] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00529] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizuma for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics b. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00530] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00531] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular

embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00532] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00533] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00534] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00535] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and

pembrolizumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00536] Accordingly, in one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00537] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.083 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.083.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00538] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.086.H4(S241P is combined with CHA.7.518.1.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00539] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CPA.9.086 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CPA.9.086.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00540] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.7H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00541] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.7 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.7.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00542] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.518.1 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.518.1.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00543] In one embodiment, antibodies containing the CDR sets from the anti-TIGIT antibody CHA.9.547.13 are combined with antibodies containing the CDR sets from the anti-PVRIG antibody CHA.7.538.1.2 and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics. In a particular embodiment, CHA.9.547.13.H4(S241P) is combined with CHA.7.538.1.2.H4(S241P) and nivolumab for use in a cancer patient whose tumor expresses PD-L1 and/or who is refractory to anti-PD-1 therapeutics.

[00544] In some embodiments, the anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3. In

some embodiments, the anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63. In some embodiments, the anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

[00545]

4. Assessment of Treatment

[00546] Generally, the antibodies of the invention, alone or in combination (PVRIG with PD-1, TIGIT with PD-1 or TIGIT with PVRIG, and/or PVRIG with both TIGIT and PD-1) are administered to patients with cancer, and efficacy is assessed, in a number of ways as described herein. Thus, while standard assays of efficacy can be run, such as cancer load, size of tumor, evaluation of presence or extent of metastasis, etc., immuno-oncology treatments can be assessed on the basis of immune status evaluations as well. This can be done in a number of ways, including both in vitro and in vivo assays. For example, evaluation of changes in immune status (e.g. presence of ICOS+ CD4+ T cells following ipi treatment) along with "old fashioned" measurements such as tumor burden, size, invasiveness, LN involvement, metastasis, etc. can be done. Thus, any or all of the following can be evaluated: the inhibitory effects of PVRIG on $CD4^+$ T cell activation or proliferation, $CD8^+$ T (CTL) cell activation or proliferation, $CD8^+$ T cell-mediated cytotoxic activity and/or CTL mediated cell depletion, NK cell activity and NK mediated cell depletion, the potentiating effects of PVRIG on Treg cell differentiation and proliferation and Treg- or myeloid derived suppressor cell (MDSC)- mediated immunosuppression or immune tolerance, and/or the effects of PVRIG on proinflammatory cytokine production by immune cells, e.g., IL-2, IFN-ɣ or TNF-α production by T or other immune cells.

[00547] In some embodiments, assessment of treatment is done by evaluating immune cell proliferation, using for example, CFSE dilution method, Ki67 intracellular staining of immune effector cells, and 3H-Thymidine incorporation method.

[00548] In some embodiments, assessment of treatment is done by evaluating the increase in gene expression or increased protein levels of activation-associated markers, including one or more of: CD25, CD69, CD137, ICOS, PD1, GITR, OX40, and cell degranulation measured by surface expression of CD107A.

[00549] In some embodiments, the assessment of treatment is done by assessing the amount of T cell proliferation in the absence of treatment, for example prior to administration of the antibodies of the invention. If, after administration, the patient has an increase in T cell proliferation, e.g. a subset of the patient's T cells are proliferating, this is an indication that the T cells were activated.

[00550] Similarly, assessment of treatment with the antibodies of the invention can be done by measuring the patient's IFN-γ levels prior to administration and post-administration to assess efficacy of treatment. This may be done within hours or days.

[00551] In general, gene expression assays are done as is known in the art. See for example Goodkind et al., Computers and Chem. Eng. 29(3):589 (2005), Han et al., Bioinform. Biol. Insights 11/15/15 9(Suppl. 1):29-46, Campo et al., Nod. Pathol. 2013 Jan; 26 suppl. 1:S97-S110, the gene expression measurement techniques of which are expressly incorporated by reference herein.

[00552] In general, protein expression measurements are also similarly done as is known in the art, see for example, Wang et al., Recent Advances in Capillary Electrophoresis-Based Proteomic Techniques for Biomarker Discovery, Methods. Mol. Biol. 2013:984:1-12; Taylor et al, BioMed Res. Volume 2014, Article ID 361590, 8 pages, Becerk et al., Mutat. Res 2011 June 17:722(2): 171-182, the measurement techniques of which are expressly incorporated herein by reference.

[00553] In some embodiments, assessment of treatment is done by assessing cytotoxic activity measured by target cell viability detection via estimating numerous cell parameters such as enzyme activity (including protease activity), cell membrane permeability, cell adherence, ATP production, co-enzyme production, and nucleotide uptake activity. Specific examples of these assays include, but are not limited to, Trypan Blue or PI staining, ^{51}Cr or ^{35}S release method, LDH activity, MTT and/or WST assays, Calcein-AM assay, Luminescent based assay, and others.

[00554] In some embodiments, assessment of treatment is done by assessing T cell activity measured by cytokine production, measure either intracellularly in culture

supernatant using cytokines including, but not limited to, IFN-γ, TNF-α, GM-CSF, IL-2, IL-6, IL-4, IL-5, IL-10, and/or IL-13 using well known techniques.

[00555] Accordingly, assessment of treatment can be done using assays that evaluate one or more of the following: (i) increases in immune response, (ii) increases in activation of αβ and/or γδ T cells, (iii) increases in cytotoxic T cell activity, (iv) increases in NK and/or NKT cell activity, (v) alleviation of αβ and/or γδ T-cell suppression, (vi) increases in pro-inflammatory cytokine secretion, (vii) increases in IL-2 secretion; (viii) increases in interferon-ɣ production, (ix) increases in Th1 response, (x) decreases in Th2 response, (xi) decreases or eliminates cell number and/or activity of at least one of regulatory T cells (Tregs).

[00556] Assays to measure efficacy

[00557] In some embodiments, T cell activation is assessed using a Mixed Lymphocyte Reaction (MLR) assay as is described in the Examples. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00558] In one embodiment, the signaling pathway assay measures increases or decreases in immune response as measured for an example by phosphorylation or de-phosphorylation of different factors, or by measuring other post translational modifications. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00559] In one embodiment, the signaling pathway assay measures increases or decreases in activation of αβ and/or γδ T cells as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00560] In one embodiment, the signaling pathway assay measures increases or decreases in cytotoxic T cell activity as measured for an example by direct killing of target cells like for an example cancer cells or by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc.

An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00561] In one embodiment, the signaling pathway assay measures increases or decreases in NK and/or NKT cell activity as measured for an example by direct killing of target cells like for an example cancer cells or by cytokine secretion or by changes in expression of activation markers like for an example CD107a, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00562] In one embodiment, the signaling pathway assay measures increases or decreases in $\alpha\beta$ and/or $\gamma\delta$ T-cell suppression, as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00563] In one embodiment, the signaling pathway assay measures increases or decreases in pro-inflammatory cytokine secretion as measured for example by ELISA or by Luminex or by Multiplex bead based methods or by intracellular staining and FACS analysis or by Alispot etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00564] In one embodiment, the signaling pathway assay measures increases or decreases in IL-2 secretion as measured for example by ELISA or by Luminex or by Multiplex bead based methods or by intracellular staining and FACS analysis or by Alispot etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00565] In one embodiment, the signaling pathway assay measures increases or decreases in interferon-ɣ production as measured for example by ELISA or by Luminex or by Multiplex bead based methods or by intracellular staining and FACS analysis or by Alispot etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00566] In one embodiment, the signaling pathway assay measures increases or decreases in Th1 response as measured for an example by cytokine secretion or by changes

in expression of activation markers. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00567] In one embodiment, the signaling pathway assay measures increases or decreases in Th2 response as measured for an example by cytokine secretion or by changes in expression of activation markers. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00568] In one embodiment, the signaling pathway assay measures increases or decreases cell number and/or activity of at least one of regulatory T cells (Tregs), as measured for example by flow cytometry or by IHC. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00569] In one embodiment, the signaling pathway assay measures increases or decreases in M2 macrophages cell numbers, as measured for example by flow cytometry or by IHC. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00570] In one embodiment, the signaling pathway assay measures increases or decreases in M2 macrophage pro-tumorigenic activity, as measured for an example by cytokine secretion or by changes in expression of activation markers. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00571] In one embodiment, the signaling pathway assay measures increases or decreases in N2 neutrophils increase, as measured for example by flow cytometry or by IHC. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00572] In one embodiment, the signaling pathway assay measures increases or decreases in N2 neutrophils pro-tumorigenic activity, as measured for an example by cytokine secretion or by changes in expression of activation markers. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00573] In one embodiment, the signaling pathway assay measures increases or decreases in inhibition of T cell activation, as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00574] In one embodiment, the signaling pathway assay measures increases or decreases in inhibition of CTL activation as measured for an example by direct killing of target cells like for an example cancer cells or by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00575] In one embodiment, the signaling pathway assay measures increases or decreases in $\alpha\beta$ and/or $\gamma\delta$ T cell exhaustion as measured for an example by changes in expression of activation markers. A decrease in response indicates immunostimulatory activity. Appropriate decreases are the same as for increases, outlined below.

[00576] In one embodiment, the signaling pathway assay measures increases or decreases $\alpha\beta$ and/or $\gamma\delta$ T cell response as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00577] In one embodiment, the signaling pathway assay measures increases or decreases in stimulation of antigen-specific memory responses as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD45RA, CCR7 etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00578] In one embodiment, the signaling pathway assay measures increases or decreases in apoptosis or lysis of cancer cells as measured for an example by cytotoxicity assays such as for an example MTT, Cr release, Calcine AM, or by flow cytometry based assays like for an example CFSE dilution or propidium iodide staining etc. An increase in

activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00579] In one embodiment, the signaling pathway assay measures increases or decreases in stimulation of cytotoxic or cytostatic effect on cancer cells. as measured for an example by cytotoxicity assays such as for an example MTT, Cr release, Calcine AM, or by flow cytometry based assays like for an example CFSE dilution or propidium iodide staining etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00580] In one embodiment, the signaling pathway assay measures increases or decreases direct killing of cancer cells as measured for an example by cytotoxicity assays such as for an example MTT, Cr release, Calcine AM, or by flow cytometry based assays like for an example CFSE dilution or propidium iodide staining etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00581] In one embodiment, the signaling pathway assay measures increases or decreases Th17 activity as measured for an example by cytokine secretion or by proliferation or by changes in expression of activation markers. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00582] In one embodiment, the signaling pathway assay measures increases or decreases in induction of complement dependent cytotoxicity and/or antibody dependent cell-mediated cytotoxicity, as measured for an example by cytotoxicity assays such as for an example MTT, Cr release, Calcine AM, or by flow cytometry based assays like for an example CFSE dilution or propidium iodide staining etc. An increase in activity indicates immunostimulatory activity. Appropriate increases in activity are outlined below.

[00583] In one embodiment, T cell activation is measured for an example by direct killing of target cells like for an example cancer cells or by cytokine secretion or by proliferation or by changes in expression of activation markers like for an example CD137, CD107a, PD1, etc. For T-cells, increases in proliferation, cell surface markers of activation (e.g. CD25, CD69, CD137, PD1), cytotoxicity (ability to kill target cells), and cytokine

production (e.g. IL-2, IL-4, IL-6, IFNγ, TNF-α, IL-10, IL-17A) would be indicative of immune modulation that would be consistent with enhanced killing of cancer cells.

[00584] In one embodiment, NK cell activation is measured for example by direct killing of target cells like for an example cancer cells or by cytokine secretion or by changes in expression of activation markers like for an example CD107a, etc. For NK cells, increases in proliferation, cytotoxicity (ability to kill target cells and increases CD107a, granzyme, and perforin expression), cytokine production (e.g. IFNγ and TNF), and cell surface receptor expression (e.g. CD25) would be indicative of immune modulation that would be consistent with enhanced killing of cancer cells.

[00585] In one embodiment, γδ T cell activation is measured for example by cytokine secretion or by proliferation or by changes in expression of activation markers.

[00586] In one embodiment, Th1 cell activation is measured for example by cytokine secretion or by changes in expression of activation markers.

[00587] Appropriate increases in activity or response (or decreases, as appropriate as outlined above), are increases of at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 98 to 99% percent over the signal in either a reference sample or in control samples, for example test samples that do not contain an anti-PVRIG antibody of the invention. Specific increases in activity are depicted in the attached figures. For example, with regard to increases in T cell proliferation, CHA.7.518.1.H4(S241P) shows an increase of about 60% and CHA.7.538.1.2.H4(S241P) shows an increase of 47%; relevant increases are shown in either T cell proliferation or IFN-γ of from about 10 to 70% with from about 20 to 60% also finding use.

[00588] Similarly, increases of at least one-, two-, three-, four- or five-fold as compared to reference or control samples show efficacy.

X. EXEMPLARY EMBODIMENTS

1. A method of treating cancer in a patient comprising:

a) providing a biopsy from said patient comprising tumor cells;

b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;

c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and

d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

2. A method according to claim 1, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

3. A method according to claim 1, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

4. A method according to claim 1, wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

5. A method according to any one of claims 1 to 4, wherein said anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

6. A method according to any one of claims 1 to 5, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

7. A method according to any one of claims 1 to 6, wherein said anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.

8. A method according to any one of claims 1 to 7, wherein said double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P);

CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

9. A method according to any one of claims 1 to 8, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P).

10. A method according to any one of claims 1 to 9, wherein said antibodies are administered simultaneously.

11. A method according to any one of claims 1 to 10, wherein said antibodies are administered sequentially.

12. A method according to any one of claims 1 to 11, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC),

lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, and MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

13. A method according to any one of claims 1 to 12, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

14. A method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-1 antibody.

15. A method according to claim 14, wherein said anti-TIGIT antibody is an antibody chosen from at least oneof CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

16. A method according to claims 14 or 15, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

17. A method according to any one of claims 14, 15, or 16, wherein said anti-PD-1 antibody is an antibody selected from the group consisting of pembrolizumab and nivolumab.

18. A method according to any one of claims 14 to 17, wherein said triple combination therapy comprises the administration of an anti-PD-1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

19. A method according to any one of claims 14 to 18, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and

CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

20. A method according to any one of claims 14 to 19, wherein said antibodies are administered simultaneously.

21. A method according to any one of claims 14 to 20 wherein said antibodies are administered sequentially.

22. A method according to any one of claims 14 to 21, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic

Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

23. A method according to any one of claims 14 to 22, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

24. A pharmaceutical dose kit comprising:

a) a container comprising a unit dosage of an anti-TIGIT antibody; and

b) a container comprising a unit dosage of an anti-PVRIG antibody.

25. A pharmaceutical dose kit comprising:

a) a container comprising a unit dosage of an anti-TIGIT antibody;

b) a container comprising a unit dosage of an anti-PVRIG antibody; and

c) a container comprising an anti-PD-1 antibody.

26. A method according to claims 24 or 25, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

27. A method according to claims 24 or 25, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

28. A method according to claims 24 or 25, wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

29. A method comprising:

a) providing a cell population from a tumor sample from a patient;

b) staining said population with labeled antibodies that bind:

i) TIGIT protein;

ii) PVRIG protein;

iii) PVR protein;

iv) PD-1 protein;

v) PD-L1 protein;

vi) PVRL2; and

vii) a relevant isotype control for the antibodies in i)-vi);

c) running fluorescence activated cell sorting (FACS);

d) for each of TIGIT, PVRIG, PVR, PD-1, PVRL2 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody;

wherein if the percentage of positive cells is > 1% for either TIGIT or PVR, and for either PVRIG or PVRL2, and for either PD-1 or PD-L1, proceeding to step e); and

e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

30. A method according to claim 27, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

31. A method according to claim 27, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

32. A method according to claim 27, wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

33. A method according to claims 29, 31, or 32, wherein said TIGIT antibody is CPA.9.086.

34. A method according to claims 29, 30, or 31, wherein said PD-1 antibody is selected from pembrolizumab, cemiplimab, and nivolumab.

35. A method according to claim 29, 30, or 32, wherein said PVRIG antibody is CHA.7.518.1.H4(S241P).

36. A method of treating cancer in a patient comprising:

a) providing a biopsy from said patient comprising tumor cells;

b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;

c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-L1 antibody; and

d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

37. A method according to claim 36, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

38. A method according to claim 36, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

39. A method according to claim 36, wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-L1 antibody described herein, including any of those described in Figure 62.

40. A method according to any one of claims 36 to 39, wherein said anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

41. A method according to any one of claims 36 to 39, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

42. A method according to any one of claims 36 to 41, wherein said anti-PD-L1 antibody is an antibody chosen from at least one of atezolizumab, avelumab, and durvalumab.

43. A method according to any one of claims 36 to 42, wherein said double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

44. A method according to any one of claims 36 to 43, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

45. A method according to any one of claims 36 to 44, wherein said antibodies are administered simultaneously.

46. A method according to any one of claims 36 to 45, wherein said antibodies are administered sequentially.

47. A method according to any one of claims 36 to 46, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

48. A method according to any one of claims 36 to 47, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

49. A method of treating cancer in a patient comprising administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody, and an anti-PD-L1 antibody.

50. A method according to claim 49, wherein said anti-TIGIT antibody is an antibody chosen from at least oneof CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

51. A method according to claims 49 or 50, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

52. A method according to any one of claims 49, 50, or 51, wherein said anti-PD-L1 antibody is an antibody selected from the group consisting of atezolizumab, avelumab, and durvalumab.

53. A method according to any one of claims 49 to 52, wherein said triple combination therapy comprises the administration of an anti-PD-L1 antibody in combination with a double-combination therapy chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

54. A method according to any one of claims 49 to 53, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), atezolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, avelumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), avelumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), durvalumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, durvalumab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), durvalumab and CHA.7.538.1.2.H4(S241P).

55. A method according to any one of claims 49 to 54, wherein said antibodies are administered simultaneously.

56. A method according to any one of claims 49 to 54, wherein said antibodies are administered sequentially.

57. A method according to any one of claims 49 to 56, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

58. A method according to any one of claims 49 to 57, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), and Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

EXAMPLES

EXAMPLE 1: FUNCTIONAL ASSAYS

[00589] The purpose of this study was to characterize the functional activity CHA.7.518.1.H4(S241P) on human T cell function either alone or in combination with an anti-TIGIT and/or anti-PD-1 antibody in primary in vitro cell-based assays. We demonstrate that CHA.7.518.1.H4(S241P) enhanced cytokine production of viral antigen-specific CD8 T cells utilized as a model surrogate antigen to study CD8 T cell responses. Combination of CHA.7.518.1.H4(S241P) with anti-TIGIT antibody lead to an additive or, in some conditions, synergistic increase in T cell function. We also performed a triple combination of CHA.7.518.1.H4(S241P), anti-TIGIT, and anti-PD-1 and observed the

greatest increase in T cell function co-cultured with PD-L1hi target tumor cells using the triple combination as compared to the double combination or the individual antibody. In a co-culture with PD-L1lo target tumor cells, the triple combination of CHA.7.518.1.H4(S241P), anti-TIGIT, anti-PD-1 did not further enhance T cell function compared to CHA.7.518.1.H4(S241P) and anti-TIGIT double combination, suggesting that CHA.7.518.1.H4(S241P) and anti-TIGIT treatment may be effective in patients who have low or negative PD-L1 expression. Taken together, we demonstrate an effect of CHA.7.518.1.H4(S241P) in enhancing human CD8+ T cell function, either individually or in combination with anti-TIGIT or anti-PD-1.

This report describes the characterization of CHA.7.518.1.H4(S241P), a fully humanized IgG4 anti-PVRIG antibody, in cell based assays. CHA.7.518.1.H4(S241P) binds to PVRIG with high affinity and specificity, and blocks the interaction of PVRIG with PVRL2. In order to understand the effects of CHA.7.518.1.H4(S241P) on T cell function, we examined the effect of CHA.7.518.1.H4(S241P) on cytokines production in an in vitro assay. This assay was designed based on the 2 signal hypothesis of T cell activation: signal 1 comes from the activation of the T cell receptor; signal 2 are immunomodulatory receptors that help to enhance or inhibit the T cell responses. The design of these assays consist of a co-culture of human T cells with a target cell line pulsed with antigen peptide derived from a viral antigen (CMV). This signal provides “signal 1” of T cell activation through the T cell receptor. These target cell lines express endogenous PVRL2, and in this context PVRL2 provides “signal 2” to the T cell.

CMV : Tumor cell line assay

[00590] CMVpp65-reactive T cells were expanded by thawing CMV-reactive donors according to CTL "Thawing Cryopreserved PBMC" protocol and 2e6 cells/ml were resuspended in medium (Gibco) supplemented with 1% glutamax (Gibco), 1% NEAA, penicillin/streptomycin (Gibco), 10% human AB serum (Corning), 1ug/ml CMV peptide, 2ng/ml IL-2 (R&D), and 10ng/ml IL-7 (R&D). PBMCs were cultured for eight days with IL-2 and IL-7 replenished at day three and day six. At Day 8, cells were harvested, and replated in low dose IL-2 (100U/ml) at 2e6/ml in complete RPMI media for 5 days. At day nine, cells

are phenotyped for CD8+T cell purity and CMV tetramer reactivity. Cells were stained with 0.25µL of CD3(clone: OKT)-allophycocyanin seven (APC-Cy7;Biolegend), 0.25ul of CD8 (clone: H1T8a)-Alexafluor 488 (AF488; Biolegend), 0.125µL of CD14 (clone: HCD14), 0.5ul of CD19 (clone:HIBCD14), 0.5ul of CD56 (clone:HCD56)-peridinin chlorophyll protein (PerCP;Biolegend), 1.25ul µL of TIGIT (clone:MBSA43)-allophycocyanin (APC;e-Bioscience) or 1.25 µL of IgG4(In house)-isotype control (APC:Biolegend), 1.25ul of CHA.7.518.1.H4(S241P)- allophycocyanin (In house), or 1.25 µL of IgG4-APC isotype control (In house) and 0.5ul of PD-1 (clone: EH12.2H7)-Brilliant Violet 421 (BV421;Biolegend) or 1.25ul of IgG1 (clone: MOPC21)-Brilliant Violet 421 (BV421;Biolegend). To assess the frequency of tetramer-reactive $CD8^+$ T cells, unlabeled PBMCs were stained after cultivation) with 10 µL of iTAg Tetramer - HLA-A*02:01 CMV pp65 (NLVPMVATV)-phycoerythrin (PE, MBL-BION) for 30 min at room temperature. Cells were washed with PBS/BSA/azide solution and resuspended in buffer). Data was acquired using a Fortessa, and analyzed using FlowJo (Treestar) and Prism (Graphpad) software.

[00591] The target cells used in the co-culture assay were Panc.05.4 and Colo205 cell lines (ATCC). These cell lines were stained with 1.25ul of PVR(SKII.4)-phycoerythrin (PE,Biolegend), 1.25ul of PVRL2 (TX31)-peridinin chlorophyll protein (PerCP5.5;Biolegend), 2.5ul PD-L1(29E.2A3)-Brilliant Violet 785 (BV785;Biolegend) and 1.25 ul of HLA-A2 (BB7.2)- allophycocyanin(APC; Biolegend) expression. 1.25ul of the corresponding isotype for each flurophore was also assessed (MOPC-21).

[00592] To setup the co-culture, tumor cell lines were harvested from culture and tumor cell lines pulsed with CMV peptide (Anaspec) for 1 hour at 37°C with periodic mixing. After the incubation, the target cells were thoroughly washed, counted, and re-suspended in complete RPMI medium. The assays were set up with a 1:1 ratio of T cells (100,000) to target cells (100,000). The target cells, T cells and 10ug/ml of each antibody treatment were added together in a 96-well U bottom plate (Costar), and incubated for 24hrs at 37°C. The antibody treatments include, CHA.7.518.1.H4(S241P) hIgG4, anti-TIGIT hIgG4 (Benchmark 26, Compugen), Anti-PD-1 hIgG4 (Benchmark 3, Compugen) and a human IgG4 isotype control (Compugen). In order to match the total antibody

concentration across all individual and combination groups, additional human IgG4 isotype control was added in to single or double combination conditions to a final total antibody concentration of 30ug/ml. After the 24hr incubation period, co-culture supernatants were analyzed for secreted cytokines, including IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-17A, IL-17F, IL-21, IL-22, TNF-α, and/or IFN-γ, with the cytometric bead array (CBA) human Th1/Th2/Th17 cytokine kit (BD Biosciences), or with the LEGENDplex™ Human Th cytokine kit (BioLegend). Data was acquired using a Fortessa, and analyzed using FlowJo (Treestar) and Prism (Graphpad) software

1. Results and Discussion

a. CMV T cell assay: CMVpp65 reactive T cells express PVRIG, TIGIT, and PD1

[00593] Human cytomegalovirus (CMV) is a widespread persistent β-herpesvirus that infects a high percentage of the population, with slightly lower seroprevalance in Western Europe and the United States (Cannon MJ et al. 2010). The immune system of patients with chronic viral infections or cancer is often impaired in function and is unable to mount an effective response against the virus or to recognize and eliminate malignant cells. In these patients, expression of inhibitory receptors increase and this was found to be associated with T-cell dysfunction. Thus, the upregulation of negative checkpoints receptors may serve as potential targets for the reversal of T cell exhaustion. CD8 T cells specific to CMV pp65 protein have been well characterized and these CMV specific T cells can be used to study the role of modulatory receptors on T cells.

[00594] Stimulation of HLA-A2+ donor PBMCs using CMV pp65 peptide, IL-2 and IL-7 resulted in a strong expansion of CMV pp65-specific T cells to purities ranging from 50-90% as determined by tetramer staining. Figure 8A shows the percentage of CMV pp65 specific T cells from several donors after expansion. The surface expression of PVRIG, TIGIT and PD-1 on T cells was assessed from CMV+ donors, and compared to respective isotype for receptor expression by flow cytometry. CMV pp65 specific T cells expressed PVRIG (median gMFI ratio: 7), TIGIT (median gMFI ratio: 37), and PD1 (median gMFI ratio: 2) on day 9 of activation (Figure 8B).

[00595] We further assessed the kinetics of expression of PVRIG, TIGIT, and PD1 relative to the expansion of CMV pp65 specific T cells in a time course. For each donor, the frequency of CMVpp65 reactive CD8+ T cells are plotted over time (Figure 9A). A significant expansion in the frequency of CMVpp65 reactive T cells (range: 50-97%) was observed in all donors, with donor 198 initially expanding at day three (Day 3 CMV + percentage: 85.7%). However, donor 198 had a loss of CMV tetramer expression at day 6 (Day 6 CMV + percentage: 50.4%). PVRIG, TIGIT and PD-1 expression of CMV-specific $CD8^+$ T cells was assessed by flow cytometry over the twelve-day time course. In donor 4, donor 198 and donor 210, TIGIT expression among CMVpp65 specific $CD8^+$ T cells increased during the twelve-day expansion period (mean gMFIr expression of three donors TIGIT expression of three donors, Day 0 gMFIr: 1.2, Day 12 gMFIr: 47) (Figure 9B). PVRIG expression of CMV+T cells also increased (mean gMFI PVRIG of three donors, Day 0 gMFIr: 0.92, Day 12 gMFIr: 8.6) (Figure 6C). PD-1 expression was also assessed, and we observed minimal induction of expression (mean gMFIr PD-1, Day 0 gMFI: 0.93, Day 12 gMFI: 2) (Figure 9C).

b. CHA.7.518.1.H4(S241P), anti-TIGIT, and anti-PD1 antibodies enhanced IFN-γ secretion

[00596] With the rationale that the upregulation of TIGIT, PVRIG, and PD-1 expression by CD8 CMV cells correlates with T cell dysfunction, we aimed to evaluate the effects of PVRIG, TIGIT, and PD-1 blockade on the capacity for pro-inflammatory cytokine production. CMVpp65 reactive T cells from 2 donors were co-cultured with CMV peptide loaded PD-L1hi (Panc04.05) and PD-L1lo (Colo205) tumor cell lines prior to flow cytometric analysis of cytokine production (Figure 10).

[00597] In the Panc.04.05 (PD-L1hi) co-culture, we observed that anti-TIGIT single blockade increased IFN-γ production compared with IgG control mAbs, whereas CHA.7.518.1.H4(S241P) or anti-PD-1 had minimal effect (Figure 11). Dual anti-TIGIT and CHA.7.518.1.H4(S241P) blockade synergistically and consistently increased the cytokine production of CD8+ T cells as compared with CHA.7.518.1.H4(S241P) or anti-TIGIT single blockade alone. In donor 4, a further increase in IFN-γ was observed with a triple combination of CHA.7.518.1.H4(S241P), anti-TIGIT, and anti-PD-1, suggesting that when

PD-L1, PVR, and PVRL2 are expressed at high levels on tumor cells, the largest increase in T cell activation is achieved with a triple combination. In Colo205 (PD-L1lo) co-cultures, anti-TIGIT blockade alone increased IFN-γ secretion whereas CHA.7.518.1.H4(S241P) or anti-PD1 antibody had minimal effect, similar to the results with Panc.04.05 co-culture. Also similar to the Panc.04.05 co-culture, dual blockade of anti-TIGIT and CHA.7.518.1.H4(S241P) also synergistically increased IFN-γ as compared anti-TIGIT, anti-PD-1, or CHA.7.518.1.H4(S241P) alone, and to a greater magnitude of either CHA.7.518.1.H4(S241P) or anti-TIGIT in combination with anti-PD-1. In contrast to Panc.04.05 (PD-L1hi), the triple combination condition for Donor 4 was not better than the dual combination of CHA.7.518.1.H4(S241P) and anti-TIGIT in the Colo205 co-culture (PD-L1lo), suggesting when PVR and PVRL2 are expressed at high levels and PD-L1 at a low level on tumor cells, double combination CHA.7.518.1.H4(S241P) and anti-TIGIT led to the greatest increase of IFN-γ expression. These findings demonstrate that TIGIT and PVRIG blockade were sufficient to enhance CD8+ T cell responses in PD-L1lo tumors and that a triple combination led to the greatest increase in T cell activation in PD-L1hi tumors.

c. SUMMARY

[00598] Human anti-CMV T cell responses are utilized as an in-vitro antigen-specific method to assess checkpoint inhibitor antibody functional capability. We observed that co-blockade of TIGIT and CHA.7.518.1.H4(S241P) lead to a greater restoration of T cell function compared with a single antibody blockade, suggesting that disrupting the TIGIT and PVRIG pathway may be more important that disrupting the PD1 pathway in CD8-tumor cell co-cultures. Furthermore, we observed that triple blockade using antibodies to PD-1, TIGIT, and PVRIG can result in the greatest increase in IFN-γ when PD-L1 positive tumor cells or immune cells are >1%, which is equivalent to PD-L1 high expression levels. These findings demonstrate that TIGIT and PVRIG blockade were sufficient to enhance CD8+ T cell responses in PD-L1lo tumors and that a triple combination led to the greatest increase in T cell activation in PD-L1hi tumors.

[00599] The present invention provides methods comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein;

v) PD-L1 protein; vi) PVRL2; and vii) a relevant isotype control for the antibodies in i)-vi); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1, PVRL2 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either TIGIT or PVR, and for either PVRIG or PVRL2, and for either PD-1 or PD-L1, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[00600] The present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; ii) PVRIG protein; iii) PVR protein; iv) PD-1 protein; v) PD-L1 protein; vi) PVRL2; and vii) a relevant isotype control for the antibodies in i)-vi); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT, PVRIG, PVR, PD-1, PVRL2 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either TIGIT or PVR, and for either PVRIG or PVRL2, and for either PD-1 or PD-L1, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[00601] The present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) TIGIT protein; and ii) PVR protein; and iii) a relevant isotype control for the antibodies in i)-ii); c) running fluorescence activated cell sorting (FACS); d) for each of TIGIT and PVR, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either TIGIT or PVR, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[00602] The present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PVRIG protein; and ii) PVRL2 protein; and iii) a relevant isotype control for the antibodies in i)-ii); c) running fluorescence activated cell sorting (FACS); d) for each of PVRIG and PVRL2, determining the percentage of cells in said population that

express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either PVRIG or PVRL2, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

[00603] The present invention provides a method comprising: a) providing a cell population from a tumor sample from a patient; b) staining said population with labeled antibodies that bind: i) PD-1 protein; and ii) PD-L1 protein; and iii) a relevant isotype control for the antibodies in i)-ii); c) running fluorescence activated cell sorting (FACS); d) for each of PD-1 and PD-L1, determining the percentage of cells in said population that express the protein relative to said isotype control antibody; wherein if the percentage of positive cells is > 1% for either PD-1 or PD-L1, proceeding to step e); and e) administering antibodies to TIGIT, PVRIG, and PD-1 to said patient.

EXAMPLE 2: EXPRESSION OF PVRIG AND PVRL2 IN HUMAN CANCER AND NORMAL ADJACENT TISSUES

[00604] The purpose of this study was to examine the expression of PVRIG and PVRL2 in human tumor and normal adjacent samples. PVRIG was observed to be expressed highest on CD8+ T cells, followed by NK cells, CD4-CD8- T cells, and by CD4+ T cells. No expression was observed on monocytes, mDCs, pDCs, or tumor cells. Of the tumor types examined, endometrial, lung and kidney tumors expressed the highest levels of PVRIG on lymphocytes. A comparison of PVRIG expression on CD4+ and CD8+ T cells from normal adjacent tissues compared to tumor tissues from the same patient showed a significant increase in PVRIG in tumor tissues. A correlation analysis of the magnitude of PVRIG expression with the magnitude of TIGIT or PD-1 expression showed a positive and significant correlation on CD4 and CD8 T cells. In addition, a co-expression single cell analysis of PD-1, TIGIT, and PVRIG showed that PVRIG is co-expressed with PD-1 and TIGIT on a subset of cells. These data support the conclusion that combination blockade of PVRIG with TIGIT and/or PD-1 will lead to increased T cells responses. The ligand for PVRIG, PVRL2, was expressed on myeloid cells (monocytes, mDCs, pDCs) and on CD45-non-immune cells from multiple tumors, likely composed of tumor epithelium and stromal cells. A comparison of PVRL2 on cells derived from normal adjacent vs tumor tissue

showed significant increase in expression of PVRL2 on monocytes and CD45- non-immune cells. A correlation analysis of the magnitude of PVRL2 expression with the magnitude of PD-L1 expression showed a positive and significant correlation on CD45- non-immune cells and monocytes. In these samples, we also assessed the co-expression of PVRIG and PVRL2 in the same sample to understand which tumor type has high co-expression of both receptor and ligands. Of the tumor types examined, we observed high expression of both PVRIG and PVRL2 in the majority of endometrial samples, kidney samples, and lung tumor samples. In summary, these data demonstrate that PVRIG and PVRL2 are expressed on leukocytes and tumor cells from the tumor microenvironment and suggest that this pathway can be exploited to regulate anti-tumor responses.

[00605] We examined the expression of PVRIG and PVRL2 using flow cytometry on cells from dissociated human tumors and matched normal adjacent tissues from multiple different tissues. The expression of immune regulators in the tumor can be used to help predict which tumor types or patients can be most responsive to a specific therapy.

[00606] Healthy human peripheral blood mononuclear cells (PBMC) donors were obtained from the Stanford Blood Bank. Buffy coats or LRS products were diluted 1:1 in 1xPBS+2% FBS and PBMCs were isolated by Ficoll-Paque gradient (Sigma). Purified PBMCs were washed 2x with PBS+2% FBS and banked in liquid nitrogen. Tumor and normal adjacent tissue (NAT) samples were provided by the Cooperative Human Tissue Network, a National Cancer Institute supported resource. The tumor type was determined based on reviewing the pathology report for each sample. The number of samples per tumor type where we examined PVRIG and PVRL2 expression is reported below.

Target	Breast	Colon, Rectal, Stomach	Endometrium & Uterine	Head&Neck	Kidney	Lung	Prostate	Ovary
PVRIG	4	15	24	4	14	8	9	5
PVRL2	6	21	28	5	16	11	12	10

[00607]

1. Tumor Dissociation Protocol

[00608] Tumor and NAT samples were cut into small pieces with a scalpel and transferred to GentleMACs™ C tubes (Miltenyi Biotec) containing an enzyme mix. Samples

were dissociated on GentleMACs (Miltenyi Biotec) as per the manufacturer's protocol. After dissociation, cells were filtered through a 100μm filter prior to FACS staining.

2. Antibodies and reagents:

[00609] To identify immune and non-immune cell populations, the following antibodies were at the manufacturer's recommended concentrations:

Table 2. The antibodies used to identify specific cell subsets is shown.

Antibody	Flourophore	Clone	Vendor	Cat
CD45	Alexa Fluor 700	HI30	BioLegend	304024
CD3	APC Cy7	OKT3	BioLegend	317342
CD8	BV 785	RPA-T8	BioLegend	301046
CD33	BV711	WM53	BioLegend	303424
CD25	BV 650	BC96	BioLegend	302634
CD127	BV 605	A019D5	BioLegend	351334
CD14	BUV395	MoP9	BD Pharmingen	563562
CD4	BUV496	SK3	BD Pharmingen	564651
CD56	PE Dazzle	HCD56	BioLegend	318348

[00610] The following antibodies were used at 5 ug/ml in the isotype control cocktail.

Table 3. The antibodies used as isotype controls for the targets of interest is shown.

Antibody	Flourophore	Clone	Vendor	Cat
mIgG1	AF647	in house	Compugen	In-house
hIgG4	PE	in house	Compugen	In-house
mIgG1	BV421	MOPC21	BioLegend	400158
mIgG1	PerCP Cy5-5	MOPC21	BioLegend	400150
mIgG1	PE Cy7	MOPC21	BioLegend	400126
mIgG1	FITC	MOPC21	BioLegend	400110

[00611] The following cocktail was used to stain the targets of interest at 5ug/ml:

Table 4. The antibodies used to analyze the targets of interest are shown

Antibody	Flourophore	Clone	Vendor	Cat
PDL1	AF647	BM1 (M1)	Compugen	In-house
PVRIG	PE	518 (H4)	BioLegend	93930
PD1	BV421	EH12.2H7 (M1)	BioLegend	329920
PVR	PerCP Cy5-5	SKII.4 (M1)	BioLegend	337612
PVRL2	PE Cy7	TX31 (M1)	BioLegend	337414
TIGIT	FITC	MBSA43 (M1)	eBioscience	11-9500-42

[00612] All isotype control antibodies and target antibodies were used at 5 ug/ml final concentration.

3. FACS Staining

[00613] $1x10^6$ cells of PBMCs or dissociated tumor cells were seed into a 96-well V-bottomed plate for staining. Samples were first stained with Aqua Live Dead (Thermo Scientific) to distinguish live cells from dead cells and with a cocktail of anti-CD16 (Biolegend), anti-CD32 (Thermo Scientific), anti-CD64 (Biolegend) Abs to block Fc receptors. Samples were washed twice with FACS buffer and stained with a relevant isotype control for the antibodies for the antibodies used or a target antibody cocktail described in the "Antibodies and Reagents" section. All staining was done for 30 minutes at 4C. Samples were then washed twice and acquired on the BD Fortessa flow cytometer. Analysis was done using FlowJo, gating on specific populations as specified in Table 1, above (all gated on live cells).

[00614] From each population with at least 100 cells, MFI values were exported and a MFI ratio (MFIr) calculated by dividing the MFI of a target by the MFI of the relevant isotype control. MFIr value greater than one denotes positive expression detected.

4. Results and Discussion

a. PVRIG is expressed on TILS from multiple tumor types and is co-expressed with TIGIT and PD1

[00615] To examine the expression of PVRIG on cells derived from tumors by flow cytometry, tumors were dissociated and stained for immune cell lineage markers to identify immune and non-immune cell subsets and for PVRIG, TIGIT, PD1, PVRL2, and PVR to examine expression of these targets on these subsets. Expression of PVRIG was detected on $CD4^+$ T cells, $CD8^+$ T cells, $CD4^-CD8^-$ T cells, and NK cells from breast, colon/rectal/stomach,

endometrium, head & neck, lung, kidney, prostate, and ovarian tumors (Figure 12A). Across all tumor tissues examined, PVRIG was expressed, from highest to lowest, on $CD8^+$ T cells, NK Cells, $CD4^-CD8^-$ T cells, and $CD4^+$ T cells. No PVRIG expression was detected on monocytes, mDCs, pDCs, or non-immune cells (Figure 1B). As $CD8^+$ T cells and NK cells are known to be important cytotoxic lymphocytes within the immune system, this suggests the PVRIG can directly modulate the activity of these cytotoxic lymphocytes.

[00616] We next examined the expression of magnitude of PVRIG in relation to the magnitude of TIGIT and PD-1 on tumor infiltrating T cells. For this analysis, we focused the analysis on endometrial samples because we had sufficient number of samples with which to perform the correlation analysis. PVRIG significantly and directly correlated with TIGIT and PD1 expression on both CD4 and CD8 T cells, suggesting that these molecules are co-regulated within the TME (Figure 13).

[00617] We further examined co-expression of PVRIG, TIGIT, and PD1 on a single cell basis on CD8 T cells. Co-expression of PVRIG with PD-1 and with TIGIT was observed on a representative lung and kidney cancer (Figure 14).

b. PVRIG expression is significantly enhanced on T cells from the tumor versus normal adjacent tissue

[00618] For a subset of colon/rectal/stomach, endometrium, kidney, lung or ovarian tumors, we were able to obtain matched tumor and normal adjacent tumor (NAT) samples from the same donor. Using these matched samples, we compared the expression of PVRIG and PD1 on cells derived from NAT or tumor samples to determine if there is modulated expression in the tumor compared to healthy tissues (Figure 15). Overall, PVRIG was significantly increased on CD4 and CD8 T cells derived from tumor tissue as compared to matched normal adjacent (Figure 15A). Within tumor types, PVRIG was upregulated by at least 2 fold in 3 of 9 colon tumors, 1 or 2 endometrium tumors, 4 of 11 kidney tumors, and 4 of 5 lung tumors (Figure 15A). In the same samples, we also evaluated PD-1 expression. A correlation analysis between PVRIG fold change (between NAT and tumor) and PD-1 fold change on CD4 and CD8 T cells showed a positive and significant correlation in these samples, suggesting that these molecules could be co-regulated in similar manner in the tumor.

c. PVRL2 is expressed on myeloid and CD45- (non-immune) cells from multiple tumors

[00619] In the same samples from which we examined PVRIG expression, we also examined the expression of PVRL2, the ligand for PVRIG. PVRL2 expression was detected on 2 major cell subsets, myeloid cells which include monocytes, mDC, and pDC populations, and CD45- non-immune cells, likely composed of tumor epithelium, stromal cells, and endothelial cells (Figure 16).

[00620] PVRL2 expression on $CD45^-$ non-immune cells was detected on cells from breast, colon/rectum/stomach, endometrial, lung, prostate, and ovarian tumors (Figure 17). The highest expression median expression of PVRL2 was detected on endometrium and ovarian tumors.

[00621] On immune cells, PVRL2 was expressed on myeloid cells from breast, colon/rectum/stomach, endometrium/uterus, head and neck, lung, kidney, prostate, and ovary tissues (.

[00622] Figure 18). The median expression of PVRL2 on myeloid cells (monocytes, mDCs, pDCs) was comparable across tumor types.

[00623] Comparing tumor tissue with normal adjacent tissue, PVRL2 expression was significantly increased on tumor CD45- cells or on monocytes from tumor tissues (Figure 19). PVRL2 expression on monocytes or CD45- cells was induced by at least 2 fold in the tumor compared to normal adjacent in 5 of 9 colon tumors, 1 of 2 endometrium tumors, 5 of 11 kidney tumors, 4 of 5 lung tumors, and 1 of 1 ovarian tumors. These data support increased expression of PVLR2 on tumor cells and on immune cells within the tumor. A correlation analysis between of PVRL2 fold change (between NAT and tumor) and PD-L1 fold change on CD45- cells and monocytes showed a positive and significant correlation in these samples, suggesting that these molecules could be co-regulated in similar manner in the tumor.

d. PVRIG and PVRL2 are co-expressed in the same tumor

[00624] We further assessed which tumor types have high expression of both PVRIG on T cells and PVRL2 on either monocytes and tumor cells. In this sample set, tumors from

endometrium, lung, and kidney tissues displayed high expression of both PVRIG on T cells and PVRL2 on either monocytes or CD45- cells (Figure 20), suggesting that these tumor types may be more responsive to CHA.7.518.1.H4(S241P) treatment.

e. CONCLUSION

[00625] The results from these studies demonstrate that PVRIG is expressed on effector lymphocytes such as CD8 T cells and NK cells within the tumor microenvironment. Both PVRIG and PVRL2 were expressed in multiple tumor samples from breast, colon/rectum/stomach, endometrial, lung, prostate, and ovarian tumors. Expression of PVRIG on T cells was significantly increased in tumor tissues as compared to matched normal adjacent tissues. Furthermore, a significant direct correlation was observed between PVRIG and PD-1 and PVRIG and TIGIT expression on CD4 and CD8 T cells from endometrial samples. On a single cell basis, co-expression of PVRIG with PD1 or with TIGIT was observed on CD8 T cells. The ligand for PVRIG, PVRL2, is expressed on antigen presenting cells (monocytes, mDCs, pDCs) and also on CD45- cells (presumably composed of epithelial, stromal, endothelial cells) from multiple tumor tissues. Induction of PVRL2 expression was detected on cells derived from tumor as compared with normal adjacent tissues. The cellular expression profile of the receptor and ligand suggest a role for this pathway in regulating effector lymphocyte responses for multiple tumor types.

EXAMPLE 3: EXPRESSION OF PVRL2 AND PD-L1 IN HUMAN CANCER AND NORMAL TISSUES BY IHC

[00626] The purpose of this study was to examine the expression of PVRL2 and PD-L1 in human healthy and cancer tissue. Two antibodies to PVRL2 were identified to stain for PVRL2 in formalin fixed paraffin embedded (FFPE) fixed samples. PD-L1 was assessed using a commercially validated antibody. Using these antibodies, we examined expression of PVRL2 and PD-L1 in serial tissue sections of a tumor microarray (TMA) composed of breast, colon, lung, ovarian, and skin tissues. PVRL2 expression was observed to be enhanced in breast, colon, lung, ovarian, and skin cancers as compared to healthy tissues. Similar staining was observed between the two PVRL2 antibodies, helping to corroborate the results obtained. PD-L1 expression was also increased in breast, colon, lung, ovarian,

and skin cancers as compared to healthy tissues. Expression of PVRL2 was observed on tumor epithelium and also on infiltrating immune cells. There was a higher incidence of PVRL2 expression than PD-L1 expression in these tumor samples. Individual tumor samples were further grouped by PD-L1 negative and positive expression, and PVRL2 expression analyzed in these subgroups. All PD-L1 positive tumors also expressed PVRL2, providing a rationale for combination treatment in tumors. In PD-L1 negative tumors, PVRL2 expression was detected in a subset of these samples, providing a rationale for targeting the PVRL2 pathway in PD-L1 negative tumors. Taken together, these data demonstrate that PVRL2 expression was enhanced in the tumor microenvironment from breast, colon, lung, ovarian, and skin cancer and provide a rationale for monotherapy and combination treatment with agents targeting the PVRL2 pathway.

Protocols

Antibodies

[00627] Anti-PVRL2 (Abcam ab135246, Sigma HPA-012759) and anti-PDL1 (SpringBio Sp142) were used in this study. Isotype control antibody (Rabbit IgG) was used as the negative control.

IHC staining

[00628] Breast, colon, lung, ovarian, skin tumor microarrays were obtained from. Each microarray contains healthy tissues from 2-4 donors and tumor tissue from 30-40 donors, present in duplicates on the slide. Anti-PVRL2 Abcam ab135246 staining was performed at 1:250 dilution with no heat-induced antigen retrieval (HIER). Anti-PVRL2 (Sigma HPA-012759) was used at 0.1 ug/ml with HIER at pH 9.5. Anti-PD-L1 (SpringBio SP142) was used at 1 ug/ml with HIER at pH6.2 based on the manufacturer's recommendation. A matching rabbit IgG isotype control was used at each of the relevant conditions. Each core was qualitatively scored based on: No staining (score 0), partial positive (score 1), positive (score 2), strong positive (score 3) by 2 individual operators. In cases of a score discrepancy between the 2 operators, the sample was reassessed by both operators for a final score. The score from the 2 cores derived from the same tumor were

averaged and one score obtained for each tumor. Scores were plotted and samples were grouped by pathology data provided by the vendor.

RESULTS AND Discussion

PVRL2 and PD-L1 expression are increased in breast, colon, lung, ovarian, and skin cancers

[00629] Two anti-PVRL2 antibodies (ab135246, HPA-012759) were tested for ability to assess PVRL2 expression in formalin fixed paraffin embedded tissues. Expression of PVRL2 and PD-L1 was assessed serial sections of a tumor microarray of breast, colon, lung, ovarian and skin cancers. Expression of PVRL2 and PD-L1 was increased in breast, colon, lung, ovarian, and skin cancers (Figure 21).

PVRL2 is expressed in PD-L1 positive and PD-L1 negative tumors.

[00630] As the expression of PVRL2 and PD-L1 was conducted on serial sections of the same TMA, we were able to examine the expression of PVRL2 and PD-L1 in each of these tumors from the same portion of the tumor (Figure 22). A subset of PD-L1 negative tumor samples, in particular lung, ovarian, breast tumors, expressed PVRL2 (as defined by at least partial positive) as detected by both anti-PVRL2 antibodies. These data show that PVRL2 can be expressed in PD-L1 negative tumors. In contrast, all PD-L1 positive tumors expressed PVRL2 as detected by both PVRL2 antibodies.

PVRL2 is expressed on the epithelial cells and on the immune compartment on the invasive front

[00631] The spatial expression of immune checkpoints at the invasive front of a tumor is important in regulating the anti-tumor response. Known checkpoint targets such as PD-1 and PD-L1 have prominent expression at the invasive front. As these TMAs are generated from punch biopsies and do not contain the whole tumor, we examined these samples for the presence of immune infiltrate at the invasive front of the tumor. We identified 1 sample where we observed PVRL2 expression in the immune infiltrate and on the tumor epithelium (Figure 23). PD-L1 expression was observed on the immune infiltrate, further suggesting this could be the invasive front of a tumor.

CONCLUSION

[00632] These results demonstrate the PVRL2 expression is enhanced in breast, colon, lung, ovarian, skin tumors as compared to healthy tissue from the same organs. PVRL2 is expressed on both tumor epithelium and on infiltrating leukocytes. We further demonstrate that all PD-L1 positive tumors express PVRL2, suggesting that agents that target PVRL2 pathway may be efficacious in combination with PD-1/PD-L1 inhibitors. In addition, PVRL2 expression was detected in PD-L1 negative tumors, suggesting that agents that target PVRL2 pathway may be efficacious in PD-L1 negative tumors.

EXAMPLE 4: ANTITUMOR RESPONSES OF MONO, DUAL AND TRIPLE COMBINATION ANTIBODY TREATMENTS IN THE CT26 TUMOR MODEL

Rationale and Objectives

[00633] To examine whether antibody blockade of PVRIG, TIGIT and PD-L1 can enhance tumor growth inhibition and survival in a syngeneic mouse tumor model compared to mono or dual antibody treatments.

Materials and Methods

In vivo tumor model

[00634] CT26 colon carcinoma cells (ATCC) were cultured in RPMI 1640 with 10% FBS, and 100 ug/mL penicillin/streptomycin. For tumor implantation, 5×10^5 CT26 cells were injected subcutaneously into the right flank of female, 8-week-old BALB/c mice. Following tumor randomization, the antibodies were administered by intra-peritoneal (i.p.) injection, starting on day 7 post tumor inoculation when tumors reached the volume of 60-90mm^3, and continued for 3 weeks for a total of 6 administrations. Tumor size was measured with electronic caliper every 2-3 days and was reported as 0.5 X W^2 X L mm^3. . Mice were sacrificed at either study termination or at the clinical endpoints, including tumor volume ≥3250 mm^3, tumor ulceration, body weight loss ≥20%, or moribund appearance.

Antibodies

[00635] The chimeric anti-mouse PVRIG antibody (Clone 407, internal production) used in these studies was engineered as a mouse IgG1 (mIgG1) antibody. This antibody was shown to bind to 293HEK cells over-expressing mouse PVRIG, and to block the binding of the ligand, mouse PVRL2. The anti-mouse PD-L1 mIgG1 antibody (Clone YW243.55.S70) was generated according to the description in WO/2010/077634. The anti-mouse TIGIT mIgG1 antibody (Clone 11A11) was generated according to the description in WO2016/028656. Synagis IgG1 was used as isotype control and produced internally. Antibodies were formulated in sterile PBS with low endotoxin (<0.05 EU/mg). The anti-PVRIG antibody was administered at a dose of 10mg/kg, anti-PD-L1 at 5mg/kg, and anti-TIGIT at 18 mg/kg.

Statistical Analysis

[00636] Two-way ANOVA with repeated measures, followed by two-way ANOVA with repeated measures for selected pairs of groups was determined by JUMP software (Statistical Discoveries™). Analyses of tumor growth measurements were performed by comparing tumor volumes measured on the last day on which all study animals were alive. Statistical differences in percentage of mice tumor free were determined by a Log Rank Mantel--Cox test. Values of $P < 0.05$ were considered significant. * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Results

In vivo efficacy of anti-TIGIT and anti-PVRIG antibodies in combination with anti-PD-L1 antibody

The in vivo efficacy of combinational therapy of mouse PVRIG, TIGIT and PD-L1 blockade was evaluated in mouse syngeneic CT26.WT ectopic subcutaneous tumor model. Treating tumor bearing mice with the anti-PVRIG antibody in combination with an anti-PD-L1 antibody resulted in tumor growth inhibition (TGI) of 47% compared to isotype control.

However, in this study no benefit was observed with the dual combination of anti-PD-L1 and anti-PVRIG antibodies compared to anti-PD-L1 antibody treatment alone. The blockade of TIGIT in the triple combination (anti-PVRIG, anti-TIGIT and anti-PD-L1) resulted in a significant improvement in TGI when compared to other dual combination treatments with the anti-TIGIT antibody (anti-PDL-1 + anti-TIGIT, anti-PVRIG + anti-TIGIT, and anti-PDL-1 + anti-TIGIT, which corresponded to 29%, 61%, and 55% TGI, respectively) (Figures 24A and C). The triple combination resulted in higher response rates (55% vs 40%) and promoted durable antitumor activity with a trend for higher survival rate until Day 35 (Figure 24B).

EXAMPLE 5: PVRIG ANTAGONISM ENHANCES T CELL EFFECTOR FUNCTION AND REDUCES TUMOR GROWTH

Abstract

[00637] Despite recent advances, the majority of patients do not derive long term benefit from checkpoint inhibitors. PVRIG is a novel immune suppressive receptor of the DNAM/TIGIT family and we demonstrate here a role of PVRIG in regulating anti-tumor responses. PVRIG binds to PVRL2 and displays significantly enhanced expression on tumor infiltrating lymphocytes as compared to lymphocytes from normal tissues. PVRIG antagonism enhanced human T cell activation and combination of PVRIG with PD-1 or TIGIT inhibitors further synergistically increased lymphocyte function. We next addressed the role fo PVRIG in preclinical tumor models. PVRIG$^{-/-}$ mice displayed significantly increased T cell activation in vitro and reduced MC38 tumor growth that was mediated by increased CD8 effector function. Antagonistic anti-PVRIG antibody significantly reduced tumor growth in combination with anti-PD-L1 or when tested in TIGIT$^{-/-}$ mice. In summary, we demonstrate that PVRIG-PVRL2 pathway was induced in human cancers and that antagonizing PVRIG-PVRL2 interactions resulted in increased T cell function and reduced tumor growth.

State of Significance

[00638] These data demonstrate that PVRIG is a promising target for the treatment of cancer and provide the rationale for testing a PVRIG inhibitor, CHA.7.518.1.H4(S241P), as a novel cancer immunotherapy agent either as monotherapy or in combination with TIGIT or PD1 blockade.

Introduction

[00639] Increasing evidence demonstrate that endogenous immune responses are critical in sculpting the initiation, progression, and suppression of cancer (1) (2). The immune status of patients as well as the content of tumor-infiltrating leukocytes (TILs) within the tumor microenvironment (TME) are key prognostic indicators of not only cancer survival rates, but also how patients respond to therapy (3) (4). T cells are a key component of TILs that can invoke an anti-tumor response, and most anti-tumor immune responses ultimately rely on the functionality of effector lymphocytes cells. An enrichment of CD8 T cells in the TME of a patient's tumor, as well as other factors that bias an immune response towards an effective CD8 T cell response such as mutational load and a Th1 polarized TME, are all key prognostic indicators for a favorable anti-tumor immune response (5) (6).

[00640] A key observation across many solid tumors is that effector T cells have an activated or 'exhausted' phenotype within the TME (7). This indicates that although T cells within the TME have initially seen cognate antigen, been activated, and trafficked to the tumor, they are subsequently not capable of invoking an effective anti-tumor response. Pre-activated or exhausted T cells are defined by increased surface expression of co-inhibitory receptors, such as PD-1 and CTLA-4 (8). Therapeutically targeting these co-inhibitory receptors with antibodies that inhibit interactions with their cognate ligands have shown remarkable clinical efficacy in patients with multiple advanced cancers (9). Mechanistically, it has been shown that targeting these co-inhibitory receptors leads to the expansion of already tumor-reactive T cells that pre-exist in the TME and to the production of T cell pools with widened T cell receptor diversity (10) (11) (12). Although checkpoint inhibitors currently in the clinic have revolutionized cancer treatment and demonstrated the power of the immune system in combating cancer, many patients still relapse and/or do not respond to treatment. Consequently, increased understanding of the immune response in cancer and targeting additional immune-based pathways will lead to additional therapeutic treatments.

[00641] Among these novel pathways, a group of receptors and ligands within the nectin and nectin-like family are currently under investigation as potential novel cancer immunotherapies. Receptors within this family include DNAM-1 (CD226), CD96 (TACTILE), TIGIT, and more recently, PVRIG (CD112R) (13) (14) (15). Of these molecules, DNAM is an

activating receptor within this subfamily, binding to 2 ligands, PVR (CD155) and PVRL2 (CD112), to deliver an activating signal to lymphocytes (16). Two receptors in this family have been shown to inhibit human lymphocyte function, TIGIT, and more recently, PVRIG (17) (18). TIGIT is reported to have a high affinity interaction with PVR, a much weaker affinity to PVRL2, and has been shown to inhibit both T cell and NK cell responses by delivering an inhibitory signal into lymphocytes through its ITSM motif (19) (20). More recently, PVRIG was shown to bind with high affinity to PVRL2 and to deliver an inhibitory signal through its ITIM motif (15). In both cases, the affinity of TIGIT to PVR and of PVRIG to PVRL2 is higher than the affinity of DNAM to either PVR or PVRL2, suggesting TIGIT and PVRIG can outcompete PVR and PVRL2 from DNAM, providing an indirect mechanism by which TIGIT and PVRIG can reduce T cell function. Within this family, PVR is also a ligand for CD96. The function of CD96 has been reported to be inhibitory on mouse lymphocytes (21) but activating on human lymphocytes (22). Based on these data, we postulate on human lymphocytes that 2 receptors, TIGIT and PVRIG, bind with high affinity to PVR and PVRL2, respectively, to deliver inhibitory signals to dampen T cell function.

[00642] Although human PVRIG has been shown to inhibit T cells response in one recent report, the role of PVRIG and PVRL2 in cancer immune surveillance is not well understood. In particular, the expression profile of this pathway in cancers and the role of PVRIG in regulating CD8 T cell anti-tumor responses has not been reported. Furthermore, functional characterization of the mouse PVRIG gene and the effect of disrupting PVRIG-PVRL2 interaction in vivo in pre-clinical tumor models has not been reported. Herein, we elucidated the role of PVRIG in a cancer setting by reporting on PVRIG and PVRL2 expression profile in cancer and the effect of PVRIG antagonism in tumor cell co-culture assays and in preclinical tumor models. We demonstrate that PVRIG has a differentiated expression profile on T cell subsets compared to TIGIT or CD96 and that PVRIG and PVRL2 expression were induced in cancer compared to normal adjacent tissues. In multiple human in vitro assay systems, a high-affinity PVRIG antagonistic monoclonal antibody (CHA.7.518.1.H4(S241P)) enhanced T cell function, in particular when combined with anti-TIGIT or anti-PD1 antibody. In addition, we report the novel characterization of mouse PVRIG using antagonistic antibodies or PVRIG deficient mice and demonstrate that inhibition of PVRIG-PVRL2 interaction reduced tumor growth, with most potent effects in

combination with PD-1 inhibition or TIGIT genetic deficiency. Collectively, this data shows that PVRIG is a critical inhibitory receptor in regulating T cell anti-tumor responses and support the development of CHA.7.518.1.H4(S241P), for clinical testing in cancer patients.

Materials and Methods

Human peripheral blood and tumor expression studies

[00643] Healthy donor human PBMCs were obtained from Stanford University in accordance with the Declaration of Helsinki. Human tissues were provided by the Cooperative Human Tissue Network, a National Cancer Institute supported resource. Human cancer tissue and matched normal adjacent tissues were dissociated into single cells as per manufacturer's protocol (Miltenyi Biotec). Dissociated cells were analyzed by flow cytometry for expression of various targets on different cell subsets. For each target expression on an individual cell subset, a fold expression value was calculated by taking the MFI value of target divided by the MFI value of the isotype control. Other investigators may have received samples from these same tissue specimens. The tumor type was determined based on reviewing the pathology report for each sample. For IHC studies, anti-PVRL2 antibody (HPA-012759, Sigma) and PD-L1 (Sp142, SpringBio) were used to stain tumor micro-arrays (Biochain institute) using conditions as described in the supplemental methods. Scoring was performed by 2 independent reviewers on duplicate cores from the same tumor.

PVRIG Antibody generation and characterization

[00644] Anti-human PVRIG and anti-mouse PVRIG antibodies were generated as detailed in the supplemental methods. Briefly, antibody binding specificity and affinity were assessed by selective binding to PVRIG engineered cells with no detectable binding to cells that do no express the gene. Antagonistic activity of these anti-PVRIG antibodies was determined using ELISA and FACS based assays in which the interaction of PVRIG with PVRL2 was disrupted. For characterization in cell based assays, antibodies were tested in several T cell-target cell co-culture assay systems consisting of target cells that express PVRL2 in culture with PBMC or tumor-derived T cells. gp100 specific T cells lines were expanded

from melanoma tumors as previously described (23). CMVpp65 reactive T cells were expanded from healthy donor PBMCs (CTL immunospot) with CMVpp65 (495-503), IL-2, and IL-7 for 10 days. For combination studies, antibodies to PD-1, TIGIT, and PVRIG were used at 10 μg/ml. Cytokine concentrations in conditioned media was determined using Cytometric Bead Array (CBA) and FACS staining was performed as described in the supplemental methods.

Characterization of mouse PVRIG expression and function

[00645] Binding interactions of mouse PVRIG with mPVRL2 and mPVR were assessed by SPR and ELISA using recombinant PVRIG, PVRL2, and PVR proteins and by FACS using ectopically engineered PVRIG and PVRL2 overexpressing cell lines or PVR or PVRL2 siRNA transfected cell lines. PVRIG and TIGIT deficient mice were generated as described in the supplemental methods. Expression analysis was performed to examine expression of PVRIG in spleen, lymph node, and tumor in various cell subsets. Cell functional assays demonstrating a T cell modulatory activity for mouse PVRIG were established using WT and PVRIG$^{-/-}$ T cells and PVRL2 Fc or PVRL2 ectopically expressed target cells as detailed in the supplemental materials and methods. CT26, MC38, and B16/Db-hmgp100 tumor models were performed as described in the supplemental methods. All studies were approved by the Institutional Animal Care and Use committee at the Tel-Aviv University (Tel-aviv, Israel) or Johns Hopkins University (Baltimore, USA).

Results

PVRIG expression is highest on effector T cells of peripheral blood and tumors

[00646] The Ig superfamily (IgSF) consists of hundreds of proteins but only a few of them are T cell inhibitory receptors. Proteins of the IgSF tend to evolve quickly (24) and therefore sequence similarity among these proteins is generally low and is not optimal for identifying novel immune receptors. To identify novel immune checkpoints, we developed bioinformatic algorithms based on shared genomic and proteomic characteristics among known immune checkpoints, such as gene structure, protein domains, predicted cellular

localization and expression pattern. Using these algorithms, we identified PVRIG as a novel immune receptor. A report has recently also demonstrated that human PVRIG (CD112R) binds to PVRL2 and inhibits T cell function (15). However, the relevance of this pathway in regulating tumor immune surveillance has not been reported. Here, we have elucidated the expression and function of PVRIG and PVRL2 in human cancers and preclinical tumor models. In peripheral blood from healthy donors, PVRIG was expressed exclusively on lymphocytes, with highest expression on CD8 T cells and NK cells (Figure 27A). Further subset analysis of T cells showed highest PVRIG expression on CD8 or CD4 memory/effector T cell subsets in comparison with Treg subset (Figure 27B, Figure 34A). The predominantly memory T-cell expression pattern differentiates PVRIG from other receptors in the family (TIGIT, CD96) which tend to have equal or higher expression on Tregs compared to memory/effector T cells. We further compared the expression kinetics of PVRIG and TIGIT post T cell activation in 2 assay systems (CMV recall response Figure 27C, DC-MLR Figure 27D, Figure 34B) and show that PVRIG has delayed kinetics of induction and more sustained expression at the late timepoint as compared to TIGIT. The preferential expression of PVRIG on memory/effector cells as compared to TIGIT suggests a unique role for PVRIG in regulating T cell responses.

[00647] The delayed and sustained induction of PVRIG expression on T cells after activation suggested that it could be expressed in the tumor microenvironment. Next, we analyzed the expression of PVRIG on leukocytes from dissociated human tumors directly ex vivo by FACS. Expression of PVRIG was detected on CD8 T cells, CD4 T cells, and NK cells from multiple tumor types (Figure 27E-G, Supplemental Figure 27C). PVRIG was co-expressed with PD-1 and TIGIT on CD4 and CD8 T cells (Figure 27F) On average, higher expression was detected on $CD4^+$ and $CD8^+$ TILs from breast, endometrial, head and neck, lung, kidney, and ovarian tumors as compared to bladder, colorectal, and prostate. In tumor samples in which PVRIG expression was low/not present ex vivo, activation with anti-CD3 and anti-CD28 enhanced the expression of PVRIG, suggesting that TIL expression of PVRIG can be further induced upon re-activation (Figure 34D). For colon, lung, kidney, endometrial, and ovarian tumors, we were able to obtain normal adjacent tissue from the same patient and perform a comparison of PVRIG expression on lymphocytes isolated from the tumor vs normal tissue. TILS showed a significant induction of PVRIG on CD4 and CD8 T cells as

compared to cells isolated from matching normal adjacent tissues (NAT) (Figure 34E). As with PBMCs, we further compared PVRIG, TIGIT, and PD1 expression on Tregs vs CD8 T cells from lung, endometrial, and kidney tumors. On TILS, TIGIT expression was higher on Tregs compared to CD8 T cells whereas for PVRIG and PD1, similar or higher expression was observed on CD8 T cells compared to Tregs (Figure 27E). Next, we examined the co-regulation of PVRIG, TIGIT, and PD-1 on T cell populations by correlation analysis of either the magnitude of expression on TILS ex vivo or the magnitude of the fold change in expression between tumor and NAT. In both analyses, CD4 and CD8 T cells displayed a positive and significant correlation between PVRIG and PD1 or TIGIT on (Figure 34F). Taken together, these data demonstrate that PVRIG is expressed on T cells and NK cells from multiple human cancers, placing PVRIG as a novel inhibitory receptor target that may be critical in regulating T cell function in the tumor.

PVRL2 Expression is Enhanced in Tumors Tissue Compared to Normal Adjacent Tissue

[00648] As PD-L1 expression has been demonstrated to help predict responses to PD-1 inhibitors, we examined whether the expression of PVRL2 was concomitant with expression of its cognate receptor, PVRIG, in human cancer tissues. Using a PVRL2 antibody that we validated for use in IHC (Figure 35A), we stained tumor microarrays (TMA) composed of lung, colon, skin, breast, ovarian/endometrial, and kidney cancer tissues. With the exception of kidney, PVRL2 expression was not present or minimally expressed in the majority of normal tissues from these organs. In tumor tissues, PVRL2 was induced in a substantial number of lung, colon, skin, breast, and ovarian/endometrial cancer samples (Figure 28A). PVRL2 expression was detected on tumor cells and immune cells at the invasive front (Figure 28B). To determine the specific immune cell subsets expressing PVRL2, we performed flow cytometry on freshly dissociated tumors. Consistent with the IHC expression profile, expression of PVRL2 was detected on $CD45^+$ immune cells, particularly myeloid cells (e.g. $CD14^+$ tumor associated macrophages (TAMs) and myeloid DCs) and on $CD45^-$ non-immune cells from multiple tumor types (Figure 28C, D). No expression of PVRL2 was detected on lymphocytes (data not shown). Comparison of PVRL2 expression on $CD45^-$ cells and TAMs isolated from colon, lung, kidney, endometrial, and ovarian tumors showed a significant induction of PVRL2 on cells isolated from the tumor as compared to cells isolated

from matching normal adjacent tissues (NAT) of the same donor (Figure 36D). To assess which tumors expressed both PVRIG and PVRL2, we examined expression of PVRIG on lymphocytes compared with PVRL2 on myeloid cells and on CD45$^-$ cells from multiple tumor types. Of the cancer types examined, endometrial, lung, and kidney cancers had the highest prevalence of PVRIG^{hi} lymphocytes and PVRL2^{hi} TAMs or CD45$^-$ non-immune cells (Figure 28E, Figure 37). These data demonstrate that the PVRIG-PVRL2 pathway may be particularly important in modulating the anti-tumor response by regulating the T cell – TAM interaction and the T cell-tumor cell interaction in endometrial, lung, and kidney cancers.

Compared to PD-L1, PVRL2 expression is differentially regulated and present in PD-L1$^-$ tumors

[00649] As PVRIG and PD-1 can be co-expressed on tumor-infiltrating lymphocytes (TILs), we also examined the co-expression of PVRL2 and PD-L1 on the same tumor by staining serial sections of the same TMA. All PD-L1-positive tumors also expressed PVRL2, indicating some overlap in the regulation of these 2 pathways and providing a rationale to combine a PVRIG inhibitor with PD-1/PD-L1 inhibitors (Figure 29A). In PD-L1negative tumors, PVRL2 was detected in a majority of these tumors across various cancer types (Figure 29A). This suggested that PVRL2 expression was more prevalent than PD-L1 in some tumors and that targeting this pathway may be particularly effective in PD-L1-negative tumors. As PD-L1 has been reported to be induced in the tumor by IFN-γ as part of the adaptive resistance model (25), we further assessed the regulation of PVR, PVRL2 and PD-L1 expression by various inflammatory stimuli on bone marrow derived dendritic cells and on tumor epithelial cell lines (Figure 29D). Treatment of immature BM-DCs with pro-inflammatory signals generally lead to an increase in PVR, PVRL2, and PD-L1 expression, demonstrating that PVR, PVRL2, and PD-L1 expression are both increased upon DC maturation. In contrast, treatment of epithelial cells with IFN-γ increased expression of PD-L1 but had no effect on the high baseline expression of PVRL2 (Figure 29E). It has been reported that PVRL2 by genomic stress, DNA damage, and tumor suppressor genes (26) (27), further supporting a differential regulation of PVRL2 expression in comparison with PD-L1. In summary, these data indicate that PD-L1 and PVRL2 can be co-regulated on antigen presenting cells such as DCs but can be differentially regulated by IFN-γ on epithelial cells.

The presence of PVRL2 in PD-L1-negative tumors suggests that targeting this pathway may be of potential benefit in patients that are non-responsive to PD-1 inhibitors.

CHA.7.518.1.H4(S241P) is a high affinity humanized monoclonal antibody to PVRIG that disrupts the interaction of PVRIG to PVRL2

[00650] To examine the functional consequences of antagonizing human PVRIG-PVRL2 interactions, we generated a high affinity, antagonistic anti-PVRIG antibody, CHA.7.518.1.H4(S241P), which blocks the interaction of PVRIG and PVRL2. This antibody selectively bound HEK293 cells ectopically expressing human PVRIG or cynomolgus macaque PVRIG and also bound Jurkat cells that endogenously express PVRIG with sub-nanomolar affinity (Figure 30A). In biochemical assays, CHA.7.518.1.H4(S241P) blocked the interaction of PVRIG Fc with PVRL2$^+$ HEK293 cells (Figure 30B) and also blocked PVRL2 Fc binding to PVRIG$^+$ HEK293 cells (Figure 30C). Using this antibody, we observed a functional effect of an antagonistic anti-PVRIG in several T cell assays. Artificial antigen-presenting cells (aAPC) ectopically expressing a cell surface anti-CD3 antibody and human PVRL2 were generated and co-cultured with primary human CD4 T cells, either in the presence of anti-PVRIG (CHA.7.518.1.H4(S241P)) or isotype control. PVRIG expression was induced on proliferating CD4 T cells upon co-culture with the CHO anti-CD3 aAPC (Figure 38A). Antagonism of PVRIG with CHA.7.518.1.H4(S241P) enhanced proliferation of CD4 T cells from multiple donors (Figure 30D). We also tested the effect of anti-PVRIG on 2 human gp100 reactive CD8 T cell lines that were derived from melanoma tumors. These T cell lines were individually co-cultured with aAPCs expressing HLA-A2 and PVRL2 (Figure 38B) in the presence of isotype control IgG or anti-PVRIG antibodies. As observed in both lines, anti-PVRIG increased IFN-γ and TNF-α production by ~20-50%. In a dose response assessment, CHA.7.518.1.H4(S241P) displayed single digit nano-molar EC50 values in multiple assays (Figure 38C, D). These data collectively demonstrate that antagonizing PVRIG-PVRL2 interactions with CHA.7.518.1.H4(S241P) resulted in increased T cell activation.

CHA.7.518.1.H4(S241P) in combination with TIGIT or PD-1 inhibitors resulted in synergistic enhancement of T cell function.

[00651] Combination of PVRIG and TIGIT blockade synergistically increased CD4 T cell function in a T cell-dendritic cell co-culture assay (15), suggesting a role for this pathway in regulating T cell-APC interactions. The effects of PVRIG and TIGIT blockade on CD8 T cells in a tumor cell co-culture setting has not been reported. As our tumor expression profiling demonstrated expression of PVRL2 on $CD45^-$ immune cells, we further explored the effect of targeting this pathway in T cell – tumor cell co-cultures using 2 T cell assay systems. We first performed a co-culture of 2 gp100 tumor antigen specific CD8 T cell lines with a melanoma cell line, MEL624, in the presence of anti-PVRIG, anti-TIGIT, or isotype control antibodies, either individually or in combination. MEL624 cells express both PVR and PVLR2 and both TIL-209 and TIL-463 expressed PVRIG, TIGIT, and PD-1 (Figure 30F). On TIL-209, we observed that anti-PVRIG or anti-TIGIT alone did not increase IFN-γ and that the combination of anti-PVRIG and anti-TIGIT synergistically increased IFN-γ production (Figure 30G). On TIL-463, we observed that anti-PVRIG or anti-TIGIT modestly increased IFN-γ production, and that combination of anti-PVRIG and anti-TIGIT additively increased IFN-γ(Figure 30G). In an additional assay system, we utilized CMVpp65-reactive CD8 T cells as a model system to study human T cell responses. HLA-$A2^+$ CMVpp65 CD8 T cells were expanded in the presence of CMVpp65 (495-503) and expression of PVRIG, TIGIT, and PD-1 was observed on day 10 (Figure 30F). PVRIG was expressed on CMVpp65 specific CD8 T cells at similar magnitude to what was observed in human cancer samples (Figure 27). As target cells, we identified a PD-$L1^{hi}$ (Panc05.04) and a PD-$L1^{lo}$ (Colo205) HLA-$A2^+$ cancer cell line that both expressed similar amounts of PVR and PVRL2 (Figure 30F). We next performed a co-culture of the CMVpp65 reactive T cells with HLA-$A2^+$ tumor cell lines pulsed with pp65 (495-503) peptide in the presence of blocking antibodies to PVRIG, TIGIT, and/or PD-1. We observed that anti-PVRIG Ab increased IFN-γ by ~50% in the co-culture with Panc05.04 cells and minimally in the co-culture with Colo205 (Figure 30H). Combination of anti-TIGIT with anti-PVRIG Ab synergistically increased IFN-γ production on both target cell lines, resulting in a greater increase in IFN-γ compared to PD-1 antibody alone (Figure 30H). Combination of anti-PVRIG and anti-PD-1 also led to synergistic increases in IFN-γ production as compared to individual antibody (Figure 30I). Taken together, these data suggest a potent synergy of combining PVRIG and TIGIT or PVRIG and PD1 blockade in increasing activation of human CD8 T cells upon interaction with tumor cells.

PVRIG deficiency resulted in increased T cell proliferation and reduced tumor growth

[00652] Although the sequence for mouse PVRIG and its interaction with mouse PVRL2 has been reported, the expression profile and immune modulatory activity of mouse PVRIG is not well understood. We first analyzed mPVRIG RNA expression and transcript in NK, NKT and T cells (Figure 31A). Activated mouse CD8 T cells had elevated PVRIG transcripts with delayed induction kinetics compared to TIGIT (Figure 31B). We confirmed that that recombinant mPVRIG bound to mPVRL2 protein by surface plasmon resonance (SPR) and ELISA performed in several assay orientations (Figure 39A-D). We also observed an interaction between mPVRIG and mPVR, although the affinity was approximately 10x less than the interaction with mPVRL2 (Figure 39E). To determine whether PVR or PVRL2 is the dominant ligand for mPVRIG, we tested the binding of mouse PVRIG Fc to B16F10 cells which express PVR and PVRL2 (data not shown). PVRIG Fc showed a dose dependent binding to B16F10 cells that was completely abolished upon PVRL2 siRNA knockdown in B16F10 cells (Figure 39F). In comparison, the binding of PVRIG Fc fusion protein was slightly, but consistently, reduced following PVR knockdown (Figure 39E) suggesting that a very weak interaction occurs between mPVRIG and mPVR. Taken together, these results demonstrate that in mice, PVRL2 is the primary ligand for PVRIG, as is the case in human.

To delineate the role of PVRIG in immune responses, we generated PVRIG deficient ($^{-/-}$) mice (Figure 40). PVRIG$^{-/-}$ mice were born at the expected Mendelian ratios, displayed no overt phenotype up to 10 months of age, and at 8 weeks of age had similar leukocyte cellularity (peripheral and lymphoid tissue) when compared to wild type mice (Figure 41). Wild-type (WT) CD8 T cells and NK cells express PVRIG and no expression of PVRIG was detected on PVRIG$^{-/-}$ cells (Figure 31C). To examine the role of PVRIG in regulating mouse T cell responses, we examined the proliferation of WT and PVRIG$^{-/-}$ T cells in 2 assay systems. WT or PVRIG$^{-/-}$ T cells were activated with immobilized anti-CD3 in the presence of soluble PVRL2 Fc or control Fc protein. Soluble PVRL2 Fc significantly inhibited WT CD4^{+} T cell proliferation but not PVRIG$^{-/-}$ CD4^{+} T cell proliferation (Figure 31D), suggesting that PVRIG$^{-/-}$ cells lack an inhibitory signal. To evaluate the role of mouse PVRIG in CD8^{+} T cell interaction with tumor cells, PVRIG$^{-/-}$ mice were bred to pmel TCR transgenic mice, which express a transgenic TCR specific to $gp100_{25–33}$ (28). Activated PVRIG$^{-/-}$ or WT Pmel CD8+ T cells were co-cultured with

B16-Db/gp100 melanoma tumor cells that endogenously express PVRL2 (data not shown) and activation and effector function evaluated. PVRIG$^{-/-}$ pmel CD8^{+} T cells showed enhanced degranulation and production of effector cytokines (IFN-γ and TNF-α) compared to WT cells (Figure 31E). These data indicate that mouse PVRIG inhibits activation and effector function of tumor-specific T cells upon co-culture with PVRL2^{+} tumor target cells.

[00653] We next studied the effects of PVRIG deficiency on tumor growth in the MC38 syngeneic model. PVRIG$^{-/-}$ mice displayed significantly reduced tumor growth compared to WT mice (Figure 32A-B). Moreover, PVRIG$^{-/-}$ mice exhibited additional anti-tumor responses following PD-L1 blockade beginning day 14, reflected in significant (p=0.052) tumor growth inhibition compared to anti-PD-L1-treated WT mice or PVRIG$^{-/-}$ mice treated with isotype control Figure 32C,D). Consistent with the reduced tumor growth, anti-PD-L1-treated PVRIG$^{-/-}$ mice displayed a significant increase in IFN-γ^{+}TNF-α^{+} effector CD8 T cells upon ex vivo stimulation, compared to anti-PD-L1-treated wild-type mice as well as isotype-treated PVRIG$^{-/-}$ mice (Figure 32E). Further, anti-PD-L1-treated PVRIG$^{-/-}$ mice also had elevated numbers of effector cytokine-producing CD8^{+} tumor-infiltrating lymphocytes (TILs), when compared to anti-PD-L1-treated wild-type mice as well as isotype-treated PVRIG$^{-/-}$ mice (Figure 32F). Transcriptomic profiling of CD45^{+} immune cells from tumors harvested midway through the experiment (day 18; mice received 2 doses of anti-PD-L1 or isotype control) showed that the gene signatures for TIL numbers and cytotoxic TILs were significantly enhanced in anti-PD-L1-treated PVRIG deficient mice relative to their wild-type counterparts (Figure 32G-H). Significant changes in T cell mediated genes (GRZB, IFN-γ) was observed in the PVRIG$^{-/-}$ + anti-PD-L1 group as compared to the other groups (Supplemental Figure 42). Taken together, these data demonstrate that PVRIG deficiency, particularly when combined with PD-L1 blockade, resulted in increased T cell activation and reduced tumor growth in vivo.

Anti-mPVRIG antibody inhibited tumor growth in combination with PD-1 antibody or TIGIT deficiency

[00654] After demonstrating that genetic deficiency of PVRIG resulted in reduced tumor growth, we next aimed to demonstrate that antibody-mediated inhibition of PVRIG-

PVRL2 interaction could improve anti-tumor immunity, in particular in combination with PD1 or TIGIT inhibitors as our human in vitro data has demonstrated. To assess this, we generated a high affinity, antagonistic anti-mPVRIG antibody. Affinity assessments of anti-mPVRIG mAb determined by FACS showed sub-nano-molar Kd (0.33 nM on HEK293 mPVRIG, 0.39 nM on D10.G4.1 cells), similar to CHA.7.518.1.H4(S241P) (Figure 39F-G). The specificity of this antibody was further confirmed as the majority of binding to D10.G4.1 cells was abrogated upon mPVRIG knockdown (Figure 39H). Anti-mPVRIG was tested for disrupting mPVRIG-mPVRL2 interaction by inhibiting the binding of mPVRIG Fc to B16F10 and the binding of mPVRL2 Fc to mPVRIG-overexpressing HEK293 cells (Figure 33A). Complete blocking of PVRIG-PVRL2 interaction by anti-mPVRIG antibody was observed in both assay formats (Figure 33A, Figure 39I), demonstrating an antagonistic anti-mPVRIG antibody. Next, we tested the in vivo efficacy of mPVRIG blockade in a syngeneic CT26 subcutaneous colon tumor model. PVRIG expression was elevated on NK and T cells in the tumor microenvironment, compared to corresponding splenic or draining lymph node subsets (Figure 33B). Treating tumor bearing mice with anti-mPVRIG blocking mAb as monotherapy failed to reduce tumor growth (data not shown). However, combination of anti-PVRIG and anti-PD-L1 mAbs effectively delayed CT26 tumor growth (Figure 33C) and increased significantly the survival of treated mice with 40% rate of complete responders (Figure 33D). Consistent with our human T cell assay data, these data demonstrate that combination of PD-1 and PVRIG inhibitors can reduce tumor growth.

[00655] We also tested the effect of ablating both PVRIG and TIGIT signaling in regulating anti-tumor responses. For these studies, we tested the efficacy of anti-mPVRIG antibody in either WT or TIGIT$^{-/-}$ mice inoculated with B16F10/Db-hmgp100 melanoma cells. Treatment of tumor bearing WT mice with anti-mPVRIG blocking mAb had minor effect compared to isotype treatment (17% TGI at day 11 and 8% TGI at endpoint, day 18). The effect of TIGIT deletion on tumor growth was minor as well, compared to WT control group (17% TGI at day 11 and 13% TGI at endpoint). However, when TIGIT deletion was combined with anti-PVRIG mAb treatment, a significant tumor growth inhibition was observed (63% at day 11 and 49% TGI at endpoint (Figure 33E, F). In accordance to tumor growth inhibition, TIGIT$^{-/-}$ mice treated with anti-PVRIG mAb 407 exhibited increased survival compared to WT control group, however, statistical significance was not achieved in this aggressive

rapidly growing tumor model (data not shown). Taken together, these data demonstrate synergistic activity of PVRIG inhibitors with PD1 or TIGIT inhibitors and are in accordance with our human functional data providing the rationale for clinical testing of CHA.7.518.1.H4(S241P) with PD1 or TIGIT inhibitors.

Discussion

[00656] Although antibodies targeting immune T cell checkpoints such as CTLA4 and PD-1 have increased cancer patient survival, the majority of cancer patients still do not display clinical benefit. One possible reason for this is the presence of additional T cell regulators that inhibit T cell anti-tumor immunity. Here, we elucidated the role of PVRIG in regulating effector T cell function and demonstrate that PVRIG antagonism increases T cell anti-tumor responses and reduces tumor growth.

[00657] PVRIG is a novel member of the nectin and nectin like family, placing it among several known immunoregulatory receptors in the family. Understanding the interplay of the receptors within this family is crucial to understanding the relevance and mechanism of action of PVRIG. Of these receptors, DNAM, TIGIT, and CD96 are most closely related to PVRIG in terms of sharing the same ligands, PVR and PVRL2. DNAM binds to both PVR and PVRL2 and delivers a costimulatory signal to lymphocytes. TIGIT is reported to bind to PVR and weakly to PVRL2. We were unable to detect an interaction between TIGIT and PVRL2 using ELISA or SPR (data not shown), suggesting that PVR is the dominant ligand for TIGIT. Using similar methods, we and a recent report detected a high affinity interaction between PVRL2 and PVRIG, suggesting that PVRIG is the dominant inhibitory receptor to PVRL2. These data suggest that TIGIT and PVRIG comprise dual signaling nodes in this axis and that blocking both is needed for maximal increase of T cell activation within this family. In addition to interacting with different ligands, we observed that PVRIG has the highest expression on effector or memory T cells, similar to PD-1 whereas TIGIT has the highest expression on regulatory T cells. Furthermore, we observed that PVRIG displayed late induction after T cell activation as compared to TIGIT. These data suggest that PVRIG has a unique role within this family, interacting with high affinity to PVRL2 and having a differentiated expression on memory cells and a late induction profile to TIGIT.

[00658] We also report here on the novel role of PVRIG in regulating anti-tumor T cell responses using PVRIG deficient mice and antagonistic anti-PVRIG antibodies. We demonstrate that mouse PVRIG was expressed on T cells and NK cells, induced upon lymphocyte activation, and is highest in the TME as compared to the periphery. Furthermore, we show that PVRIG deficiency led to increased T cell function in-vitro and reduced tumor growth in-vivo. An antagonistic antibody to PVRIG reduced tumor growth when combined with anti-PD-L1 or genetic deficiency of TIGIT, demonstrating a necessary role of PVRIG in regulating T cell responses. These novel data provide in vivo proof of concept using preclinical tumor models that targeting PVRIG in combination with PD1 or TIGIT antagonism is a potential novel therapy for the treatment of cancers.

[00659] We report here on a high affinity anti-human PVRIG antibody that disrupts the interaction of PVRIG and PVRL2 which we are pursuing for testing in clinical trials. To determine potential cancer indications that could inform on patient selection in clinical trials, we examined the expression profile of this axis in human cancers by FACS and IHC. For PVRIG, we observed that the mean expression of PVRIG on CD4 and CD8 T cells by FACS highest in endometrial, lung, kidney, and ovarian cancers, although this difference did not achieve statistical difference with other cancer types as determined by ANOVA with a Tukey's multiple comparison test with the current number of samples. As PVRIG is induced upon T cell activation and given that the majority of tumor infiltrating T cells are antigen experienced, it is perhaps not surprising that the median PVRIG expression was similar across tumor samples and cancer types. We observed that PVRIG expression was correlated with PD-1 and TIGIT expression, suggesting that the interplay of these 3 inhibitory receptors will be important in regulating the anti-tumor response. In this report, we observed a synergistic increase in T cell function when PVRIG antibodies were combined with TIGIT antibodies in a CD8 T cell tumor cell co-culture, better than PD-1 in combination with PVRIG or TIGIT inhibitors. These data, along with a previous study demonstrating a role for PVRIG and TIGIT in regulating DC-T cell interactions, show that this pathway could be involved in regulating T cell-APC and T cell-tumor cell interactions, and provide multiple mechanisms by which targeting PVRIG could increase the anti-tumor immune response.

[00660] As expression of PD-L1 has been correlated with clinical response to PD-1 inhibitors, we also analyzed PVRL2 expression in tumors by FACS and IHC to assess whether certain cancer types have higher expression. Assessing dissociated tumor cells, we observed that mean PVRL2 expression on macrophages from endometrial, head & neck, kidney, lung, and ovarian samples were higher when compared to other tumor types. Mean PVRL2 expression on $CD45^-$ non immune cells was higher on breast, colorectal, endometrial, lung, ovarian, and prostate cancers compared to other cancers. Based on the PVRIG and PVRL2 expression, we determined that endometrial, head & neck, lung, kidney, and ovarian cancers have a greater incidence of tumors with high PVRIG and PVRL2 expression and that these are potential cancers that could response to inhibitors of this pathway.

[00661] We did observe that PVRL2 expression can be modulated on antigen producing cells in vitro by inflammatory mediators whereas PVRL2 expression on cancer cells was not altered. These data suggest that PVRL2 expression on antigen presenting cells can be regulated by inflammation and could be an indicator of an inflamed tumor. Indeed, we did observe that all PD-L1+ tumors also express PVRL2, both on the tumor cells and in the immune compartment. Expression of PVRL2 on myeloid cells could help predict responses to PVRIG inhibitors in a combination setting with PD-1 or TIGIT to further enhance the anti-tumor effect. Interestingly, a portion of PD-L1 negative tumors also expressed PVRL2, primarily on the tumor cells and not on the immune cells. PVR and PVRL2 expression on epithelial cells is reported to be induced in tumorigenesis by xyz and also in response to stress and DNA damage. These data are consistent with our in vitro finding that the regulation of PVRL2 expression on tumor cells is not dependent on IFN-γ. As PD-L1 is induced in an adaptive resistance setting in response to IFN-γ and is associated with an inflammatory response, the expression of PVRL2 in the absence of PD-L1 suggests that PVRL2 expression is more prevalent than PD-L1 and that PVRL2 is expressed in non-inflamed tumors. Based on the above, it is possible that the presence of PVR and PVRL2 contribute to suppressing immune responses independently of PD-L1 and that inhibitors of PVRIG and TIGIT could be of particular importance in patients that are PD-L1 negative or non-responders/progressors to PD-1 inhibitors.

[00662] In summary, this report provides several novel insights into PVRIG biology, including characterizing the expression of this axis in human cancers, demonstrating a prominent role for PVRIG/TIGIT in regulating the CD8-tumor cell interaction, and showing that PVRIG antagonism in combination with PD-1 inhibition or TIGIT deficiency lead to a synergistic reduction in tumor growth. These data extend our current understanding of PVRIG biology and provide rationale for clinical testing of CHA.7.518.1.H4(S241P), a high affinity anti-PVRIG antibody, in patients with cancer.

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EXAMPLE 6: TUMOR CELL KILLING ASSAY

[00663] The effect of an anti-human TIGIT antibody and CHA.7.518.1.H4(S241P), either alone or in combination, on tumor cell killing was assessed by an in vitro co-culture assay with human CMV-specific $CD8^+$ T cells. The HLA-$A2^+$ target cell lines used in the assay were the melanoma cell line, Mel624, which stably expresses human PVR and PVRL2, and the pancreatic adenocarcinoma cell line, Panc05.04, which expresses endogenous levels of human PVR and PVRL2. Both tumor cell lines were stably transduced with a luciferase reporter gene through lentiviral transduction (System Biosciences). Mel624 and Panc05.04 cells were pulsed with the CMV pp65 peptide at 0.0033 μg/ml or 0.01 μg/ml at 37 °C for 1 hour, respectively. Cells were then washed and plated at 20,000 cells/well. A benchmark anti-human TIGIT antibody and CHA.7.518.1.H4(S241P) were added to the culture in combination, or with a control hIgG4 isotype antibody at 10 μg/ml. Human CMV-specific $CD8^+$ T cells from three different donors, specified as Donor 4, Donor 72, and Donor 234 were added at 100,000 cells/well. Co-cultures were incubated at 37 °C for 16 hours. After the incubation, plates were removed from the incubator and allowed to equilibrate to room temperature for 30 minutes. Bio-Glo luciferase substrate (Promega) was added to each well and the mixture equilibrated for 10 minutes at room temperature protected from light. Luminesce or relative light units (RLU) was quantified on an EnVision multi-label reader (Perkin Elmer) with an ultra-sensitive luminescence detector. Percent specific killing was calculated by [(RLU for treatment antibody – RLU for medium alone)/RLU for medium alone] x 100.

Results

[00664] Figure 43A and B show the effect of the anti-TIGIT antibody and CHA.7.518.1.H4(S241P) treatment on killing of the Mel624 and Panc05.04 cells, respectively. When added to the co-culture alone, both the anti-TIGIT antibody and CHA.7.518.1.H4(S241P) induced signficant T cell killing of the tumor cell lines compared to the isotype control antibody. For the anti-TIGIT antibody the percent specific killing ranged from 19-41% for the Mel624 cells, and 3-44% for the Panc05.04 cells across the 3 different CMV-reactive donors tested. For CHA.7.518.1.H4(S241P), the percent specific killing ranged from 16-20% for the Mel624 cells, and 0.21-29% for the Panc05.04 cells. In some cases, an additive effect on tumor cell killing was observed in the combined treatment of the anti-TIGIT antibody and CHA.7.518.1.H4(S241P).

[00665] To determine whether the effect of an anti-TIGIT antibody and CHA.7.518.1.H4(S241P) on tumor cell killing was dose-dependent, the assay was carried out with a 10 point, 2-fold dilution series for each antibody starting at 0.5 μg/ml for the anti-TIGIT antibodies, and 10 μg/ml for CHA.7.518.1.H4(S241P) (Figure 44). Mel624 killing decreased in a dose-dependent manner when either anti-TIGIT antibody, BM26 or CPA.9.086, were combined with CHA.7.518.1.H4(S241P). More potent killing was observed for the CPA.9.086 and CHA.7.518.1.H4(S241P) combination with an EC_{50} of 0.40 ± 0.49 nM, compared to the BM26 and CHA.7.518.1.H4(S241P) combination with an EC_{50} of 2.6 ± 1.7 nM.

EXAMPLE 7: BIOPHYSICAL MEASUREMENT OF KD

[00666] KinExA equilibrium experiments were performed using a KinExA 3200 instrument (Sapidyne Instruments, Boise, ID, USA) at 22°C. Recombinant His-tagged human TIGIT was obtained from Sino Biologicals (Beijing, China) and reconstituted into 1XPBS. All antigen and antibody samples for KinExA analyses were prepared in degassed PBST buffer (PBS with 0.05% tween 20) with 100 μg/mL filtered BSA and 0.02% sodium azide. The secondary detection antibody used was Alexa Flour 647-labeled goat anti-human IgG (H+L) (Jackson ImmunoResearch Laboratories) diluted 400- to 700-fold in the PBST buffer (with BSA and azide) described above from a 0.5 mg/mL stock in 1X PBS, pH 7.4. For each KinExA experiment, ~20 μg of human TIGIT was diluted into 1 mL of 50 mM sodium carbonate, pH 9.2 which was added directly to 50 mg of azlactone beads (Ultralink Support,

Thermo Scientific, Rockford, IL, USA) and rocked overnight at 4°C. After rocking, the beads were rinsed once with 1 M Tris buffer, pH 8.5, containing 10 mg/mL BSA and rocked for one hour at room temperature in the same buffer. Coupled beads were added to the bead reservoir in the KinExA instrument and diluted to ~30 mL with 1X HBS-N (0.01 M Hepes, 0.15M NaCl, GE Healthcare) containing 0.02% sodium azide which was also the running buffer for the KinExA instrument. All antigen-coupled beads were used immediately after preparation.

[00667] For two replicate measurements of K_D for CPA.9.086 (Table 1), 14 concentrations of TIGIT ranging from 957 aM – 212 pM were equilibrated at room temperature for ~72 hours with 2.5 pM CPA.9.086 binding sites and 1.8pM CPA.9.086 binding sites. For CPA.9.083, 14 concentrations of TIGIT ranging from 478 aM – 196pM were equilibrated for ~72 hours with 1.8pM CPA.9.083 binding sites. For duplicate measurements of the benchmark antibody, BM26 hIgG4, 14 concentrations of TIGIT ranging from 9.6fM – 3.53nM were equilibrated for ~72 hours with 20pM BM26 binding sites and 8.0 pM BM26 binding sites. For CHA.9.547.13, 14 concentrations of TIGIT ranging from 10.5fM – 2.2nM were equilibrated for ~72 hours with 8pM mAb CHA.9.547.13 binding sites. The volume flowed through the bead pack for each equilibrated sample for all experiments ranged from 4mL to 11mL at a flow rate of 0.25 mL/min. Data were fit with a 1:1 "standard equilibrium" binding model using KinExA Pro software (Version 4.2.10; Sapidyne Instruments) to estimate K_D and generate the 95% confidence interval (CI) of the curve fit.

Results

[00668] Both CPA.9.083 and CPA.9.086 bound to human TIGIT with femtomolar binding affinity, while CHA.9.547.13 and BM26 bound with picmolar affinity. Thus, CPA.9.083 and CPA.9.086 bound to human TIGIT with the highest affinity of the four different antibodies tested.

Table 1: K_D measurements of anti-human TIGIT hIgG4 antibodies determined by KinExA

Antibody	**K_D ± 95% CI (n=1)**	**K_D ± 95% CI (n=2)**
CHA.9.547.13	18.8 ± 5.8pM	Not determined
CPA.9.083	694 ± 277fM	Not determined
CPA.9.086	553 ± 230fM	665 ± 378fM
BM26	8.2 ± 2.8pM	11.2 ± 3.6pM

EXAMPLE 8: DEVELOPMENT AND FUNCTIONAL CHARACTERIZATION OF CPA.9.086, A NOVEL THERAPEUTIC ANTIBODY TARGETING THE IMMUNE CHECKPOINT TIGIT

[00669] Background: TIGIT is a coinhibitory receptor that is highly expressed on lymphocytes, including effector and regulatory CD4+ T cells (Tregs), effector CD8+ T cells, and NK cells, that infiltrate different types of tumors. Engagement of TIGIT with its reported ligands, poliovirus receptor (PVR) and PVR-like proteins (PVRL2 and PVRL3) directly suppresses lymphocyte activation. PVR is also broadly expressed in tumors, suggesting that the TIGIT-PVR signaling axis may be a dominant immune escape mechanism for cancer. We report here the biophysical and functional characterization of CPA.9.086, a therapeutic antibody targeting TIGIT. We also demonstrate that co-blockade of TIGIT and a new checkpoint inhibitor, PVRIG, augments T cell responses.

[00670] Materials and Methods: Human phage display and mouse hybridoma antibody discovery campaigns were conducted to generate therapeutic anti-TIGIT antibodies. The resulting antibodies were evaluated for their ability to bind to recombinant and cell surface-expressed human TIGIT with high affinity. Cross-reactivity of the antibodies to cynomolgus macaque and mouse TIGIT was also examined. A subset of antibodies that bound with high affinity to human TIGIT, and cross-reactive to cynomolgus TIGIT were further characterized for their ability to block the interaction between TIGIT and PVR. Blocking antibodies were screened for their ability to enhance antigen-specific T

cell activation in vitro either alone, or in combination with an anti-PVRIG antibody, CHA.7.518.1.H4(S241P).

[00671] **Results**: We identified a lead antibody, CPA.9.086, that binds to human TIGIT with high femtomolar affinity. This antibody bound to TIGIT endogenously expressed on human CD8+ T cells with higher affinity than tested benchmark antibodies, and was also cross-reactive to both cynomolgus and mouse TIGIT. When tested for in vitro activity, CPA.9.086 augmented cytokine secretion and tumor cell killing by CMV-specific CD8+ T cells with superior or equivalent potency to the tested benchmark antibodies. Combination of CPA.9.086 with an anti-PD1 antibody or CHA.7.518.1.H4(S241P) resulted in enhanced CMV-specific CD8+ T cell activity. Furthermore, we demonstrated that TIGIT is predominantly expressed on Tregs and effector CD8+ T cells from solid tumors compared to peripheral blood, suggesting that these populations will likely be preferentially targeted by CPA.9.086.

[00672] **Conclusion**: We describe the development of a very high affinity antagonistic TIGIT antibody, CPA.9.086, that is currently in preclinical development. We postulate that the femtomolar affinity of CPA.9.086 could result in lower and less frequent dosing in patients. CPA.9.086 can enhance human T cell activation either alone or in combination with other checkpoint antibodies. Thus, our data demonstrates the utility of targeting TIGIT, PD1, and PVRIG for the treatment of cancer.

EXAMPLE 9: Analysis of the TIGIT/PVRIG axis in human cancers to support indication selection and biomarkers for co-treatment

[00673] **Background**: PVRIG and TIGIT were identified by Compugen's Predictive Discovery Platform as immune inhibitory receptors and have been reported to inhibit anti-tumor activity. We are pursuing clinical development of antagonistic antibodies to PVRIG (e.g. CHA7.518.1.H4(S241P)) and to TIGIT (e.g. CPA.9.083.H4(S241P)). Here, we analyzed primary human cancer tissues and immune cells to characterize expression in the TIGIT/PVRIG axis to support indication selection and combination strategies for these antibodies.

[00674] **Methods**: CHA7.518.1.H4(S241P) and CPA.9.083.H4(S241P) were identified based on ability to block the interaction of PVRIG and TIGIT with their cognate ligands (PVRL2 and PVR respectively) and were screened for their ability to enhance antigen-specific CD8 T cell activation in a co-culture with tumor cell lines. Immunohistochemistry and Flow cytometry were performed to assess receptor/ligand expression in dissociated bladder, breast, colorectal, head and neck, lung, kidney, ovarian, prostate, and stomach tumors.

[00675] **Results**: Among the cancers examined, PVRIG and PVRL2 expression was highest in endometrial, lung, kidney, ovarian, and head and neck cancers compared to normal adjacent tissue. From dissociated tumors, PVRIG expression was detected on T and NK TILs whereas PVRL2 expression was detected on $CD45^-$ cells and myeloid cells. A co-expression analysis of PVRIG, TIGIT, and PD1 demonstrated that PVRIG was co-expressed with both TIGIT and PD1 and that $PVRIG^+TIGIT^+PD1^+$ cells comprised a major proportion of CD8 TILs. In comparison to PD-L1, PVRL2 expression was more prevalent across several cancer types and expression of PVRL2 was detected in PD-L1 negative samples. In vitro, combination of CHA7.518.1.H4(S241P) with PD1 inhibitors or CPA.9.083.H4(S241P) enhanced CD8 cytokine production and cytotoxic activity, with the triple combination of CHA7.518.1.H4(S241P), CPA.9.083.H4(S241P), and PD-1 antibody yielding the greatest increase in functional activity. Several immune receptors were induced in response of PVRIG blockade by CHA7.518.1.H4(S241P) on CD8 T cells. Taken together, these data support indication selection and combination strategies for CHA7.518.1.H4(S241P) and CPA.9.083.H4(S241P) and potential biomarkers that could be indicators of response.

[00676] **Conclusions**: In summary, we demonstrate that PVRIG and PVRL2 are induced in the tumor microenvironment of human cancers, and the potential of CHA7.518.1.H4(S241P) as a cancer therapeutic, either as a monotherapy or as a dual- or triple-combination therapy with antibodies targeting TIGIT, and PD-1. These data highlight the potential of this combination approach to expand the immune checkpoint inhibitor responsive cancer patient population, including those who are non-responsive to PD-1 inhibitors.

EXAMPLE 10: PVRIG Expression is Associated With T Cell Exhaustion and Synergizes With TIGIT to Inhibit Anti-Tumor Responses

ABSTRACT

[00677] By employing a unique computational discovery platform, we identified a novel checkpoint receptor family comprised of 2 inhibitory receptors in the nectin family, TIGIT and PVRIG. PVRIG and TIGIT are both expressed upon T cell activation, but display a difference in relative expression among T cell subsets and expression kinetics. PVRIG binds to PVRL2 whereas TIGIT binds to several ligands, among which we observed that PVR is the dominant functional ligand for TIGIT. The distinct expression profile of PVRIG and a unique high affinity PVRIG-PVRL2 interaction suggest that PVRIG has a unique role in regulating immunity. Using novel PVRIG-/- mice, we observed that genetic deficiency of PVRIG resulted in increased T cell responses and reduced tumor growth in preclinical models, demonstrating the potential of targeting this pathway in cancer. To further define a clinical niche for a PVRIG antagonist, we interrogated the expression of TIGIT/PVRIG and PD-1 axis in human tumor samples. Among the human cancers examined, PVRIG and TIGIT expression on tumor derived T cells were highest in endometrial, lung, kidney, and ovarian cancers. A co-expression analysis of PVRIG, TIGIT, and PD1 demonstrated that PVRIG was correlated and co-expressed with both TIGIT and PD1 and that $PVRIG^{+}TIGIT^{+}PD1^{+}$ cells comprised a major percentage of CD8 tumor infiltrating lymphocytes (TILs). Interestingly, PVRIG and not TIGIT expression on $CD8^{+}$ TILs were associated with an exhausted $Eomes^{hi}T\text{-}bet^{lo}$ phenotype. PVR, PVRL2, and PD-L1 also displayed tissue specific differences in relative expression level, with endometrial and ovarian tumors having a higher ratio of PVRL2 expression relative to PVR or PD-L1. Culture of primary human TILs with anti-PVRIG (CHA7.518.1.H4(S241P)) and anti-TIGIT (CPA.9.083.H4(S241P)) antagonistic antibodies enhanced T cell function to a similar or greater magnitude compared to PD-1 blockade. See, Figures 54 through 60.

CHA7.518.1.H4(S241P) & CPA.9.083.H4(S241P) TARGET PVRIG AND TIGIT IN THE NECTIN & NECTIN-LIKE FAMILY: CONCLUSIONS

[00678] PVRIG and TIGIT are non-redundant checkpoint receptors and promising targets for the treatment of cancer

[00679] In tumors with higher PVRL2 than PVR, the PVRIG/PVRL2 interaction could be more dominant and require direct targeting of PVRIG

EXAMPLE 11: New Preclinical Data Demonstrating the Distinctive Features of the PVRIG Pathway in Immuno-Oncology and the Potential of CHA7.518.1.H4(S241P) in Treating Multiple Solid Tumors

Data further strengthens rationale for Clinical Development Plan and Biomarker Strategy for CHA7.518.1.H4(S241P)

CHA7.518.1.H4(S241P) Shown to be Safe at High Doses in GLP Toxicity Study

[00680] Provides new preclinical data demonstrating the distinctive features of the PVRIG pathway in Immuno-Oncology and the potential of CHA7.518.1.H4(S241P), a first-in-class therapeutic antibody candidate targeting PVRIG in treating multiple solid tumors. The data, presented at the Keystone Symposia Conference, A3: T Cell Dysfunction, Cancer and Infection, being held January 16-20, 2018 (an provided in Example 9 and related figures), demonstrate the possible dominance of the PVRIG/TIGIT axis in immuno-oncology and support the Company's clinical development program and biomarker strategy for CHA7.518.1.H4(S241P) as a monotherapy and in combination with CPA.9.083.H4(S241P).

[00681] The poster titled "PVRIG Expression is Associated with T Cell Exhaustion and Synergizes with TIGIT to Inhibit Anti-Tumor Responses" (Poster no. 2028) includes data showing that expression of PVRL2, the ligand for PVRIG, is more dominant in several tumor types including lung , breast, endometrial, and ovarian, than the expression of PVR, the ligand for TIGIT. These results suggest that PVRIG may be the dominant checkpoint in patient populations with tumor expressing elevated PVRL2, many of which are not responsive to PD-1 inhibitors. Therefore, these patients may have an increased likelihood of responding to CHA7.518.1.H4(S241P) as a monotherapy treatment.

[00682] In addition, expression studies show that PVRIG and TIGIT and their respective ligands are commonly expressed in the tumor types listed above as well as kidney and head & neck cancers, indicating that in patient populations where the two pathways are operative the blockade of both TIGIT and PVRIG may be needed in order to

sufficiently stimulate the anti-tumor immune response. Furthermore, data also indicates that exhausted TILs found in multiple tumor types are largely co-expressing the triple three checkpoints -, TIGIT, PD-1 and PVRIG, further supporting the relevance of a triple combination in such patient populations.

[00683] Our growing understanding of the PVRIG-TIGIT axis and the interplay between the various axis components also shed light on the evolution of the PVRIG/PVRL2 pathway in the transition from mouse to humans, resulting in a less active pathway in mice. Our data clearly demonstrates that the mouse biology in connection of this pathway is underestimating the human impact this pathway may have on anti-tumor immunity, suggesting that CHA7.518.1.H4(S241P) may have an even greater therapeutic impact than the one seen in preclinical studies.

[00684] "The potential dominance of the PVRIG pathway and its interactions with the TIGIT and PD-1 pathways demonstrated in our preclinical studies coupled with the expression profiles provide the biological rationale to support our clinical approach to test CHA7.518.1.H4(S241P) as a monotherapy and in dual and triple combination as we are preparing to initiate our clinical Phase 1b trial. While keeping our all comers trial design, our biomarker strategy will be driven by these expression profiles, in order to enrich for patients most likely to respond to CHA7.518.1.H4(S241P)," stated Anat Cohen-Dayag, PhD, President and CEO of Compugen. "We are also encouraged by results of the GLP toxicity study for CHA7.518.1.H4(S241P), showing it to be safe at high doses. Our data lead us to believe that the PVRIG pathway and CHA7.518.1.H4(S241P), our first-in-class therapeutic antibody, may hold significant clinical value as the basis of new cancer immunotherapies to meet the needs of patient populations non-responsive or refractory to current immune checkpoint inhibitor therapy."

About CHA7.518.1.H4(S241P) and CPA.9.083.H4(S241P)

[00685] CHA7.518.1.H4(S241P) is a humanized hybridoma antibody that binds with high affinity to PVRIG, a novel B7/CD28-like immune checkpoint target candidate discovered by Compugen, indicating blockage of this target's interaction with PVRL2. Blockade of PVRIG by CHA7.518.1.H4(S241P) has demonstrated potent, reproducible enhancement of T cell activation, consistent with the desired mechanism of action of

activating T cells in the tumor microenvironment to generate anti-tumor immune responses. In addition, CHA7.518.1.H4(S241P) combined with antagonist anti-PD-1 antibodies has demonstrated synergistic effect on human T cell stimulation, indicating the potential of these combinations to further enhance immune response against tumors.

[00686] CPA.9.083.H4(S241P), Compugen's antibody targeting TIGIT, was developed for combination use with CHA7.518.1.H4(S241P). Preclinical data strongly support the dual blockade of the two negative costimulatory arms of the axis – TIGIT and PVRIG – that results in a more robust T cell response to antigen stimulation, and therefore may result in an enhanced anti-tumor immune response.

EXAMPLE 12: In vivo Efficacy and Survival with triple combo treatment

Rationale and Objectives

[00687] This example provides regarding whether the combination of mouse TIGIT, PVRIG and PD-L1 blockade can significantly enhance tumor growth inhibition (TGI) and survival in a syngeneic mouse tumor model.

Protocols

Animals

[00688] Female mice of 5 week-age were purchased from Charles River Laboratories. The mice were housed at the Compugen USA animal facility with food and water provided, ad libitum, and acclimated for a minimum of 6 days prior to initiation of the study. All studies were approved by the Institutional Animal Care and Use Committee at the Compugen USA (South San Francisco, CA).

Syngeneic mouse tumor model

[00689] 5×10^5 CT26 colon carcinoma (ATCC) cells were inoculated subcutaneously (s.c.) into the right flank of female Balb/c mice, and grown for up to 8 days. Mice with tumors measuring 30-60mm^3 were randomized (day of randomization designated day 0) into 3 groups of 10 mice per group. Animals received a 200 µL intraperitoneal (i.p.) injection of either a mouse IgG1 (mIgG1) isotype control antibody (referred to as Synagis), a dual combination of an anti-TIGIT mIgG1 and anti-PVRIG mIgG1 antibodies, or a triple

combination of anti-TIGIT mIgG1, anti-PVRIG mIgG1, and anti-PD-L1 mIgG1 antibodies. The anti-TIGIT mIgG1 antibody is a chimeric version of CPA.9.086 that contains the human variable heavy and light chains of CPA.9.086 and the constant region of mIgG1. The antibodies were administered at fixed-doses of 10mg/kg anti-TIGIT, 10mg/kg anti-PVRIG, and a suboptimal dose of anti-PD-L1 at 3mg/kg starting on day 8 three times per week for 2 weeks. Tumor growth is determined by caliper measurement of length (L) and width (W); wherein the tumor size is calculated with the formula $(L \times W^2)/2$. Tumor size were not allowed to exceed $2000mm^3$, which was designated as the study endpoint, and mice were subsequently euthanized.

Statistical Analysis

[00690] Two-way ANOVA with repeated measures, followed by two-way ANOVA with repeated measures for selected pairs of groups was performed using prism software. Analyses of tumor growth measurements were performed by comparing tumor volumes measured on the last day on which all study animals were alive. Statistical differences in percentage of mice tumor free were determined by a Log Rank Mantel–Cox test.

Results and Summary

[00691] In this study, the effect of blocking three different immune checkpoint pathways, TIGIT, PVRIG and PD-L1, on TGI and survival in mice was examined. Using the mouse colon carcinoma CT26 model, the combination of the anti-TIGIT mIgG1 with the anti-PVRIG mIgG1 resulted in small but significant TGI (20.7% TGI at day 25) compared to the mice dosed with the isotype control antibody. When the three antibodies were combined, TGI increased to 58.3% at day 25, which was statistically and significantly efficacious compared to the dual combination ($p<0.001$ by two-way ANOVA at day 25). Although none of the mice were tumor free (CR) by the end of the study (day 28), the enhanced efficacy in triple combination was associated with increased survival compared to dual combination. Triple blockade demonstrated significant enhancement of overall survival with 90% survival at the study endpoint (day 28). In addition to the antitumor efficacy reported here, there was no significant body weight changes in all groups observed (data not shown). Taken together, the triple combination was well tolerated and produced a superior antitumor effect in colon carcinoma *in vivo* compared to the dual combination of TIGIT and PVRIG blockade alone. *See*, Figure 61.

WHAT IS CLAIMED IS:

1. A method of treating cancer in a patient comprising:

a) providing a biopsy from said patient comprising tumor cells;

b) measuring the frequency of PD-L1 positive tumor cells or immune cells in said biopsy;

c) if said frequency of PD-L1 positive tumor cells or immune cells is greater than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a triple combination therapy comprising an anti-TIGIT antibody, an anti-PVRIG antibody and an anti-PD-1 antibody; and

d) if said frequency of PD-L1 positive tumor cells or immune cells is less than 1% compared to staining the same tumor cells with a relevant isotype control antibody for the antibodies used, administering a double combination therapy comprising an anti-TIGIT antibody and an anti-PVRIG antibody.

2. A method according to claim 1, wherein said anti-TIGIT antibody is an antibody chosen from any anti-TIGIT antibody described herein, including any of those described in Figure 3.

3. A method according to claim 1, wherein said anti-PVRIG antibody is an antibody chosen from any anti-PVRIG antibody described herein, including any of those described in Figure 5 and/or Figure 63.

4. A method according to claim 1 wherein said anti-PD-1 antibody is an antibody chosen from any anti-PD-1 antibody described herein, including any of those described in Figure 7.

5. A method according to claims 1 to 4, wherein said anti-TIGIT antibody is an antibody chosen from at least one of CPA.9.083.H4(S241P), CPA.9.086.H4(S241P), CHA.9.547.7.H4(S241P), and CHA.9.547.13.H4(S241P).

6. A method according to claims 1 to 5, wherein said anti-PVRIG antibody is an antibody chosen from at least one of CHA.7.518.1.H4(S241P) and CHA.7.538.1.2.H4(S241P).

7. A method according to claims 1 to 6, wherein said anti-PD-1 antibody is an antibody chosen from at least one of pembrolizumab, cemiplimab, and nivolumab.

8. A method according to any one of claims 1 to 7, wherein said double combination therapy is chosen from the administration of CPA.9.083.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P) and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P) and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P) and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P) and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P) and CHA.7.538.1.2.H4(S241P).

9. A method according to any one of claims 1 to 8, wherein said triple combination therapy is chosen from the administration of CPA.9.083.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), pembrolizumab and CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, nivolumab and CHA.7.538.1.2.H4(S241P); CHA.9.547.13.H4(S241P), nivolumab and CHA.7.538.1.2.H4(S241P); CHA.7.538.1.2.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.7.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.518.1.H4(S241P); CPA.9.083.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CPA.9.086.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P); CHA.9.547.7.H4(S241P, cemiplimab and CHA.7.538.1.2.H4(S241P); and CHA.9.547.13.H4(S241P), cemiplimab and CHA.7.538.1.2.H4(S241P).

10. A method according to any one of claims 1 to 9, wherein said antibodies are administered simultaneously.

11. A method according to any one of claims 1 to 10, wherein said antibodies are administered sequentially.

12. A method according to any one of claims 1 to 11, wherein said cancer is selected from the group consisting of prostate cancer, liver cancer (HCC), colorectal cancer, ovarian cancer, endometrial cancer, breast cancer, triple negative breast cancer, pancreatic cancer, stomach (gastric) cancer, cervical cancer, head and neck cancer, thyroid cancer, testis cancer, urothelial cancer, lung cancer (small cell lung, non-small cell lung), melanoma, non melanoma skin cancer (squamous and basal cell carcinoma), glioma, renal cancer (RCC), lymphoma (NHL or HL), Acute myeloid leukemia (AML), T cell Acute Lymphoblastic Leukemia (T-ALL), Diffuse Large B cell lymphoma, testicular germ cell tumors, mesothelioma, esophageal cancer, Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

13. A method according to any one of claims 1 to 12, wherein said cancer is selected from the group consisting of triple negative breast cancer, stomach (gastric) cancer, lung cancer (small cell lung, non-small cell lung), Merkel Cells cancer, MSI-high cancer, KRAS mutant tumors, adult T-cell leukemia/lymphoma, and Myelodysplastic syndromes (MDS).

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Figure 1A

Human IgG1 constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 1)
Human IgG1 D265A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV[A]VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 2)
Human IgG1 N297A constant region
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY[A]STYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 3)
Human IgG2 constant region
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVD
KTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV
HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 4)
Human IgG3 constant region
ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVD
KRVELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
(SEQ ID NO: 5)

Figure 1B

Human IgG4 constant region (Wild Type)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 6)

Human IgG4 constant region (S241P hinge mutant)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 7)

Human kappa light chain

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
SSPVTKSFNRGEC (SEQ ID NO: 8)

Human lambda light chain

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS
TVEKTVAPTECS (SEQ ID NO: 9)

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Figure 2

Human TIGIT extra-cellular domain

MMTGTIETTGNISAEKGGSIILQCHLSSTTAQVTQVNWEQQDQLLAICNADLGWHISPSFKDRVAPGPGLGLTLQSLTVNDTGEYFCIYHTYPD
GTYTGRIFLEVLESSVAEHGARFQIP (SEQ ID NO: 10)

Cynomolgus macaque TIGIT extra-cellular domain

MMTGTIETTGNISAKKGGSVILQCHLSSTMAQVTQVNWEQHDHSLLAIRNAELGWHIYPAFKDRVAPGPGLGLTLQSLTMNDTGEYFCTYHT
YPDGTYRGRIFLEVLESSVAEHSARFQIP (SEQ ID NO: 11)

Human PVRIG extra-cellular domain

TPEVWVQVRMEATELSSFTIRCGFLGSGSISLVTVSWGGPNGAGGTTLAVLHPERGIRQWAPARQARWETQSSISLILEGSGASSPCANTTFCCK
FASFPEGSWEACGSLPPSSDPGLSAPPTPAPILRAD (SEQ ID NO: 12)

Cynomolgus macaque PVRIG extra-cellular domain
TPEVWVQVQMEATELSSFTVHCGFLGPGSISLVTVSWGGPDGAGGTKLAVLHPELGTRQWAPARQARWETQSSISLALEDSGASSPFANTTFC
CKFASFPEGSWESCGSLPPSSDPGLSAPPTPVPILRAD (SEQ ID NO: 13)

Human PD-1 extra-cellular domain

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVR
ARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV (SEQ ID NO: 14)

Cynomolgus PD-1 extra-cellular domain

PGWFLESPDRPWNAPTFSPALLLVTEGDNATFTCSFSNASESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTRLPNGRDFHMSVVR
ARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQALV (SEQ ID NO: 15)

Figure 3A: CPA.9.018

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAKEMLVQDYYYMDVWGQGTTVTVSS	16
vhCDR1	GFTFSSYG	17
vhCDR2	IRYDGSNK	18
vhCDR3	AKEMLVQDYYYMDV	19
Full length HC (IgG4(S241P); **CPA.9.018.H4(S241P)**)	QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAKEMLVQDYYYMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	20
Variable light (vl) domain	DVVMTQSPLSLPVSPGEPASISCRSSQNLLHRNGINYLNWYLQKPGQSPQLLIYWGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ GLQIPPTFGQGTKVDIKR	21
vlCDR1	QNLLHRNGINY	22
vlCDR2	WGS	23
vlCDR3	MQGLQIPPT	24
Full length light chain (**(CPA.9.018.H4(S241P)**)	DVVMTQSPLSLPVSPGEPASISCRSSQNLLHRNGINYLNWYLQKPGQSPQLLIYWGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ GLQIPPTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	25

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Figure **3B : CPA.9.027**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	26
vhCDR1	GFTFSSYA	27
vhCDR2	ISYDGSNK	28
vhCDR3	ARDPLPLHYYGMDV	29
Full length HC (IgG4(S241P); **CPA.9.027.H4(S241P)**)	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	30
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDSLSSLQLGGGTQLAVLG	31
vlCDR1	SSNMGRRP	32
vlCDR2	SQN	33
vlCDR3	AVWDDSLSSLQ	34
Full length light chain **(CPA.9.027.H4(S241P))**	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDSLSSLQLGGGTQLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	35

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Figure **3C: CPA.9.049**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	36
vhCDR1	GFTFSSYA	37
vhCDR2	ISYDGSNK	38
vhCDR3	ARDPLPLHYYGMDV	39
Full length HC (IgG4(S241P); CPA.9.049.H4(S241P))	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	40
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDSLFSLLLGGGTQLAVLG	41
vlCDR1	SSNMGRRP	42
vlCDR2	SQN	43
vlCDR3	AVWDDSLFSLL	44
Full length light chain (CPA.9.049.H4(S241P))	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDSLFSLLLGGGTQLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	45

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Figure 3**D: CPA.9.057**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARQGAAAGNPFDIWGQGTMVTVSS	46
vhCDR1	GGSISSSSYY	47
vhCDR2	IYYSGST	48
vhCDR3	ARQGAAAGNPFDI	49
Full length HC (IgG4(S241P); CPA.9.057.H4(S241P))	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARQGAAAGNPFDIWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDK SRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	50
Variable light (vl) domain	QSVLTQPPSVSGTPGQRVTISCSGSSSNIGSNFVYWHQQLTGTAPKLLIYRNTQRPSGVPDRFSGSKSGTSASLAIGGLRSEDE ADYYCATWDDSLSAWVFGGGTKLTVLG	51
vlCDR1	SSNIGSNF	52
vlCDR2	RNT	53
vlCDR3	ATWDDSLSAWV	54
Full length light chain (CPA.9.057.H4(S241P))	QSVLTQPPSVSGTPGQRVTISCSGSSSNIGSNFVYWHQQLTGTAPKLLIYRNTQRPSGVPDRFSGSKSGTSASLAIGGLRSEDE ADYYCATWDDSLSAWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVET TTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	55

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Figure 3**E: CPA.9.059**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGARYSYGQYPYWGQGTLVTVSS	56
vhCDR1	GFTVSSNY	57
vhCDR2	IYSGGST	58
vhCDR3	ARGARYSYGQYPY	59
Full length HC (IgG4(S241P); **CPA.9.059.H4(S241P)**)	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGARYSYGQYPYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	60
Variable light (vl) domain	DIQLTQSPSFLSASVGDRVTITCRASHDISSLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFATY YCLQLDSFPTWTFGQGTKVEIKR	61
vlCDR1	HDISSL	62
vlCDR2	AAS	63
vlCDR3	LQLDSFPTWT	64
Full length light chain **(CPA.9.059.H4(S241P))**	DIQLTQSPSFLSASVGDRVTITCRASHDISSLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFATY YCLQLDSFPTWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	65

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Figure **3F: CPA.9.083**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGTPVYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	**66**
vhCDR1	GFTFSSYA	67
vhCDR2	ISYDGTPV	68
vhCDR3	ARDPLPLHYYGMDV	69
Full length HC (IgG4(S241P); CPA.9.083.H4(S241P))	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGTPVYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	70
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDGDRRSLQLGGGTQLAVLG	71
vlCDR1	SSNMGRRP	72
vlCDR2	SQN	73
vlCDR3	AVWDGDRRSLQ	74
Full length light chain (CPA.9.083.H4(S241P))	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDGDRRSLQLGGGTQLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGV ETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	75

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Figure 3G: **CPA.9.086**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYAGEVKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	**76**
vhCDR1	GFTFSSYA	77
vhCDR2	ISYAGEVK	78
vhCDR3	ARDPLPLHYYGMDV	79
Full length HC (IgG4(S241P); **CPA.9.086.H4(S241P)**)	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYAGEVKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	80
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDIGRVLQLGGGTQLAVLG	81
vlCDR1	SSNMGRRP	82
vlCDR2	SQN	83
vlCDR3	AVWDDIGRVLQ	84
Full length light chain **(CPA.9.086.H4(S241P))**	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCAVWDDIGRVLQLGGGTQLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	85

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Figure **3H: CPA.9.089**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDRTPVYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	86
vhCDR1	GFTFSSYA	87
vhCDR2	ISYDRTPV	88
vhCDR3	ARDPLPLHYYGMDV	89
Full length HC (IgG4(S241P); CPA.9.089.H4(S241P))	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDRTPVYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	90
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCATWDDSLPRLNFGGGTKLAVLG	91
vlCDR1	SSNMGRRP	92
vlCDR2	SQN	93
vlCDR3	ATWDDSLPRLN	94
Full length light chain (CPA.9.089.H4(S241P))	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCATWDDSLPRLNFGGGTKLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	95

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Figure **3I: CPA.9.093**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYEGDRKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSS	96
vhCDR1	GFTFSSYA	97
vhCDR2	ISYEGDRK	98
vhCDR3	ARDPLPLHYYGMDV	99
Full length HC (IgG4(S241P); CPA.9.093.H4(S241P))	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYEGDRKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDPLPLHYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	100
Variable light (vl) domain	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCATWDDSTPHGVFGGGTKLAVLG	101
vlCDR1	SSNMGRRP	102
vlCDR2	SQN	103
vlCDR3	ATWDDSTPHGV	104
Full length light chain (CPA.9.093.H4(S241P))	QSALTQPRSASGNPGQRVTISCSGSSSNMGRRPVNWYQQIPGTAPKLLIYSQNQRPSGVPDRFSGSQSGTSASLTISGLQSE DEAEYFCATWDDSTPHGVFGGGTKLAVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVE TTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	105

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Figure 3J: **CPA.9.101**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGAPLFGQYPYWGQGTLVTVSS	106
vhCDR1	GFTVSSNY	107
vhCDR2	IYSGGST	108
vhCDR3	ARGAPLFGQYPY	109
Full length HC (IgG4(S241P); CPA.9.101.H4(S241P))	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGAPLFGQYPYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	110
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASHAIASLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFAT YYCLQLDSFPTWTFGQGTKVEIKR	111
vlCDR1	HAIASL	112
vlCDR2	AAS	113
vlCDR3	LQLDSFPTWT	114
Full length light chain (CPA.9.101.H4(S241P))	DIQMTQSPSSLSASVGDRVTITCRASHAIASLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFAT YYCLQLDSFPTWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	115

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Figure **3K: CPA.9.103**

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGARPNGQYPYWGQGTLVTVSS	116
vhCDR1	GFTVSSNY	117
vhCDR2	IYSGGST	118
vhCDR3	ARGARPNGQYPY	119
Full length HC (IgG4(S241P); CPA.9.103.H4(S241P))	EVQLVETGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARGARPNGQYPYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV DKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	120
Variable light (vl) domain	DIQLTQSPSFLSASVGDRVTITCRASHGIKSLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFATY YCLQLDSFPTWTFGQGTKVEIKR	121
vlCDR1	HGIKSL	122
vlCDR2	AAS	123
vlCDR3	LQLDSFPTWT	124
Full length light chain (CPA.9.103.H4(S241P))	DIQLTQSPSFLSASVGDRVTITCRASHGIKSLFSWYQQKPGKAPKLLIYAASTLQTGVPSRFSGSASGTEFTLTISSLQPEDFATY YCLQLDSFPTWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	125

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Figure 3**L:**

BM26 hIgG4 (BM26-H4) (WO2016/028656A1, Clone 31C6)

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGSSVKMSCKASGYTFSSYVMHWVKQKPGQGLEWIGYIDPYNDGAKYNEKFKGKATLTSDKSSSTAY MELSSLTSEDSAVYYCARGGPYGWYFDVWGAGTTVTVSS	126
vhCDR1	GYTFSSYV	127
vhCDR2	IDPYNDGA	128
vhCDR3	ARGGPYGWYFDV	129
Full length HC (IgG4(S241P))	EVQLQQSGPELVKPGSSVKMSCKASGYTFSSYVMHWVKQKPGQGLEWIGYIDPYNDGAKYNEKFKGKATLTSDKSSSTAY MELSSLTSEDSAVYYCARGGPYGWYFDVWGAGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	130
Variable light (vl) domain	DIQMTQSPASLSASVGETVTITCRASEHIYSYLSWYQQKQGKSPQLLVYNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFG TYYCQHHFGSPLTFGAGTTLELK	131
vlCDR1	EHIYSY	132
vlCDR2	NAK	133
vlCDR3	QHHFGSPLT	134
Full length light chain	DIQMTQSPASLSASVGETVTITCRASEHIYSYLSWYQQKQGKSPQLLVYNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFG TYYCQHHFGSPLTFGAGTTLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	135

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Figure 3**M:**

BM29 hIgG4 (BM29-H4) (US2016/0176963A1, Clone 22G2)

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVHLQESGPGLVKPSETLSLTCTVSGGSVSSGIYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDYYVSGNYYNVDYYFFGVDVWGQGTTVTVSS	136
vhCDR1	GGSVSSGIYY	137
vhCDR2	IYYSGST	138
vhCDR3	ARDYYVSGNYYNVDYYFFGVDV	139
Full length HC (IgG4(S241P))	QVHLQESGPGLVKPSETLSLTCTVSGGSVSSGIYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDYYVSGNYYNVDYYFFGVDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	140
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQRSNWPPLFTFGPGTKVDIK	141
vlCDR1	QSVSSY	142
vlCDR2	DAS	143
vlCDR3	QQRSNWPPLFT	144
Full length light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQRSNWPPLFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	145

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Figure 3**N: CHA.9.536.1**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTLHWVRQAPGQGLEWMGGINPNNGGTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARSGYYDYSFAYWGQGTLVTVSS	146
vhCDR1	GYTFTEYTLH	147
vhCDR2	GINPNNGGTS	148
vhCDR3	SGYYDYSFAY	149
Full length HC (IgG4(S241P); **CHA.9.536.1.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTLHWVRQAPGQGLEWMGGINPNNGGTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	150
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYS TPFTFGQGTKLEIK	151
vlCDR1	RASQDVKNAVV	152
vlCDR2	SPSYRYT	153
vlCDR3	QQHYSTPFT	154
Full length light chain **(CHA.9.536.1.H4(S241P)**	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYS TPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC	155

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Figure 3**O: CHA.9.536.3**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRVTMTVDTSTS TVYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	156
vhCDR1	GYTFTEYTLH	157
vhCDR2	GINPNNGGTS	158
vhCDR3	SGYYDYSFAY	159
Full length HC (IgG4(S241P) **CHA.9.536.3.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRVTMTVDTSTS TVYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	160
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIK	161
vlCDR1	RASQDVKNAVV	162
vlCDR2	SPSYRYT	163
vlCDR3	QQHYSTPFT	164
Full length light chain **(CHA.9.536.1.H4(S241P))**	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	165

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Figure 3**P: CHA.9.536.4**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRVTMTVDTSTS TVYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	166
vhCDR1	GYTFTEYTLH	167
vhCDR2	GINPNNGGTS	168
vhCDR3	SGYYDYSFAY	169
Full length HC (IgG4(S241P); **CHA.9.536.4.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRVTMTVDTSTS TVYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	170
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIK	171
vlCDR1	RASQDVKNAVV	172
vlCDR2	SPSYRYT	173
vlCDR3	QQHYSTPFT	174
Full length light chain **(CHA.9.536.4.H4(S241P))**	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	175

Figure 3**Q: CHA.9.536.5**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDTSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	176
vhCDR1	GYTFTEYTLH	177
vhCDR2	GINPNNGGTS	178
vhCDR3	SGYYDYSFAY	179
Full length HC (IgG4(S241P); **CHA.9.536.5.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDTSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	180
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIK	181
vlCDR1	RASQDVKNAVV	182
vlCDR2	SPSYRYT	183
vlCDR3	QQHYSTPFT	184
Full length light chain **(CHA.9.536.5.H4(S241P)**)	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	185

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Figure 3**R: CHA.9.536.6**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDTSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	186
vhCDR1	GYTFTEYTLH	187
vhCDR2	GINPNNGGTS	188
vhCDR3	SGYYDYSFAY	189
Full length HC (IgG4(S241P); CHA.9.536.6.H4(S241P))	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDTSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	190
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIK	191
vlCDR1	RASQDVKNAVV	192
vlCDR2	SPSYRYT	193
vlCDR3	QQHYSTPFT	194
Full length light chain (CHA.9.536.6.H4(S241P))	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	195

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Figure 3S: **CHA.9.536.7**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDKSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	196
vhCDR1	GYTFTEYTLH	197
vhCDR2	GINPNNGGTS	198
vhCDR3	SGYYDYSFAY	199
Full length HC (IgG4(S241P); **CHA.9.536.7.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDKSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	200
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIK	201
vlCDR1	RASQDVKNAVV	202
vlCDR2	SPSYRYT	203
vlCDR3	QQHYSTPFT	204
Full length light chain **(CHA.9.536.7.H4(S241P)**)	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	205

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Figure 3T: **CHA.9.536.8**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDKSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSS	206
vhCDR1	GYTFTEYTLH	207
vhCDR2	GINPNNGGTS	208
vhCDR3	SGYYDYSFAY	209
Full length HC (IgG4(S241P); **CHA.9.536.8.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKTSGYTFTEYTLHWVRQAPGQGLEWIGGINPNNGGTSYAQKFQGRATLTVDKSTS TAYMELSSLRSEDTAVYYCAGSGYYDYSFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	210
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIK	211
vlCDR1	RASQDVKNAVV	212
vlCDR2	SPSYRYT	213
vlCDR3	QQHYSTPFT	214
Full length light chain **(CHA.9.536.8.H4(S241P)**)	DIQMTQSPSSLSASVGDRVTITCRASQDVKNAVVWYQQKPGKAPKLLIYSPSYRYTGVPSRFSGSGSGTDFTF TISSVQPEDFATYYCQQHYSTPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	215

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Figure 3**U: CHA.9.560.1**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNGYYVGMDYWGQGTLVTVSS	216
vhCDR1	GYTFTNYGMN	217
vhCDR2	WINTYTGEPT	218
vhCDR3	GNGYYVGMDY	219
Full length HC (IgG4(S241P); **CHA.9.560.1.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	220
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNHANWFQQKPGQAPRTLIYGTNGRGSWTPARFSGSLLGGKAALTL SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	221
vlCDR1	RSSTGAVTTSNHAN	222
vlCDR2	GTNGRGS	223
vlCDR3	ALWFSNHWV	224
Full length light chain **(CHA.9.560.1.H4(S241P)**)	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNHANWFQQKPGQAPRTLIYGTNGRGSWTPARFSGSLLGGKAALTL SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	225

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Figure 3V: **CHA.9.560.3**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTLDTSTS TAYMELSSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	226
vhCDR1	GYTFTNYGMN	227
vhCDR2	WINTYTGEPT	228
vhCDR3	GNGYYVGMDY	229
Full length HC (IgG4(S241P); CHA.9.560.3.H4(S241P))	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTLDTSTS TAYMELSSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	230
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	231
vlCDR1	GSSTGAVTTSNHAN	232
vlCDR2	GTNGRGS	233
vlCDR3	ALWFSNHWV	234
Full length light chain (CHA.9.560.3.H4(S241P))	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	235

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Figure 3W: **CHA.9.560.4**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTLDTSTS TAYMELSSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	236
vhCDR1	GYTFTNYGMN	237
vhCDR2	WINTYTGEPT	238
vhCDR3	GNGYYVGMDY	239
Full length HC (IgG4(S241P); **CHA.9.560.4.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTLDTSTS TAYMELSSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	240
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	241
vlCDR1	GSSTGAVTTSNHAN	242
vlCDR2	GTNGRGS	243
vlCDR3	ALWFSNHWV	244
Full length light chain **(CHA.9.560.4.H4(S241P))**	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	245

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Figure **3X: CHA.9.560.5**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDTSTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	246
vhCDR1	GYTFTNYGMN	247
vhCDR2	WINTYTGEPT	248
vhCDR3	GNGYYVGMDY	249
Full length HC (IgG4(S241P); **CHA.9.560.5.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDTSTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	250
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	251
vlCDR1	GSSTGAVTTSNHAN	252
vlCDR2	GTNGRGS	253
vlCDR3	ALWFSNHWV	254
Full length light chain **(CHA.9.560.5.H4(S241P)**)	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	255

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Figure **3Y: CHA.9.560.6**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDTSTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	256
vhCDR1	GYTFTNYGMN	257
vhCDR2	WINTYTGEPT	258
vhCDR3	GNGYYVGMDY	259
Full length HC (IgG4(S241P); CHA.9.560.6.H4(S241P))	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDTSTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	260
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	261
vlCDR1	GSSTGAVTTSNHAN	262
vlCDR2	GTNGRGS	263
vlCDR3	ALWFSNHWV	264
Full length light chain (CHA.9.560.6.H4(S241P))	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	265

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Figure **3Z: CHA.9.560.7**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDASTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	266
vhCDR1	GYTFTNYGMN	267
vhCDR2	WINTYTGEPT	268
vhCDR3	GNGYYVGMDY	269
Full length HC (IgG4(S241P); **CHA.9.560.7.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDTSTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	270
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	271
vlCDR1	GSSTGAVTTSNHAN	272
vlCDR2	GTNGRGS	273
vlCDR3	ALWFSNHWV	274
Full length light chain **(CHA.9.560.7.H4(S241P)**)	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSWTPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	275

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Figure **3AA: CHA.9.560.8**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDASTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSS	276
vhCDR1	GYTFTNYGMN	277
vhCDR2	WINTYTGEPT	278
vhCDR3	GNGYYVGMDY	279
Full length HC (IgG4(S241P); **CHA.9.560.8.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTFTLDASTS TAYLEISSLRSEDTAVYYCSRGNGYYVGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	280
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVL	281
vlCDR1	GSSTGAVTTSNHAN	282
vlCDR2	GTNGRGS	283
vlCDR3	ALWFSNHWV	284
Full length light chain **(CHA.9.560.8.H4(S241P)**)	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNHANWVQQKPGQAFRGLIRGTNGRGSGVPARFSGSLLGGKAALTI SGAQPEDEAEYYCALWFSNHWVFGGGTKLTVLQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	285

Figure **3BB: CHA.9.546.1**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCARWLLSYYAMDYWGQGTLVTVSS	286
vhCDR1	GFTFSSYIMS	287
vhCDR2	TISGGGTNTY	288
vhCDR3	WLLSYYAMDY	289
Full length HC (IgG4(S241P); **CHA.9.546.1.H4(S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCARWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	290
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	291
vlCDR1	RASQNINVWLT	292
vlCDR2	KASNLHT	293
vlCDR3	QQGQSYPYT	294
Full length light chain **(CHA.9.546.1.H4(S241P))**	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	295

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Figure **3CC: CHA.9.547.1**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	296
vhCDR1	GFTFSSYIMS	297
vhCDR2	TISGGGTNTY	298
vhCDR3	WLLSYYAMDY	299
Full length HC (IgG4(S241P); **CHA.9.547.1.H4(S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	300
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	301
vlCDR1	RASQNINVWLT	302
vlCDR2	KASNLHT	303
vlCDR3	QQGQSYPYT	304
Full length light chain **(CHA.9.547.1.H4(S241P)**)	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	305

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Figure **3DD: CHA.9.547.2**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	306
vhCDR1	GFTFSSYIMS	307
vhCDR2	TISGGGTNTY	308
vhCDR3	WLLSYYAMDY	309
Full length HC (IgG4(S241P); **CHA.9.547.2.H4(S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	310
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	311
vlCDR1	RASQNINVWLT	312
vlCDR2	KASNLHT	313
vlCDR3	QQGQSYPYT	314
Full length light chain **(CHA.9.547.2.H4(S241P))**	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	315

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Figure **3EE: CHA.9.547.3**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	316
vhCDR1	GFTFSSYIMS	317
vhCDR2	TISGGGTNTY	318
vhCDR3	WLLSYYAMDY	319
Full length HC (IgG4(S241P); CHA.9.547.3.H4(S241P))	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	320
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	321
vlCDR1	RASQNINVWLT	322
vlCDR2	KASNLHT	323
vlCDR3	QQGQSYPYT	324
Full length light chain (CHA.9.547.3.H4(S241P))	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	325

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Figure **3FF: CHA.9.547.4**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	326
vhCDR1	GFTFSSYIMS	327
vhCDR2	TISGGGTNTY	328
vhCDR3	WLLSYYAMDY	329
Full length HC (IgG4(S241P); CHA.9.547.4.H4(S241P))	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	330
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	331
vlCDR1	RASQNINVWLT	332
vlCDR2	KASNLHT	333
vlCDR3	QQGQSYPYT	334
Full length light chain CHA.9.547.4.H4(S241P))	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	335

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Figure **3GG: CHA.9.547.6**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	336
vhCDR1	GFTFSSYIMS	337
vhCDR2	TISGGGTNTY	338
vhCDR3	WLLSYYAMDY	339
Full length HC (IgG4(S241P); **CHA.9.547.6.H4(S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	340
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	341
vlCDR1	RASQNINVWLT	342
vlCDR2	KASKSHT	343
vlCDR3	QQGQSYPYT	344
Full length light chain **(CHA.9.547.6.H4(S241P))**	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	345

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Figure **3HH: CHA.9.547.7**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	346
vhCDR1	GFTFSSYIMS	347
vhCDR2	TISGGGTNTY	348
vhCDR3	WLLSYYAMDY	349
Full length HC (IgG4(S241P) for CHA.9.547.7.H4(S 241P))	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	350
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	351
vlCDR1	RASQNINVWLT	352
vlCDR2	KASKSHT	353
vlCDR3	QQGQSYPYT	354
Full length light chain for CHA.9.547.7.H4(S 241P)	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	355

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Figure **3II: CHA.9.547.8**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	356
vhCDR1	GFTFSSYIMS	357
vhCDR2	TISGGGTNTY	358
vhCDR3	WLLSYYAMDY	359
Full length HC (IgG4(S241P); CHA.9.547.8.H4(S241P))	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	360
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	361
vlCDR1	RASQNINVWLT	362
vlCDR2	KASKSHT	363
vlCDR3	QQGQSYPYT	364
Full length light chain (CHA.9.547.8.H4(S241P))	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	365

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Figure **3JJ: CHA.9.547.9**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	366
vhCDR1	GFTFSSYIMS	367
vhCDR2	TISGGGTNTY	368
vhCDR3	WLLSYYAMDY	369
Full length HC (IgG4(S241P); **CHA.9.547.9.H4(S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	370
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	371
vlCDR1	RASQNINVWLT	372
vlCDR2	KASKSHT	373
vlCDR3	QQGQSYPYT	374
Full length light chain **(CHA.9.547.9.H4(S241P)**)	DIQMTQSPSSLSASVGDRITITCRASQNINVWLTWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	375

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Figure **3KK: CHA.9.541.1**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	376
vhCDR1	GYTITNYGMN	377
vhCDR2	WINTYTGEPT	378
vhCDR3	GNGNPLGMDY	379
Full length HC (IgG4(S241P); **CHA.9.541.1.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRVTMTRDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	380
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	381
vlCDR1	GNGNPLGMDY	382
vlCDR2	DTSKLAS	383
vlCDR3	FQGSGYPLT	384
Full length light chain **(CHA.9.541.1.H4(S241P))**	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	385

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Figure **3LL: CHA.9.541.3**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	386
vhCDR1	GYTITNYGMN	387
vhCDR2	WINTYTGEPT	388
vhCDR3	GNGNPLGMDY	389
Full length HC (IgG4(S241P); CHA.9.541.3.H4(S241P))	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	390
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	391
vlCDR1	GNGNPLGMDY	392
vlCDR2	DTSKLAS	393
vlCDR3	FQGSGYPLT	394
Full length light chain (CHA.9.541.3.H4(S241P))	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	395

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Figure **3NN: CHA.9.541.4**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	396
vhCDR1	GYTITNYGMN	397
vhCDR2	WINTYTGEPT	398
vhCDR3	GNGNPLGMDY	399
Full length HC (IgG4(S241P); **CHA.9.541.4.H4(S241P)**)	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	400
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	401
vlCDR1	GNGNPLGMDY	402
vlCDR2	DTSKLAS	403
vlCDR3	FQGSGYPLT	404
Full length light chain **(CHA.9.541.4.H4(S241P)**)	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	405

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Figure **3OO CHA.9.541.5**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	406
vhCDR1	GYTITNYGMN	407
vhCDR2	WINTYTGEPT	408
vhCDR3	GNGNPLGMDY	409
Full length HC (IgG4(S241P); **CHA.9.541.5.H4(S241P))**	QVQLVQSGAEVKKPGASVKVSCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTMTLDTSTS TVYMELSSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	410
Variable light (vl) domain	EIVLTQSPATLSLSPGERVTMSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSM EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	411
vlCDR1	GNGNPLGMDY	412
vlCDR2	DTSKLAS	413
vlCDR3	FQGSGYPLT	414
Full length light chain **(CHA.9.541.5.H4(S241P))**	EIVLTQSPATLSLSPGERVTMSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSM EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	415

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Figure **3PP: CHA.9.541.6**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	416
vhCDR1	GYTITNYGMN	417
vhCDR2	WINTYTGEPT	418
vhCDR3	GNGNPLGMDY	419
Full length HC (IgG4(S241P); **CHA.9.541.6.H4(S241P)**)	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	420
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	421
vlCDR1	GNGNPLGMDY	422
vlCDR2	DTSKLAS	423
vlCDR3	FQGSGYPLT	424
Full length light chain **(CHA.9.541.6.H4(S241P)**)	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLLIYDTSKLASGIPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	425

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Figure **3QQ: CHA.9.541.7**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	426
vhCDR1	GYTITNYGMN	427
vhCDR2	WINTYTGEPT	428
vhCDR3	GNGNPLGMDY	429
Full length HC (IgG4(S241P) CHA.9.541.7.H4(S241P))	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	430
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	431
vlCDR1	GNGNPLGMDY	432
vlCDR2	DTSKLAS	433
vlCDR3	FQGSGYPLT	434
Full length light chain (CHA.9.541.7.H4(S241P))	EIVLTQSPATLSLSPGERATLSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSL EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	435

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Figure **3RR: CHA.9.541.8**

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSS	436
vhCDR1	GYTITNYGMN	437
vhCDR2	WINTYTGEPT	438
vhCDR3	GNGNPLGMDY	439
Full length HC (IgG4(S241P); CHA.9.541.8.H4(S241P))	QVQLVQSGAEVKKPGASVKISCKASGYTITNYGMNWVRQAPGQGLEWMGWINTYTGEPTYAQKFQGRFTITLDTSTS TVYLEISSLRSEDTAVYYCARGNGNPLGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	440
Variable light (vl) domain	EIVLTQSPATLSLSPGERVTMSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSM EPEDFAVYYCFQGSGYPLTFGQGTKLEIK	441
vlCDR1	GNGNPLGMDY	442
vlCDR2	DTSKLAS	443
vlCDR3	FQGSGYPLT	444
Full length light chain (CHA.9.541.8.H4(S241P))	EIVLTQSPATLSLSPGERVTMSCGNGNPLGMDYWYQQKPGQAPRLWIYDTSKLASGVPARFSGSGSGTDYTLTISSM EPEDFAVYYCFQGSGYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	445

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 355: CHA.9.547.10

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	446
vhCDR1	GFTFSSYIMS	447
vhCDR2	TISGGGTNTY	448
vhCDR3	WLLSYYAMDY	449
Full length HC for **CHA.9.547.10.H4 (S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	450
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	451
vlCDR1	RASQNINVWLS	452
vlCDR2	KASKSHT	453
vlCDR3	QQGQSYPYT	454
Full length light chain For **CHA.9.547.10.H4 (S241P)**	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	455

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Figure 3TT: CHA.9.547.11

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	456
vhCDR1	GFTFSSYIMS	457
vhCDR2	TISGGGTNTY	458
vhCDR3	WLLSYYAMDY	459
Full length HC for **CHA.9.547.11.H4 (S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVSTISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	460
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	461
vlCDR1	RASQNINVWLS	462
vlCDR2	KASKSHT	463
vlCDR3	QQGQSYPYT	464
Full length light chain For **CHA.9.547.11.H4 (S241P)**)	DIQMTQSPSSLSASVGDRITITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	465

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Figure 3UU: CHA.9.547.12

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	466
vhCDR1	GFTFSSYIMS	467
vhCDR2	TISGGGTNTY	468
vhCDR3	WLLSYYAMDY	469
Full length HC For **CHA.9.547.12.H4 (S241P)**)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	470
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	471
vlCDR1	RASQNINVWLS	472
vlCDR2	KASKSHT	473
vlCDR3	QQGQSYPYT	474
Full length light chain for **CHA.9.547.12.H4 (S241P)**)	DIQMTQSPSSLSASVGDRVTITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	475

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Figure 3VV: CHA.9.547.13

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSS	476
vhCDR1	GFTFSSYIMS	477
vhCDR2	TISGGGTNTY	478
vhCDR3	WLLSYYAMDY	479
Full length HC for CHA.9.547.13.H4 (S241P)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYIMSWVRQAPGKGLEWVATISGGGTNTYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAKWLLSYYAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	480
Variable light (vl) domain	DIQMTQSPSSLSASVGDRITITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIK	481
vlCDR1	RASQNINVWLS	482
vlCDR2	KASKSHT	483
vlCDR3	QQGQSYPYT	484
Full length light chain for CHA.9.547.13.H4 (S241P)	DIQMTQSPSSLSASVGDRITITCRASQNINVWLSWYQQKPGKAPKLLIYKASKSHTGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQGQSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	485

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Figure 3WW: CHA.9.543

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVRQSHGKNLEWLGLIFPYNGGTSYNQNFKGKATLTVDTSSSTAY MELLSLTSVDSAVYYCARGVRFALDYWGQGTSVSVSS	486
vhCDR1	GYSFTGYTMN	487
vhCDR2	LIFPYNGGTS	488
vhCDR3	GVRFALDY	489
Full length HC for **CHA.9.543.H4(S241P)**)	Mouse hybridoma, sequence not available	
Variable light (vl) domain	DVVMTQTPLSLPVSFGDQVSISCRSSQSLANSYGNTYLSWYLHKPGQSPQLLIYEISNRFSGVPDRFSGSGSGTDFTLNISTIKP EDLGMYYCLQGTHQPWTFGGGTKLEIK	490
vlCDR1	RSSQSLANSYGNTYLS	491
vlCDR2	EISNRFS	492
vlCDR3	LQGTHQPWT	493
Full length light chain for **CHA.9.543.H4(S241P)**)	Mouse hybridoma, sequence not available	

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Figure 3XX: BM26 mouse IgG1 (BM26-M1) (WO2016/028656A1, Clone 31C6)

What	Sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGSSVKMSCKASGYTFSSYVMHWVKQKPGQGLEWIGYIDPYNDGAKYNEKFKGKATLTSDKSSSTAY MELSSLTSEDSAVYYCARGGPYGWYFDVWGAGTTVTVSS	494
vhCDR1	GYTFSSYV	495
vhCDR2	IDPYNDGA	496
vhCDR3	ARGGPYGWYFDV	497
Full length HC	EVQLQQSGPELVKPGSSVKMSCKASGYTFSSYVMHWVKQKPGQGLEWIGYIDPYNDGAKYNEKFKGKATLTSDKSSSTAY MELSSLTSEDSAVYYCARGGPYGWYFDVWGAGTTVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTW NSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKD VLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAP IEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNV QKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK	498
Variable light (vl) domain	DIQMTQSPASLSASVGETVTITCRASEHIYSYLSWYQQKQGKSPQLLVYNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFG TYYCQHHFGSPLTFGAGTTLELK	499
vlCDR1	EHIYSY	500
vlCDR2	NAK	501
vlCDR3	QHHFGSPLT	502
Full length light chain	DIQMTQSPASLSASVGETVTITCRASEHIYSYLSWYQQKQGKSPQLLVYNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFG TYYCQHHFGSPLTFGAGTTLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQ DSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC	503

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Figure 3YY: BM29 mouse IgG1 (BM29-M1) (US2016/0176963A1, Clone 22G2)

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVHLQESGPGLVKPSETLSLTCTVSGGSVSSGIYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDYYVSGNYYNVDYYFFGVDVWGQGTTVTVSS	504
vhCDR1	GGSVSSGIYY	505
vhCDR2	IYYSGST	506
vhCDR3	ARDYYVSGNYYNVDYYFFGVDV	507
Full length HC	QVHLQESGPGLVKPSETLSLTCTVSGGSVSSGIYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDYYVSGNYYNVDYYFFGVDVWGQGTTVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEP VTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIF PPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNS AAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVY SKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK	508
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQRSNWPPLFTFGPGTKVDIK	509
vlCDR1	QSVSSY	510
vlCDR2	DAS	511
vlCDR3	QQRSNWPPLFT	512
Full length light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVY YCQQRSNWPPLFTFGPGTKVDIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC	513

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Figure 3AAA

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:10 from US2017281764)	DVQLVESGGGLVQPGGSRKLSCAASGFTFSNFGMHWVRQAPEKGLEWVAFISSGSS SIYYADTVKGRFTISRDNPKNTLFLQMTSLRSEDTAMYYCARMRLDYYAMDYWGQ GTSVTVSS	514
vhCDR1 (SEQ ID NO:11 from US2017281764)	NFGMH	515
vhCDR2 (SEQ ID NO:12 from US2017281764)	FISSGSSSIYYADTVKG	516
vhCDR3 (SEQ ID NO:13 from US2017281764)	MRLDYYAMDY	517
Light chain (SEQ ID NO:14 from US2017281764)	DVQITQSPSYLAASPGETITINCRASKSISKYLAWYQEKPGKTNKLLIYSGSTLQSGIPS RFSGSGSGTDFTLTISSLEPEDFAMYYCQQHNEYPWTFGGGTKLEIK	518
vlCDR1 (SEQ ID NO:15 from US2017281764)	RASKSISKYLA	519
vlCDR2 (SEQ ID NO:16 from US2017281764)	SGSTLQS	520
vlCDR3 (SEQ ID NO:17 from US2017281764)	QQHNEYPWT	521

Figure 3BBB

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:18 from US2017281764)	EVQLQQSGPELVKPGASVKISCKTSGYTFTEYTMHWVKQSHGKNLEWIGGINPNNG GTSYNQKFKGRATLTVDKSSSTAYMELRSLTSDDSAVYYCARPGWYNYAMDYWG QGTSVTVSS	522
vhCDR1 (SEQ ID NO:19 from US2017281764)	EYTMH	523
vhCDR2 (SEQ ID NO:20 from US2017281764)	GINPNNGGTSYNQKFKG	524
vhCDR3 (SEQ ID NO:21 from US2017281764)	PGWYNYAMDY	525
Light chain (SEQ ID NO:22 from US2017281764)	DIVMTQSHKFMSTSVGDRVNITCKASQGVSTAVAWYQQKPGQSPKLLIYSASYRYT GVPDRFTGSGSGTDFTFTISSVQAEDLAVYHCQQHYITPWTFGGGTKLEIK	526
vlCDR1 (SEQ ID NO:23 from US2017281764)	KASQGVSTAVA	527
vlCDR2 (SEQ ID NO:24 from US2017281764)	SASYRYT	528
vlCDR3 (SEQ ID NO:25 from US2017281764)	QQHYITPWT	529

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Figure 3CCC

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:26 from US2017281764)	EVQLVESGGGLVKPGGSLKLSCAASGFAFSDYDMSWVRQTPEKRLEWVAYISDGGY NTYYPDTVKGRFTISRDNAKNTLYLQMSSLKSEDTAIYYCARQILLRYYFDYWGQGT TLTVSS	530
vhCDR1 (SEQ ID NO:27 from US2017281764)	DYDMS	531
vhCDR2 (SEQ ID NO:28 from US2017281764)	YISDGGYNTYYPDTVKG	532
vhCDR3 (SEQ ID NO:29 from US2017281764)	QILLRYYFDY	533
Light chain (SEQ ID NO:30 from US2017281764)	DIVMSQSPSSLAVSVGEKVTMTCKSSQSLLYSSNQKNYLAWYQQKPGQSPKLLIYW ASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYHSYPWTFGGGTKLEIK	534
vlCDR1 (SEQ ID NO:31 from US2017281764)	KSSQSLLYSSNQKNYLA	535
vlCDR2 (SEQ ID NO:32 from US2017281764)	WASTRES	536
vlCDR3 (SEQ ID NO:33 from US2017281764)	QQYHSYPWT	537

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Figure 3DDD

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:35 from US2017281764)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAFISSGSSSIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARMRLDYYAMDYWGQGTMVTVSS	538
Light chain (SEQ ID NO:37 from US2017281764)	DIQMTQSPSSLSASVGDRVTITCRASKSISKYLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPWTFGGGTKVEIK	539

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:34 from US2017281764)	MDSRLNLVFLVLILKGVQCEVQLVESGGGLVQPGGSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVAFISSGSSSIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARMRLDYYAMDYWGQGTMVTVSS	540
Light chain (SEQ ID NO:36 from US2017281764)	MRFQVQVLGLLLLWISGAQCDIQMTQSPSSLSASVGDRVTITCRASKSISKYLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPWTFGGGTKVEIK	541

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Figure 3EEE

From WO2015009856 (GENENTECH, INC. and F. HOFFMANN-LA ROCHE AG; see also, WO2016011264)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:15 from WO2015009856)	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRSGSGIVF YADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTFDSWGQGTLVT VSS	542
vhCDR1 (SEQ ID NO:4 from WO2015009856)	GFTFSSFTMH	543
vhCDR2 (SEQ ID NO:5 from WO2015009856)	FIRSGSGIVFYADAVRG	544
vhCDR3 (SEQ ID NO:6 from WO2015009856)	RPLGHNTFDS	545
Light chain (SEQ ID NO:13 from WO2015009856)	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLLIYYASI RFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGDGTKLEIKR	546
vlCDR1 (SEQ ID NO:1 from WO2015009856)	KSSQSLYYSGVKENLLA	547
vlCDR2 (SEQ ID NO:2 from WO2015009856)	ASIRFT	548
vlCDR3 (SEQ ID NO:3 from WO2015009856)	QQGINNPLT	549

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Figure 3FFF

From WO2015009856 (GENENTECH, INC. and F. HOFFMANN-LA ROCHE AG; see also, WO2016011264)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:16 from WO2015009856)	EVQLQQSGPELVKPGTSMKISCKASGYSFTGHLMNWVKQSHGKNLEWIGLIIPYNGGTSYNQKFKGKATLTVDKSSSTAYMELLSLTSDDSAVYFCSRGLRGFYAMDYWGQGTSVTVSS	550
vhCDR1 (SEQ ID NO:10 from WO2015009856)	GYSFTGHLMN	551
vhCDR2 (SEQ ID NO:11 from WO2015009856)	LIIPYNGGTSYNQKFKG	552
vhCDR3 (SEQ ID NO:12 from WO2015009856)	GLRGFYAMDY	553
Light chain (SEQ ID NO:14 from WO2015009856)	DVVLTQTPLSLSVSFGDQVSISCRSSQSLVNSYGNTFLSWYLHKPGQSPQLLIFGISNRFSGVPDRFSGSGSGTDFTLKISTIKPEDLGMYYCLQGTHQPPTFGPGTKLEVK	554
vlCDR1 (SEQ ID NO:7 from WO2015009856)	RSSQSLVNSYGNTFLS	555
vlCDR2 (SEQ ID NO:8 from WO2015009856)	GISNRFS	556
vlCDR3 (SEQ ID NO:9 from WO2015009856)	LQGTHQPPT	557

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Figure 3GGG

From US 9713641 (Table 5, reproduced herein; SEQ ID NOs: are from US 9713641)

Sequences and germlines (GL) of TIGIT ABPs

Ab	VH GL	CDR-H1[1] (SEQ ID NOS 558-562)	CDR-H2[2] (SEQ ID NOS 563-567)	CDR-H3[3] (SEQ ID NOS 568-572)	VH Protein (SEQ ID NOS 573-577)	VL GL	CDR-L1[4] (SEQ ID NOS 578-582)	CDR-L2[5] (SEQ ID NOS 583-587)	CDR-L3[6] (SEQ ID NOS 588-592)	VL Protein (SEQ ID NOS 593-597)
MAB1-IgG4	VH 4-39	GSITSSSYYWG (SEQ ID NO 48)	SIYYSGATFYNPSLKS (SEQ ID NO 36)	ARDANYYGSAWAFDP (SEQ ID NO 29)	QLQLQESGPGLVKPSETLSLTCTVSGSITSSSYYWGWIRQPPGKGLEWIGSIYYSGATFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO 4)	VK3-11	RASQSVSSYLA (SEQ ID NO 70)	DASNRAT (SEQ ID NO 67)	QQHFNLPT (SEQ ID NO 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO 25)
MAB2-IgG4	VH 4-39	GSISSSKYYWG (SEQ ID NO 49)	SIYYSGSTFYNPSLKS (SEQ ID NO 37)	ARDANYYGSAWAFDP (SEQ ID NO 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSKYYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO 5)	VK3-11	RASQSVSSYLA (SEQ ID NO 70)	DASNRAT (SEQ ID NO 67)	QQHFNLPT (SEQ ID NO 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO 25)
MAB3-IgG4	VH 4-39	GSISSTSHYWG (SEQ ID NO 50)	SIYYSGSTFYNPSLKS (SEQ ID NO 37)	ARDANYYGSAWAFDP (SEQ ID NO 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO 6)	VK3-11	RASQSVSSYLA (SEQ ID NO 70)	DASNRAT (SEQIDO :67)	QQHFNLPT (SEQ ID NO 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO 25)
MAB4-IgG4	VH 4-39	GSISSTSHYWG(SEQ ID NO 50)	SIYYSGSTFYNPSLKS (SEQ ID NO 37)	ARDANYYGGAWAFDP (SEQ ID NO 30)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGGAWAFDPWGQGTLVTVSS (SEQ ID NO 7)	VK3-11	RASQSVSSYLA (SEQ ID NO 70)	DASNRAT (SEQ ID NO 67)	QQHFNLPT (SEQ ID NO 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO 25)
MAB5-IgG4	VH 4-39	GSISSTSHYWG(SEQ ID NO 50)	SIYYSGSTFYNPSLKG (SEQ ID NO 38)	ARDANYYGSAWAFDP (SEQ ID NO 29)	QLQLQESGPGLVKPSETLSLTCTVSGGSISSTSHYWGWIRQPPGKGLEWIGSIYYSGSTFYNPSLKGRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDANYYGSAWAFDPWGQGTLVTVSS (SEQ ID NO 8)	VK3-11	RASQSVSSYLA (SEQ ID NO 70)	DASNRAT (SEQ ID NO 67)	QQHFNLPT (SEQ ID NO 63)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHFNLPTFGGGTKVEIK (SEQ ID NO 25)

[1] Includes CDR-H1 as defined by both the Chothia and Kabat numbering systems, inclusive of the boundaries of both numbering systems.
[2] According to the Kabat numbering system.
[3] According to the IMGT numbering system.
[4] According to the Kabat and Chothia numbering systems.
[5] According to the Kabat and Chothia numbering systems.
[6] According to the Kabat, Chothia, and IMGT numbering systems.

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Figure 3HHH

From US 9713641 (Table 5, reproduced herein; SEQ ID NOs: are from US 9713641)

	Sequences and germlines (GL) of TIGIT ABPs									
Ab	VH GL	CDR-H1[7] (SEQ ID NOS 598-602)	CDR-H2[8] (SEQ ID NOS 603-607)	CDR-H3[9] (SEQ ID NOS 608-612)	VH Protein (SEQ ID NOS 613-617)	VL GL	CDR-L1[10] (SEQ ID NOS 618-622)	CDR-L2[11] (SEQ ID NOS 623-627)	CDR-L3[12] (SEQ ID NOS 628-632)	VL Protein (SEQ ID NOS 633-637)
MAB6-IgG4	VH 4-39	GSIESGSYYWG (SEQ ID NO 51)	SIYYSGGTYYNPSLKS (SEQ ID NO 39)	ARDGVLTLNKRSFDI (SEQ ID NO 31)	QLQLQESGPGLVKPSETLSLTCTVSGSIESGSYYWGWIRQPPGKGLEWIGSIYYSGGTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO 9)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB7-IgG4	VH 4-31	GSIESGVYYWG (SEQ ID NO 52)	SIYYSGSTYYNPSLKS (SEQ ID NO 40)	ARDGVLTLNKRSFDI (SEQ ID NO 31)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGVYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO 10)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB8-IgG4	VH 4-39	GSIASGSYYWG (SEQ ID NO 53)	SIYYSGQTYYNPSLKS (SEQ ID NO 41)	ARDGVLTLNKRSFDI (SEQ ID NO 31)	QLQLQESGPGLVKPSETLSLTCTVSGGSIASGSYYWGWIRQPPGKGLEWIGSIYYSGQTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO 11)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB9-IgG4	VH 4-31	GSIESGLYYWG (SEQ ID NO 54)	SIYYSGSTYYNPSLKS (SEQ ID NO 40)	ARDGVLTLNKRSFDI (SEQ ID NO 31)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLTLNKRSFDIWGQGTMVTVSS (SEQ ID NO 12)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB10-IgG4	VH 4-31	GSIESGLYYWG (SEQ ID NO 54)	SIYYSGSTYYNPSLKS (SEQ ID NO 40)	ARDGVLALNKRSFDI (SEQ ID NO 32)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRATISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO 13)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)

[7] Includes CDR-H1 as defined by both the Chothia and Kabat numbering systems, inclusive of the boundaries of both numbering systems.
[8] According to the Kabat numbering system.
[9] According to the IMGT numbering system.
[10] According to the Kabat and Chothia numbering systems.
[11] According to the Kabat and Chothia numbering systems.
[12] According to the Kabat, Chothia, and IMGT numbering systems.

Figure 3III
From US 9713641 (Table 5, reproduced herein; SEQ ID NOs: are from US 9713641)

Sequences and germlines (GL) of TIGIT ABPs

Ab	VH GL	CDR-H1[13] (SEQ ID NOS 638-642)	CDR-H2[14] (SEQ ID NOS 643-647)	CDR-H3[15] (SEQ ID NOS 648-652)	VH Protein (SEQ ID NOS 653-657)	VL GL	CDR-L1[16] (SEQ ID NOS 658-662)	CDR-L2[17] (SEQ ID NOS 663-667)	CDR-L3[18] (SEQ ID NOS 668-672)	VL Protein (SEQ ID NOS 673-677)
MAB1 1-IgG4	VH 4-31	GSIESGLYYWG(SEQ ID NO 54)	SIYYSGSTYYNPSLKS (SEQ ID NO 40)	ARDGVLALNKRSFDI (SEQ ID NO 32)	QVQLQESGPGLVKPSQTLSLTCTVSGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO 14)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB1 2-IgG4	VH 4-31	GSIESGLYYWG(SEQ ID NO 54)	SIYYSGSTYYNPSLKS (SEQ ID NO 40)	ARDGVLALNKRSFDI (SEQ ID NO 32)	QVQLQESGPGLVKPSQTLSLTCTASGGSIESGLYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDGVLALNKRSFDIWGQGTMVTVSS (SEQ ID NO 15)	VK3-20	RASQSVSSSYLA (SEQ ID NO 71)	GASSRAT (SEQ ID NO 68)	QQHTVRPPLT (SEQ ID NO 64)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHTVRPPLTFGGGTKVEIK (SEQ ID NO 26)
MAB1 3-IgG4	VH 1-46	YTFGNYYMH (SEQ ID NO 58)	IINPSLGLTSYAQKFQG (SEQ ID NO 42)	ARGGRTTWIGAFDI (SEQ ID NO 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYYMHWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO 16)	VK3-15	RASQSVSSNLA (SEQ ID NO 72)	GASTRAT (SEQ ID NO 69)	QQYVVWPPLT (SEQ ID NO 65)	EIVMTQSPATISVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)
MAB1 4-IgG4	VH 1-46	YTFPAYYMH (SEQ ID NO 59)	IINPSLGLTSYAQKFQG (SEQ ID NO 42)	ARGGRTTWIGAFDI (SEQ ID NO 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFPAYYMHWVRQAPGQGLEWMGIINPSLGLTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO 17)	VK3-15	RASQSVSSNLA (SEQ ID NO 72)	GASTRAT (SEQ ID NO 69)	QQYVVWPPLT (SEQ ID NO 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)
MAB1 5-IgG4	VH 1-46	YTFREYYMH (SEQ ID NO 60)	IINPSIGLTSYARKFQG (SEQ ID NO 45)	ARGGRTTWIGAFDI (SEQ ID NO 33)	QVQLVQSGAEVKKPGASVKVSCKASGYTFREYYMHWVRQAPGQGLEWMGIINPSIGLTSYARKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGGRTTWIGAFDIWGQGTMVTVSS (SEQ ID NO 18)	VK3-15	RASQSVSSNLA (SEQ ID NO 72)	GASTRAT (SEQ ID NO 69)	QQYVVWPPLT (SEQ ID NO 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)

[13] Includes CDR-H1 as defined by both the Chothia and Kabat numbering systems, inclusive of the boundaries of both numbering systems.
[14] According to the Kabat numbering system.
[15] According to the IMGT numbering system.
[16] According to the Kabat and Chothia numbering systems.
[17] According to the Kabat and Chothia numbering systems.
[18] According to the Kabat, Chothia, and IMGT numbering systems.

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Figure 3JJJ
From US 9713641 (Table 5, reproduced herein; SEQ ID NOs: are from US 9713641)

Sequences and germlines (GL) of TIGIT ABPs

Ab	VH GL	CDR-H1[19] (SEQ ID NOS 678-683)	CDR-H2[20] (SEQ ID NOS 684-689)	CDR-H3[21] (SEQ ID NOS 690-695)	VH Protein (SEQ ID NOS 696-701)	VL GL	CDR-L1[22] (SEQ ID NOS 702-707)	CDR-L2[23] (SEQ ID NOS 708-713)	CDR-L3[24] (SEQ ID NOS 714-719)	VL Protein (SEQ ID NOS 720-725)
MAB16-IgG4	VH 1-46	YTFRR YYMH (SEQ ID NO 60)	IINPSIGL TSYARK FQG (SEQ ID NO 43)	ARGGRT TWIGAL DI (SEQ ID NO 34)	QVQLVQSGAEVKKPGASVKVSCKASGYT FREYYMHWVRQAPGQGLEWMGIINPSIGL TSYARKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARGGRTTWIGALDIWGQGT MVTVSS (SEQ ID NO 19)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYVVW PPLT (SEQ ID NO 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAV YYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)
MAB17-IgG4	VH 1-46	YTFPA YYIH (SEQ ID NO 61)	IINPSLG LTSYAR KFQG (SEQ ID NO 44)	ARGGRT TWIGAL DI (SEQ ID NO 34)	QVQLVQSGAEVKKPGASVKVSCKASGYT FPAYYIHWVRQAPGQGLEWMGIINPSLGL TSYARKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARGGRTTWIGALDIWGQG TMVTVSS (SEQ ID NO 20)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYVVW PPLT (SEQ ID NO 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAV YYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)
MAB18-IgG4	VH 1-46	YTFPA YYMH (SEQ ID NO 59)	IINPSLGL TSYARKF QG (SEQ ID NO 44)	ARGGRTT WIGAFDI (SEQ ID NO 33)	QVQLVQSGAEVKKPGASVKVSCKASGYT FPAYYMHWVRQAPGQGLEWMGIINPSLG LTSYARKFQGRVTMTRDTSTSTVYMELSS LRSEDTAVYYCARGGRTTWIGAFDIWGQ GTMVTVSS (SEQ ID NO 21)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYVVW PPLT (SEQ ID NO 65)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAV YYCQQYVVWPPLTFGGGTKVEIK (SEQ ID NO 27)
MAB19-IgG4	VH 1-46	YTFTS HYMG (SEQ ID NO 62)	VINPSM GATSYA QKFQG (SEQ ID NO 45)	ARLHVS GSYYPA YLDY (SEQ ID NO 35)	QVQLVQSGAEVKKPGASVKVSCKASGYT FTSHYMGWVRQAPGQGLEWMGVINPSM GATSYAQKFQGRVTMTRDTSTLSTVYME LSSLRSEDTAVYYCARLHVSGSYYPAYLD YWGQGTMVTVSS (SEQ ID NO 22)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYIVFP WT (SEQ ID NO 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFA VYYCQQYIVFPWTFGGGTKVEIK (SEQ ID NO 28)
MAB20-IgG4	VH 1-46	YTFTSH YMG (SEQ ID NO 62)	IINPSMG AISYAQ KFQG (SEQ ID NO 46)	ARLHVS GSYYPA YLDY (SEQ ID NO 35)	QVQLVQSGAEVKKPGASVKVSCKASGYTF TSHYMGWVRQAPGQGLEWVGIINPSMGAT SYAQKFQGRVTMTRDTSTSTVYMELSSLAS EDTAVYYCARLHVSGSYYPAYLDYWGQG TMVTVSS (SEQ ID NO 23)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYIVFP WT (SEQ ID NO 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFA VYYCQQYIVFPWTFGGGTKVEIK (SEQ ID NO 28)
MAB21-IgG4	VH 1-46	YTFTSH YMG (SEQ ID NO 62)	IINPSMG ATSYTQ KFRG (SEQ ID NO 47)	ARLHVS GSYYPA YLDY (SEQ ID NO 35)	QVQLVQSGAEVKKPGASVKVSCKASGYTF TSHYMGWVRQAPGQGLEWMGIINPSMGA TSYTQKFRGRVTMTRDTSTSTVYMELSSLA SEDTAVYYCARLHVSGSYYPAYLDYWGQ GTMVTVSS (SEQ ID NO 24)	V K 3-1 5	RASQSV SSNLA (SEQ ID NO 72)	GASTRA T (SEQ ID NO 69)	QQYIVFP WT (SEQ ID NO 66)	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPG QAPRHLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFA VYYCQQYIVFPWTFGGGTKVEIK (SEQ ID NO 28)

[19] Includes CDR-H1 as defined by both the Chothia and Kabat numbering systems, inclusive of the boundaries of both numbering systems.
[20] According to the Kabat numbering system.
[21] According to the IMGT numbering system.
[22] According to the Kabat and Chothia numbering systems.
[23] According to the Kabat and Chothia numbering systems.
[24] According to the Kabat, Chothia, and IMGT numbering systems.

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Figure 3KKK

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:7 from WO2016028656)	EVQLQESGPGLVKPSQSLSLTCSVTGSSIASDYWGWIRKFPGNKMEWMGFITYSGSTSY NPSLKSRISITRDTSKNQFFLQLHSVTTDDTATYSCARMPSFITLASLSTWEGYFDFWGP GTMVTVSS	726
vhCDR1 (SEQ ID NO:1 from WO2016028656)	SDYWG	727
vhCDR2 (SEQ ID NO:2 from WO2016028656)	FITYSGSTSYNPSLKS	728
vhCDR3 (SEQ ID NO:3 from WO2016028656)	MPSFITLASLSTWEGYFDF	729
Light chain (SEQ ID NO:8 from WO2016028656)	DIQMTQSPSLLSASVGDRVTLNCKASQSIHKNLAWYQQKLGEAPKFLIYYANSLQTGIPS RFSGSGSGTDFTLTISGLQPEDVATYFCQQYYSGWTFGGGTKVELK	730
vlCDR1 (SEQ ID NO:4 from WO2016028656)	KASQSIHKNLA	731
vlCDR2 (SEQ ID NO:5 from WO2016028656)	YANSLQT	732
vlCDR3 (SEQ ID NO:6 from WO2016028656)	QQYYSGWT	733

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Figure 3LLL

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:9 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	734
vhCDR1 (WO2016028656)	DYWG	735
vhCDR2 (WO2016028656)	FITYSGSTSYNPSLKS	736
vhCDR3 (WO2016028656)	MPSFITLASLSTWEGYFDF	737

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:10 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	738
vhCDR1 (from WO2016028656)	SDYWG	739
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	740
vhCDR3 (WO2016028656)	MPSFITLASLSTWEGYFDF	741

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Figure 3MMM

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:11 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGT MVTVSS	742
vhCDR1 (from WO2016028656)	SDYWG	743
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	744
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	745

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:12 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSISSDYWGWIRQPPGKGLEWMGFITYSGSTSYN PSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	746
vhCDR1 (from WO2016028656)	SDYWG	747
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	748
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	749

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3OOO

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:13 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	750
vhCDR1 (from WO2016028656)	SDYWG	751
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	752
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	753

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:14 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGGSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRITISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGT MVTVSS	754
vhCDR1 (from WO2016028656)	SDYWG	755
vhCDR2 from WO2016028656)	GFITYSGSTSYNPSLKS	756
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	757

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3PPP

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:15 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRITISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGT MVTVSS	758
vhCDR1 (from WO2016028656)	SDYWG	759
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	760
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	761

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:16 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSISSDYWGWIRQPPGKGLEWMGFITYSGSTSYN PSLKSRITISVDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	762
vhCDR1 (from WO2016028656)	SDYWG	763
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	764
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	765

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3QQQ

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:17 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGYSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQ GTMVTVSS	766
vhCDR1 (from WO2016028656)	SDYWG	767
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	768
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	769

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:18 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGYSISSDYWGWIRQPPGKGLEWIGFI TYSGSTSYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFI TLASLSTWEGYFDFWGQGTMVTVSS	770
vhCDR1 (from WO2016028656)	SDYWG	771
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	772
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	773

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Figure 3RRR

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:19 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGYSISSDYWGWIRQPPGKGLEWIGFI TYSGSTSYNPSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFI TLASLSTWEGYFDFWGQGTMVTVSS	774
vhCDR1 (from WO2016028656)	SDYWG	775
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	776
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	777

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:20 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGSSISSDYWGWIRQPPGKGLEWMGFI TYSGSTSYNPSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFI TLASLSTWEGYFDFWGQGTMVTVSS	778
vhCDR1 (from WO2016028656)	SDYWG	779
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	780
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	781

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Figure 3SSS

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:21 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGYSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYN PSLKSRVTISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQ GTMVTVSS	782
vhCDR1 (from WO2016028656)	SDYWG	783
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	784
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	785

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:22 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGYSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYN PSLKSRITISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	786
vhCDR1 (from WO2016028656)	SDYWG	787
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	788
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	789

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Figure 3TTT

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:37 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSSAS	790
vhCDR1 (from WO2016028656)	SDYWG	791
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	792
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	793

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:38 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	794
vhCDR1 (from WO2016028656)	SDYWG	795
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	796
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	797

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3UUU

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:39 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRKPPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	798
vhCDR1 (from WO2016028656)	SDYWG	799
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	800
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	801

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:40 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRQPPGKKLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	802
vhCDR1 (from WO2016028656)	SDYWG	803
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	804
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	805

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Figure 3VVV

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:41 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRQPPGKGMEWIGFITYSGSTSYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGTMVTVSS	806
vhCDR1 (from WO2016028656)	SDYWG	807
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	808
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	809

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:42 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRKPPGKKMEWIGFITYSGSTSYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGTMVTVSS	810
vhCDR1 (from WO2016028656)	SDYWG	811
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	812
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	813

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3WWW

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:43 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRQFPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTADDTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	814
vhCDR1 (from WO2016028656)	SDYWG	815
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	816
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	817

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:44 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCTVSGSSIASDYWGWIRKPPGKKMEWIGFITYSGSTSYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQ GTMVTVSS	818
vhCDR1 (from WO2016028656)	SDYWG	819
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	820
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	821

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Figure 3XXX

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:45 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCSVTGSSIASDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	822
vhCDR1 (from WO2016028656)	SDYWG	823
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	824
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	825

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:46 from WO2016028656)	EVQLQQSGAGLLKPSETLSLTCSVTGSSIASDYWGWIRQPPGKGLEWIGFITYSGSTSYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQ GTMVTVSS	826
vhCDR1 (from WO2016028656)	SDYWG	827
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	828
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	829

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Figure 3YYY

From WO2016028656 (Table 4, reproduced herein)

What	Sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:47 from WO2016028656)	EVQLQESGPGLVKPPGTLSLTCSVTGSSIASDYWGWVRQPPGKGLEWIGFITYSGSTSYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGTMVTVSS	830
vhCDR1 (from WO2016028656)	SDYWG	831
vhCDR2 (from WO2016028656)	FITYSGSTSYNPSLKS	832
vhCDR3 (from WO2016028656)	MPSFITLASLSTWEGYFDF	833

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3ZZZ

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:23 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGSSISSDYWGWIRQPPGKGLEWIGFITYSGSTSYNP SLKSRITISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQGT MVTVSS	834
vhCDR1 (SEQ ID NO: from WO2016028656)	SDYWG	835
vhCDR2 (SEQ ID NO: from WO2016028656)	FITYSGSTSYNPSLKS	836
vhCDR3 (SEQ ID NO: from WO2016028656)	MPSFITLASLSTWEGYFDF	837

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3AAAA
From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:24 from WO2016028656)	EVQLQESGPGLVKPSETLSLTCAVSGSSISSDYWGWIRQPPGKGLEWMGFITYSGSTSYN PSLKSRITISRDTSKNQFSLKLHSVTAADTAVYYCARMPSFITLASLSTWEGYFDFWGQG TMVTVSS	838
vhCDR1 (from WO2016028656)	SDYWG	839
vhCDR2 (WO2016028656)	FITYSGSTSYNPSLKS	840
vhCDR3 (WO2016028656)	MPSFITLASLSTWEGYFDF	841

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:25 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKLLIYYANSLQTGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	842
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	843
vlCDR2 (from WO2016028656)	YANSLQT	844
vlCDR3 (from WO2016028656)	QQYYSGWT	845

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3BBBB

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:26 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKFLIYYANSLQTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	846
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	847
vlCDR2 (from WO2016028656)	YANSLQT	848
vlCDR3 (from WO2016028656)	QQYYSGWT	849

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:27 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKFLIYYANSLQTGIPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	850
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	851
vlCDR2 (from WO2016028656)	YANSLQT	852
vlCDR3 (from WO2016028656)	QQYYSGWT	853

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3CCCC

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:28 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKVPKLLIYYANSLQTGVP SRFSGSGSGTDFTLTISSLQPEDVATYYCQQYYSGWTFGGGTKVEIK	854
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	855
vlCDR2 (from WO2016028656)	YANSLQT	856
vlCDR3 (from WO2016028656)	QQYYSGWT	857

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:29 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKVPKFLIYYANSLQTGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQQYYSGWTFGGGTKVEIK	858
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	859
vlCDR2 (from WO2016028656)	YANSLQT	860
vlCDR3 (from WO2016028656)	QQYYSGWT	861

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3DDDD

From WO2016028656 (Table 4, reproduced herein)

What	sequences	SEQ ID NO:
Light chain (SEQ ID NO:30 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKVPKFLIYYANSLQTGIPS RFSGSGSGTDFTLTISSLQPEDVATYYCQQYYSGWTFGGGTKVEIK	862
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	863
vlCDR2 (from WO2016028656)	YANSLQT	864
vlCDR3 (from WO2016028656)	QQYYSGWT	865

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:48 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKLLIYYANSLQTGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	866
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	867
vlCDR2 (WO2016028656)	YANSLQT	868
vlCDR3 (WO2016028656)	QQYYSGWT	869

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3EEEE

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:49 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKFLIYYANSLQTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	870
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	871
vlCDR2 (WO2016028656)	YANSLQT	872
vlCDR3 (WO2016028656)	QQYYSGWT	873

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:50 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKLLIYYANSLQTGVP SRFSGSGSGTDFTLTISSLQPEDFATYFCQQYYSGWTFGGGTKVEIK	874
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	875
vlCDR2 (WO2016028656)	YANSLQT	876
vlCDR3 (WO2016028656)	QQYYSGWT	877

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3FFFF

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:51 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKFLIYYANSLQTGVPS RFSGSGSGTDFTLTISSLQPEDFATYFCQQYYSGWTFGGGTKVEIK	878
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	879
vlCDR2 (WO2016028656)	YANSLQT	880
vlCDR3 (WO2016028656)	QQYYSGWT	881

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:52 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCKASQSIHKNLAWYQQKPGKAPKLLIYYANSLQTGIPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWTFGGGTKVEIK	882
vlCDR1 (from WO2016028656)	KASQSIHKNLAW	883
vlCDR2 (WO2016028656)	YANSLQT	884
vlCDR3 (WO2016028656)	QQYYSGWT	885

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3GGGG

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:63 from WO2016028656)	DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWIRQFPGNKLEWMGYISNSGSAS YNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYYCATLIYYDYGGAMNFWGQGTSVT VSS	886
vhCDR1 (from WO2016028656)	GYSITSDYAWN	887
vhCDR2 (WO2016028656)	YISNSGSASYNPSLKS	888
vhCDR3 (WO2016028656)	LIYYDYGGAMNF	889

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Figure 3HHHH

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:62 from WO2016028656)	DIVMTQSHKFMSTSVGDRVSITCKASQGVSTTVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTG SGSGTDFTFTISSVQSEDLAVYYCQHYYSTPWTFGGGTKLEIK	890
vlCDR1 (from WO2016028656)	KASQGVSTTVA	891
vlCDR2 (WO2016028656)	SASYRYT	892
vlCDR3 (WO2016028656)	QHYYSTPWT	893
vlCDR2 variant (WO2016028656)	YASNLQT	894
vlCDR2 variant (WO2016028656)	YASSLQT	895
vlCDR2 variant (WO2016028656)	YASTLQT	896
vlCDR2 variant (WO2016028656)	YATTLQT	897
vlCDR2 variant (WO2016028656)	YASYLQT	898
vlCDR2 variant (WO2016028656)	YANQLQT	899
vlCDR2 variant (WO2016028656)	YAGSLQT	900
vlCDR2 variant (WO2016028656)	YASQLQT	901
vlCDR2 variant (WO2016028656)	YADSLQT	902

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Figure 3IIII

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:62 from WO2016028656)	DIVMTQSHKFMSTSVGDRVSITCKASQGVSTTVAWYQQKPGQSPKLLIYSASYRYTGVPDRFTG SGSGTDFTFTISSVQSEDLAVYYCQHYYSTPWTFGGGTKLEIK	903
vlCDR1 (from WO2016028656)	KASQGVSTTVA	904
vlCDR2 (WO2016028656)	SASYRYT	905
vlCDR3 (WO2016028656)	QHYYSTPWT	906
vlCDR3 variant (WO2016028656)	QQYYSGFT	907
vlCDR3 variant (WO2016028656)	QQYYSGYT	908
vlCDR3 variant (WO2016028656)	QQYYSGIT	909
vlCDR3 variant (WO2016028656)	QQYYSGVT	910
vlCDR3 variant (WO2016028656)	QQYYSGLT	911

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 3JJJJ

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:63 from WO2016028656)	DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWIRQFPGNKLEWMGYISNSGSAS YNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYYCATLIYYDYGGAMNFWGQGTSVT VSS	912
vhCDR1 (from WO2016028656)	GYSITSDYAWN	913
vhCDR2 (WO2016028656)	YISNSGSASYNPSLKS	914
vhCDR3 (WO2016028656)	LIYYDYGGAMNF	915
vHCDR3 variant (WO2016028656)	MPSFITLASLSTFEGYFDF	916
vHCDR3 variant (WO2016028656)	MPSFITLASLSTYEGYFDF	917
vHCDR3 variant (WO2016028656)	MPSFITLASLSTIEGYFDF	918
vHCDR3 variant (WO2016028656)	MPSFITLASLSTVEGYFDF	919
vHCDR3 variant (WO2016028656)	MPSFITLASLSTLEGYFDF	920

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Figure 3KKKK

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:94 from WO2016028656)	EVQLQQSGPELVKPGSSVKMSCKASGYTFSSYVMHWVKQKPGQGLEWIGYIDPYNDGAKYNEK FKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCARGGPYGWYFDVWGAGTTVTVSS	921
vhCDR1 (from WO2016028656)	SYVMH	922
vhCDR2 (WO2016028656)	YIDPYNDGAKYNEKFK	923
vhCDR3 (WO2016028656)	GPYGWYFDV	924
vHCDR2 variant (WO2016028656)	YIDPYNrGAKYNEKFG	925
vHCDR2 variant (WO2016028656)	YIDPYNlGAKYNEKFG	926
vHCDR2 variant (WO2016028656)	YIDPYNkGAKYNEKFG	927
vHCDR2 variant (WO2016028656)	YIDPYNfGAKYNEKFG	928
vHCDR2 variant (WO2016028656)	YIDPYNsGAKYNEKFG	929
vHCDR2 variant (WO2016028656)	YIDPYNyGAKYNEKFG	930
vHCDR2 variant (WO2016028656)	YIDPYNvGAKYNEKFG	931
vHCDR2 variant (WO2016028656)	YIDPYNDrAKYNEKFKG	932
vHCDR2 variant (WO2016028656)	YIDPYNDnAKYNEKFKG	933
vHCDR2 variant (WO2016028656)	YIDPYNDqAKYNEKFKG	934
vHCDR2 variant (WO2016028656)	YIDPYNDeAKYNEKFKG	935
vHCDR2 variant (WO2016028656)	YIDPYNDlAKYNEKFKG	936
vHCDR2 variant (WO2016028656)	YIDPYNDkAKYNEKFKG	937
vHCDR2 variant (WO2016028656)	YIDPYNDsAKYNEKFKG	938
vHCDR2 variant (WO2016028656)	YIDPYNDyAKYNEKFKG	939
vHCDR2 variant (WO2016028656)	YIDPYNDvAKYNEKFKG	940

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Figure 3LLLL

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:94 from WO2016028656)	DIQMTQSPASLSASVGETVTITCRASEHIYSYLSWYQQKQGKSPQLLVYNAKTLAEGVPSRFSGSG SGTQFSLKINSLQPEDFGTYYCQHHFGSPLTFGAGTTLELK	941
vlCDR1 (from WO2016028656)	RASEHIYSYLS	942
vlCDR2 (WO2016028656)	NAKTLAE	943
vlCDR3 (WO2016028656)	QHHFGSPLT	944
vLCDR2 variant (WO2016028656)	AAKTLAE	945
vLCDR2 variant (WO2016028656)	YAKTLAE	946
vLCDR2 variant (WO2016028656)	WAKTLAE	947
vLCDR2 variant (WO2016028656)	SAKTLAE	948
vLCDR2 variant (WO2016028656)	TAKTLAE	949
vLCDR2 variant (WO2016028656)	IAKTLAE	950
vLCDR2 variant (WO2016028656)	VAKTLAE	951
vLCDR2 variant (WO2016028656)	NNKTLAE	952
vLCDR2 variant (WO2016028656)	NIKTLAE	953
vLCDR2 variant (WO2016028656)	NLLTLAE	954
vLCDR2 variant (WO2016028656)	NTKTLAE	955
vLCDR2 variant (WO2016028656)	NVKTLAE	956

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Figure 3MMMM

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:124 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQRLEWIGYIDPYNDGAKYS QKFQGRVTLTRDTSASTAYMELSSLRSEDTAVYYCARGGPYGWYFDVWGQGTTVTVSS	957
vhCDR1 (from WO2016028656)	SYVMHW	958
vhCDR2 (from WO2016028656)	YIDPYNDGAKYSQKFQ	959
vhCDR3 (from WO2016028656)	GGPYGWYFDV	960

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:125 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQRLEWIGYIDPYNDGAKYS QKFQGRVTLTSDKSASTAYMELSSLRSEDTAVYYCARGGPYGWYFDVWGQGTTVTVSS	961
vhCDR1 (from WO2016028656)	SYVMH	962
vhCDR2 (from WO2016028656)	YIDPYNDGAKYSQKFQ	963
vhCDR3 (from WO2016028656)	GGPYGWYFDV	964

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Figure 3NNNN

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:126 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKY AQKFQGRVTLTRDTSTSTVYMELSSLRSEDTAVYYCARGGPYGWYFDVWGQGTTVTVSS	965
vhCDR1 (from WO2016028656)	SYVMH	966
vhCDR2 (from WO2016028656)	YIDPYNDGAKYAQ	967
vhCDR3 (SEQ ID NO:13 from WO2016028656)	GGPYGWYFDV	968

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:127 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKY AQKFQGRVTLTSDKSTSTVYMELSSLRSEDTAVYYCARGGPYGWYFDVWGQGTTVTVSS	969
vhCDR1 (from WO2016028656)	SYVMH	970
vhCDR2 (from WO2016028656)	YIDPYNDGAKYAQKFQ	971
vhCDR3 (from WO2016028656)	GGPYGWYFDV	972

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Figure 3OOOO

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:128 from WO2016028656)	EVQLVQSGAEVKKPGSSVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKYA QKFQGRVTLTSDKSTSTAYMELSSLRSEDTAVYYCARGGPYGWYFDVWGQGTTVTVSS	973
vhCDR1 (from WO2016028656)	SYVMH	974
vhCDR2 (from WO2016028656)	YIDPYNDGAKYAQKFQ	975
vhCDR3 (from WO2016028656)	GGPYGWYFDV	976

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:129 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKY AQKFQGRVTLTSDKSISTAYMELSRLRSDDTVVYYCARGGPYGWYFDVWGQGTTVTVSS	977
vhCDR1 (from WO2016028656)	SYVMH	978
vhCDR2 (from WO2016028656)	YIDPYNDGAKYAQKFQ	979
vhCDR3 (from WO2016028656)	GGPYGWYFDV	980

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Figure 3PPPP

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:130 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCRASEHIYSYLSWYQQKPGKAPKLLIYNAKTLAEGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQHHFGSPLTFGQGTRLEIK	981
vlCDR1 (from WO2016028656)	RASEHIYSYLS	982
vlCDR2 (from WO2016028656)	NAKTLAE	983
vlCDR3 (from WO2016028656)	QHHFGSPLT	984

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:131 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCRASEHIYSYLSWYQQKPGKAPKLLIYNAKTLAEGVPSRFSGSGSGTQFTLTISSLQPEDFATYYCQHHFGSPLTFGQGTRLEIK	985
vlCDR1 (from WO2016028656)	RASEHIYSYLS	986
vlCDR2 (from WO2016028656)	NAKTLAE	987
vlCDR3 (from WO2016028656)	QHHFGSPLT	988

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Figure 3QQQQ

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:132 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCRASEHIYSYLSWYQQKPGKVPKLLIYNAKTLAEGVPSRFSG SGSGTDFTLTISSLQPEDVATYYCQHHFGSPLTFGQGTRLEIK	989
vlCDR1 (from WO2016028656)	RASEHIYSYLS	990
vlCDR2 (from WO2016028656)	NAKTLAE	991
vlCDR3 (from WO2016028656)	QHHFGSPLT	992

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:133 from WO2016028656)	DIQMTQSPSSLSASVGDRVTITCRASEHIYSYLSWYQQKPGKVPKLLIYNAKTLAEGVPSRFSG SGSGTQFTLTISSLQPEDVATYYCQHHFGSPLTFGQGTRLEIK	993
vlCDR1 (from WO2016028656)	RASEHIYSYLS	994
vlCDR2 (from WO2016028656)	NAKTLAE	995
vlCDR3 (from WO2016028656)	QHHFGSPLT	996

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Figure 3RRRR

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:129 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKYA QKFQGRVTLTSDKSISTAYMELSRLRSDDTVVYYCARGGPYGWYFDVWGQGTTVTVSS	997
vhCDR2 variant (from WO2016028656)	YIDPYNDGAKYAQKFQG	998
vhCDR2 variant (from WO2016028656)	YIDPYNDGAKYSQKFQG	999

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:129 from WO2016028656)	EVQLVQSGAEVKKPGASVKVSCKASGYTFSSYVMHWVRQAPGQGLEWIGYIDPYNDGAKYAQ KFQGRVTLTSDKSISTAYMELSRLRSDDTVVYYCARGGPYGWYFDVWGQGTTVTVSS	1000
vhCDR3 variant (from WO2016028656)	GGPYGAYFDV	1001
vhCDR3 variant (from WO2016028656)	GGPYGDYFDV	1002
vhCDR3 variant (from WO2016028656)	GGPYGEYFDV	1003
vhCDR3 variant (from WO2016028656)	GGPYGFYFDV	1004
vhCDR3 variant (from WO2016028656)	GGPYGGYFDV	1005
vhCDR3 variant (from WO2016028656)	GGPYGIYFDV	1006
vhCDR3 variant (from WO2016028656)	GGPYGKYFDV	1007
vhCDR3 variant (from WO2016028656)	GGPYGNYFDV	1008
vhCDR3 variant (from WO2016028656)	GGPYGQYFDV	1009
vhCDR3 variant (from WO2016028656)	GGPYGRYFDV	1010
vhCDR3 variant (from WO2016028656)	GGPYGSYFDV	1011
vhCDR3 variant (from WO2016028656)	GGPYGTYFDV	1012
vhCDR3 variant (from WO2016028656)	GGPYGVYFDV	1013
vhCDR3 variant (from WO2016028656)	GGPYGYYFDV	1014

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Figure 3SSSS

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
VH 18G10 (SEQ ID NO:136 from WO2016028656)	QVQLMESGPGLVQPSQTLSLTCTVSGFPLTSYTVHWVRQPPGKGLEWIGAIWSSGSTDYNSA LKSRLNINRDSSKSQVFLKMNSLQTEDTAIYFCTKSGWAFFDYWGQGVMVTVSS	1015
VL 18G10 (SEQ ID NO:137 from WO2016028656)	DIQMTQSPSLLSASVGDRVTLNCIASQNIYKSLAWYQLKLGEAPKLLIYNANSLQAGIPSRFSG SGSGTDFALTISGLQPEDVATYFCQQYSGGYTFGAGTKLELK	1016

From WO2016028656 (Table 4, reproduced herein)

What	sequence	SEQ ID NO:
VH 11A11 (SEQ ID NO:138 from WO2016028656)	EVQLVESGGDLVQPGRSLKISCVASGFTFSDYYMAWVRLAPQKGLEWVASISYEGSRTHYGD SVRGRFIISRDNPKNILYLQMNSLGSEDTATYFCARHTGTLDWLVYWGQGTLVIVSS	1017
VL 11A11 (SEQ ID NO:139 from WO2016028656)	NIVMAQSPKSMSISAGDRVTMNCKASQNVDNNIAWYQQKPGQSPKLLIFYASNRYSGVPDR FTGGGYGTDFTLTIKSVQAEDAAFYYCQRIYNFPTFGSGTKLEIK	1018

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Figure 4A

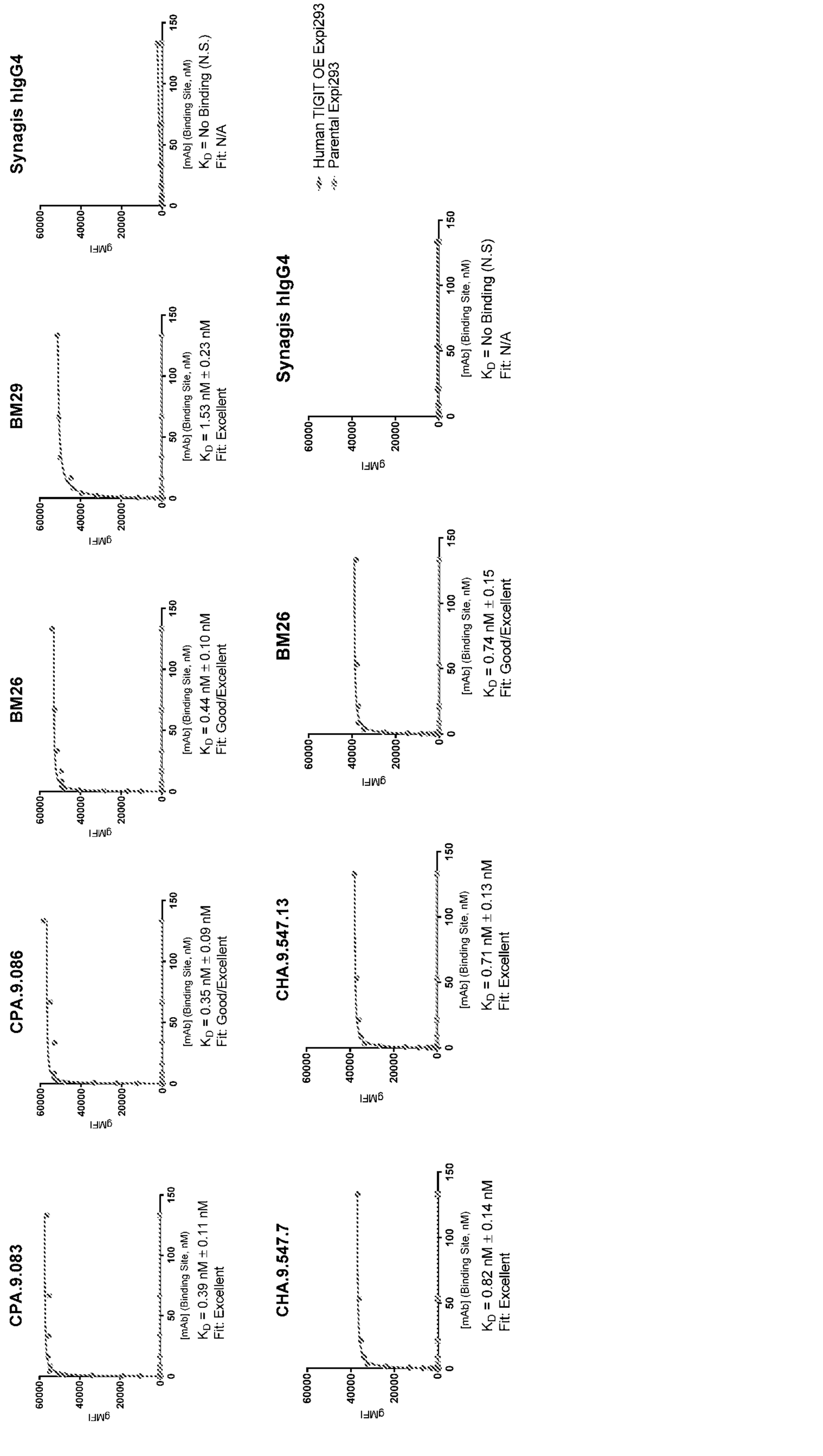
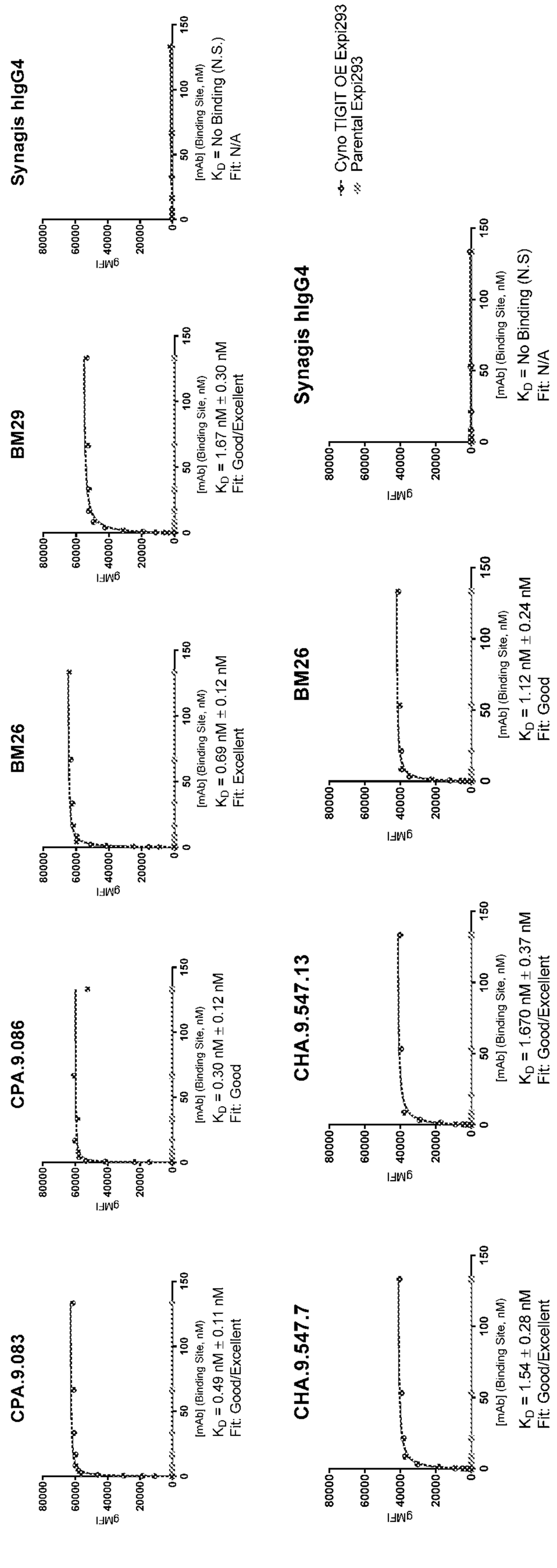

Human TIGIT OE Expi293
Parental Expi293
Synagis hIgG4
K_D = No Binding (N.S.)
Fit: N/A
BM29
K_D = 1.53 nM ± 0.23 nM
Fit: Excellent
BM26
K_D = 0.44 nM ± 0.10 nM
Fit: Good/Excellent
BM26
K_D = 0.74 nM ± 0.15
Fit: Good/Excellent
CPA.9.086
K_D = 0.35 nM ± 0.09 nM
Fit: Good/Excellent
CHA.9.547.13
K_D = 0.71 nM ± 0.13 nM
Fit: Excellent
CPA.9.083
K_D = 0.39 nM ± 0.11 nM
Fit: Excellent
CHA.9.547.7
K_D = 0.82 nM ± 0.14 nM
Fit: Excellent
gMFI
[mAb] (Binding Site, nM)
0
20000
40000
60000
50
100
150

Figure 4B


Synagis hIgG4
BM29
BM26
Synagis hIgG4
CPA.9.086
BM26
CHA.9.547.13
CPA.9.083
CHA.9.547.7
gMFI
[mAb] (Binding Site, nM)
Cyno TIGIT OE Expi293
Parental Expi293
K_D = No Binding (N.S.)
Fit: N/A
K_D = 1.67 nM ± 0.30 nM
Fit: Good/Excellent
K_D = 0.69 nM ± 0.12 nM
Fit: Excellent
K_D = 1.12 nM ± 0.24 nM
Fit: Good
K_D = No Binding (N.S)
Fit: N/A
K_D = 0.30 nM ± 0.12 nM
Fit: Good
K_D = 1.670 nM ± 0.37 nM
Fit: Good/Excellent
K_D = 0.49 nM ± 0.11 nM
Fit: Good/Excellent
K_D = 1.54 ± 0.28 nM
Fit: Good/Excellent

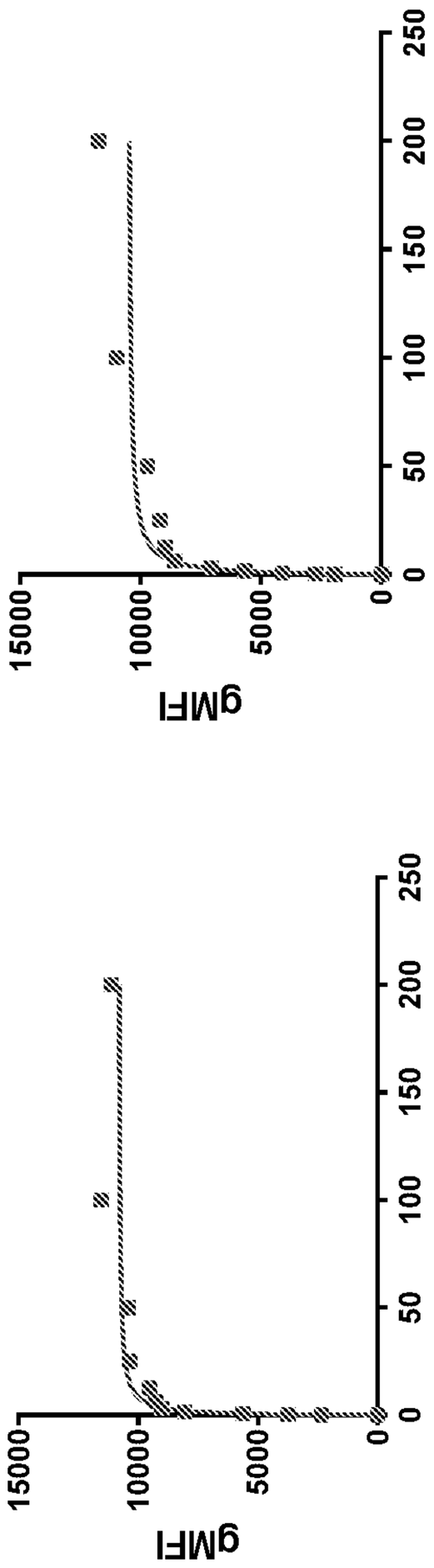

CPA.9.086
gMFI
15000
10000
5000
0
0
50
100
150
200
250
[mAb] (Binding Site, nM)
K_D = 1.32 ± 0.44nM
CPA.9.083
gMFI
15000
10000
5000
0
0
50
100
150
200
250
[mAb] (Binding Site, nM)
K_D = 0.70 ± 0.16nM

Figure 4C

Figure 5A
CHA.7.518.1

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNINWVRQAPGQGLEWMGYIYPYIGGSGYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSS	1019
vhCDR1	GYTFTDYN	1020
vhCDR2	IYPYIGGS	1021
vhCDR3	AREDKTARNAMDY	1022
Full length HC (IgG4(S241P))	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNINWVRQAPGQGLEWMGYIYPYIGGSGYAQKFQGRVTMTRDTST STVYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE	1023
Full length HC for CHA.7.518.1.H4(S241P)	PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCRVSENIYSNLAWYQQKPGKAPKLLIYEATNLAEGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQHFWGTPYTFGQGTKLEIK	1024
vlCDR1	ENIYSN	1025
vlCDR2	EAT	1026
vlCDR3	QHFWGTPYT	1027
Full length light chain for CHA.7.518.1.H4(S241P)	DIQMTQSPSSLSASVGDRVTITCRVSENIYSNLAWYQQKPGKAPKLLIYEATNLAEGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQHFWGTPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1028

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Figure 5B
CHA.7.538.1.2

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPGQGLEWIGVINPGSGGIYYAQKFQGRVTMTADTSTSTVY MELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSS	1029
vhCDR1	GYAFTNYL	1030
vhCDR2	INPGSGGI	1031
vhCDR3	ARSETHDTWFAY	1032
Full length HC (IgG4(S241P) Full length HC for CHA.7.538.1.2. H4(S241P)	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPGQGLEWIGVINPGSGGIYYAQKFQGRVTMTADTSTSTVY MELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK	1033
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWFQQKPGKAPKALIYLASTRHTGVPSRFSGSGSGTDFTLTISSVQPEDFA TYYCLQHWNYPYTFGQGTKLEIK	1034
vlCDR1	QSVRIA	1035
vlCDR2	LAS	1036
vlCDR3	LQHWNYPYT	1037
Full length light chain for CHA.7.538.1.2. H4(S241P)	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWFQQKPGKAPKALIYLASTRHTGVPSRFSGSGSGTDFTLTISSVQPEDFA TYYCLQHWNYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1038

Figure 5C

From Zhu (WO 2017/041004)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:5 from WO 2017/041004)	EVQLQQSGAELVRSGASVKMSCKVNDYTFTNYNMHWLRQTPGQGLEWIGYIYPGNGDTNY NQKFKGKATLTADTSSSTAYMQISLTSEDPAVYFCARQGIHYYYIDVWGAGTTVTVSSG	1039
vhCDR1 (SEQ ID NO:6 from WO 2017/041004)	DYTFTNYNMH	1040
vhCDR2 (SEQ ID NO:7 from WO 2017/041004)	YIYPGNGDTNYNQ	1041
vhCDR3 (SEQ ID NO:8 from WO 2017/041004)	QGIHYYYIDV	1042
Light chain (SEQ ID NO:3 from WO 2017/041004)	DIEMTQSPATLSVTPGDRVSLSCRASQSIRDYLHWYQQKSHESPRLLIKYVSQSISGIPS RFSGSGSGSEFTLSINSVEPEDVGVYYCQNGHSLPLTFGSGTKLEIKRTV	1043
vlCDR1 (SEQ ID NO:9 from WO 2017/041004)	RASQSIRDYLH	1044
vlCDR2 (SEQ ID NO:10 from WO 2017/041004)	YVSQSIS	1045
vlCDR3 (SEQ ID NO:11 from WO 2017/041004)	QNGHSLPLT	1046

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Figure 5D

From Zhu (WO 2017/041004)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:32 from WO 2017/041004)	QVQLQQSGAELAKPGASVKMSCKASGYTFTSDWMHWVKQRPGQGLEWIGYINPSTGYTEY NQKFKDKATLTADKSSSTAYMQLRSLTSEDSAVYYCARGSSGSWFAYWGQGTLVTVSA	1047
vhCDR1 (SEQ ID NO:34 from WO 2017/041004)	SDWMH	1048
vhCDR2 (SEQ ID NO:35 from WO 2017/041004)	YINPSTGYTEYNQKFKD	1049
vhCDR3 (SEQ ID NO:36 from WO 2017/041004)	GSSGSWFAY	1050
Light chain (SEQ ID NO:33 from WO 2017/041004)	DIVLTQSPASLAVSLGQRATISCRASQSVSTSSYSYMHWYQQKPGQPPKLLIKYASNLESGVPA RFSGSGSGTDFTLNIHPVEEEDTATYYCQHSWEIPYTFGGGTKLEIK	1051
vlCDR1 (SEQ ID NO:37 from WO 2017/041004)	RASQSVSTSSYSYMH	1052
vlCDR2 (SEQ ID NO:38 from WO 2017/041004)	YASNLES	1053
vlCDR3 (SEQ ID NO:39 from WO 2017/041004)	QHSWEIPYT	1054

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Figure 5E

From Zhu (WO 2017/041004)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:32 from WO 2017/041004)	QVQLQQSGAELAKPGASVKMSCKASGYTFTSDWMHWVKQRPGQGLEWIGYINPSTGYTEY NQKFKDKATLTADKSSSTAYMQLRSLTSEDSAVYYCARGSSGSWFAYWGQGTLVTVSA	1055
vhCDR1 (SEQ ID NO:34 from WO 2017/041004)	SDWMH	1056
vhCDR2 (SEQ ID NO:35 from WO 2017/041004)	YINPSTGYTEYNQKFKD	1057
vhCDR3 (SEQ ID NO:36 from WO 2017/041004)	GSSGSWFAY	1058
Light chain (SEQ ID NO:40 from WO 2017/041004)	DVVMTQTPLTLSVTIGQPASISCKSSQSLLNSDGKTYLNWLLQRPGQSPKRLIYLVSKLD SGVPDRFTGSGSGTDFTLKISRVEAEDLGVYYCWQGTHFPRTFGGGTKLEIK	1059
vlCDR1 (SEQ ID NO:41 from WO 2017/041004)	KSSQSLLNSDGKTYLN	1060
vlCDR2 (SEQ ID NO:42 from WO 2017/041004)	LVSKLDS	1061
vlCDR3 (SEQ ID NO:43 from WO 2017/041004)	WQGTHFPRT	1062

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Figure 5F

From WO 2018/017864 (334M5 antibody)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:30 from WO 2018/017864)	EVQLQQSVAELVRPGTSVTISCKASGYTFTNYWLGWVKQRPGHGLEWIGDIFPGGDYPNY NEKFKGKATLTADTSSSTAYMQLSSLTSEDSSVYFCTRGYFDVWGAGTTVTVSS	1063
vhCDR1 (SEQ ID NO:31 from WO 2018/017864)	TNYWLG	1064
vhCDR2 (SEQ ID NO:32 from WO 2018/017864)	DIFPGGDYPNYNEKFKG	1065
vhCDR3 (SEQ ID NO:33 from WO 2018/017864)	TRGYFDV	1066
Light chain (SEQ ID NO:25 from WO 2018/017864)	DIQMTQSPSSLSVSAGEKVTMSCKSSQSLLNSENQKNYLAWFQQKPGQPPKMLIYGASTR ESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDHSYPFTFGSGTKLEIKR	1067
vlCDR1 (SEQ ID NO:26 from WO 2018/017864)	KSSQSLLNSENQKNYLA	1068
vlCDR2 (SEQ ID NO:27 from WO 2018/017864)	GASTRES	1069
vlCDR3 (SEQ ID NO:28 from WO 2018/017864)	QNDHSYP	1070

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Figure 7A

Pembrolizumab (Anti-PD1 hIgG4)

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVLSGGGFVQPGGSLKLSCAASGFTFSSYAMSWVRQNPERRLVWVATITGGGRNTYYPDSVKGRFTISR DNAKNTLYLQMSSLRSEDTAMYYCTRQGYDGYTWFAYWGQGTLVTVSS	1071
vhCDR1	GFTFSSYA	1072
vhCDR2	ITGGGRNT	1073
vhCDR3	TRQGYDGYTWFAY	1074
Full length HC	EVQLVLSGGGFVQPGGSLKLSCAASGFTFSSYAMSWVRQNPERRLVWVATITGGGRNTYYPDSVKGRFTISR DNAKNTLYLQMSSLRSEDTAMYYCTRQGYDGYTWFAYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSPGK	1075
Variable light (vl) domain	DIVLTQSPTSLAVSLGQRATISCRASESVDNSGISFMNWFQQKPGQPPKLLIYAASNPGSGVPARFSGSGSGT DFSLNIHPMEEDDTAMYFCQQSKEVPWTFGGGTELEIKR	1076
vlCDR1	ESVDNSGISF	1077
vlCDR2	AAS	1078
vlCDR3	QQSKEVPWT	1079
Full length light chain	DIVLTQSPTSLAVSLGQRATISCRASESVDNSGISFMNWFQQKPGQPPKLLIYAASNPGSGVPARFSGSGSGT DFSLNIHPMEEDDTAMYFCQQSKEVPWTFGGGTELEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	1080

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Figure 7B

Pembrolizumab (Anti-PD1 from WO2016028656)

What	sequence	SEQ ID NO:
Full length HC (SEQ ID NO:33 from WO2016028656)	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRV TLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTK VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVM HEALHNHYTQKSLSLSLGK	1081
Full length light chain (SEQ ID NO:34 from WO2016028656)	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPARFSGSGSGTD FTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1082

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Figure 7C

Nivolumab (Anti-PD1 hIgG4)

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTI SRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS	1083
vhCDR1	GITFSNSG	1084
vhCDR2	IWYDGSKR	1085
vhCDR3	ATNDDY	1086
Full length HC	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTI SRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	1087
Variable light (vl) domain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKR	1088
vlCDR1	QSVSSY	1089
vlCDR2	DAS	1090
vlCDR3	QQSSNWPRT	1091
Full length light chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1092

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Figure 7D

Nivolumab (Anti-PD1 from WO2016028656)

What	sequence	SEQ ID NO:
Full length heavy chain (SEQ ID NO:35 from WO2016028656)	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTI SRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES KYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK	1093
Full length light chain (SEQ ID NO:36 from WO2016028656)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1094

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Figure 7E

Cemiplimab (REGN2810; anti-PD1)

What	sequence	SEQ ID NO:
Variable heavy (vh) domain (SEQ ID NO:1 from US20170174779)	EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYF ADSVKGRFTISRDNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSS	1095
vhCDR1 (SEQ ID NO:3 from US20170174779)	GFTFSNFG	1096
vhCDR2 (SEQ ID NO:4 from US20170174779)	ISGGGRDT	1097
vhCDR3 (SEQ ID NO:5 from US20170174779)	VKWGNIYFDY	1098
Variable light (vl) domain (SEQ ID NO:2 from US20170174779)	DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPS RFSGSGSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR	1099
vlCDR1 (SEQ ID NO:6 from US20170174779)	LSINTF	1100
vlCDR2 (SEQ ID NO:7 from US20170174779)	AAS	1101
vlCDR3 (SEQ ID NO:8 from US20170174779)	QQSSNTPFT	1102

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 7F

Cemiplimab (REGN2810; anti-PD1)

What	sequence	SEQ ID NO:
Full length heavy chain (SEQ ID NO:9 from US20170174779)	EVQLLESGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFADSVKGRFTISR DNSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	1103
Full length light chain (SEQ ID NO:10 from US20170174779)	DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDFTLTI RTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1104

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 8

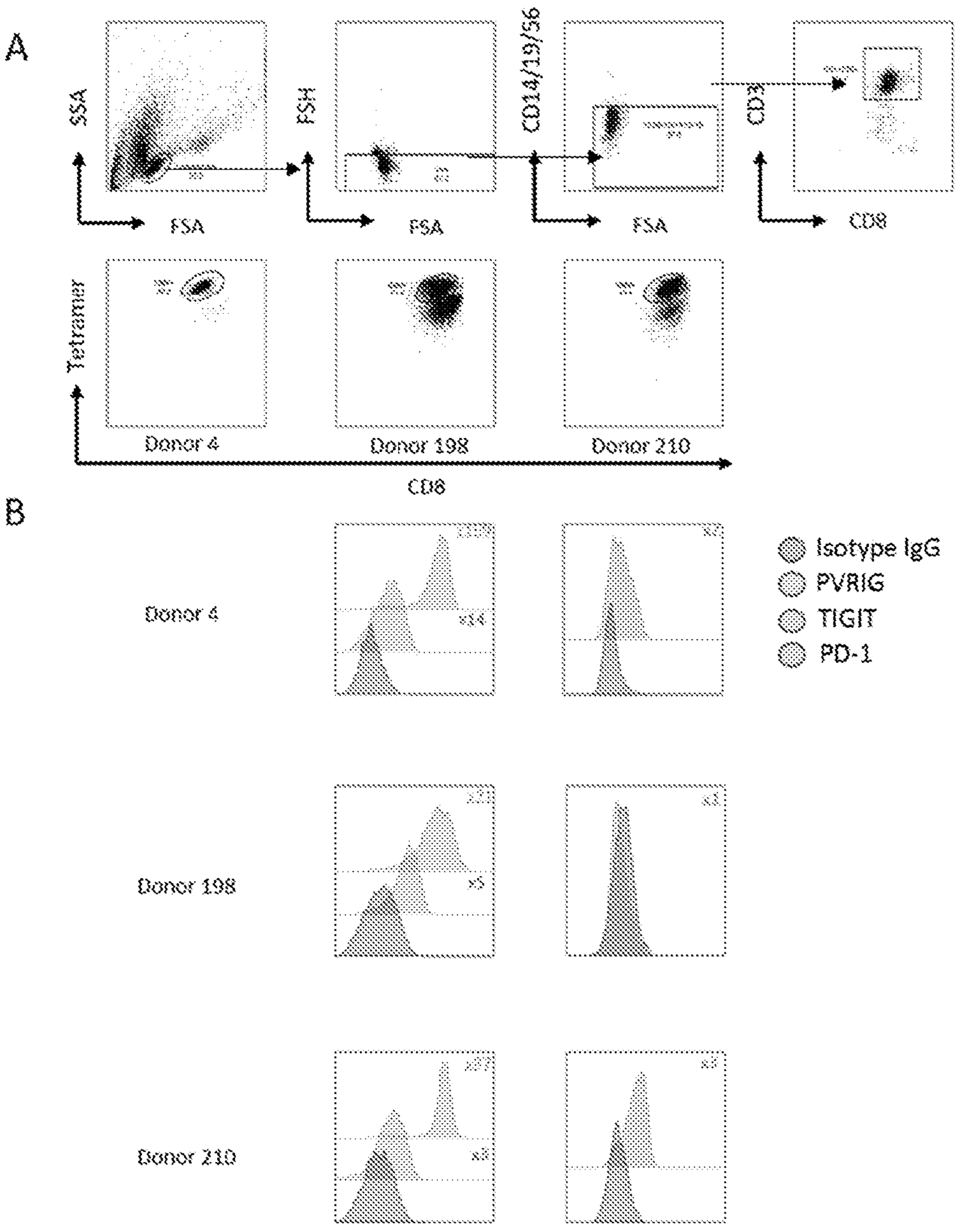

A
SSA
FSA
FSH
FSA
CD14/19/56
FSA
CD3
CD8
Tetramer
Donor 4
Donor 198
Donor 210
CD8
B
Donor 4
Donor 198
Donor 210
Isotype IgG
PVRIG
TIGIT
PD-1

FIGURE 9

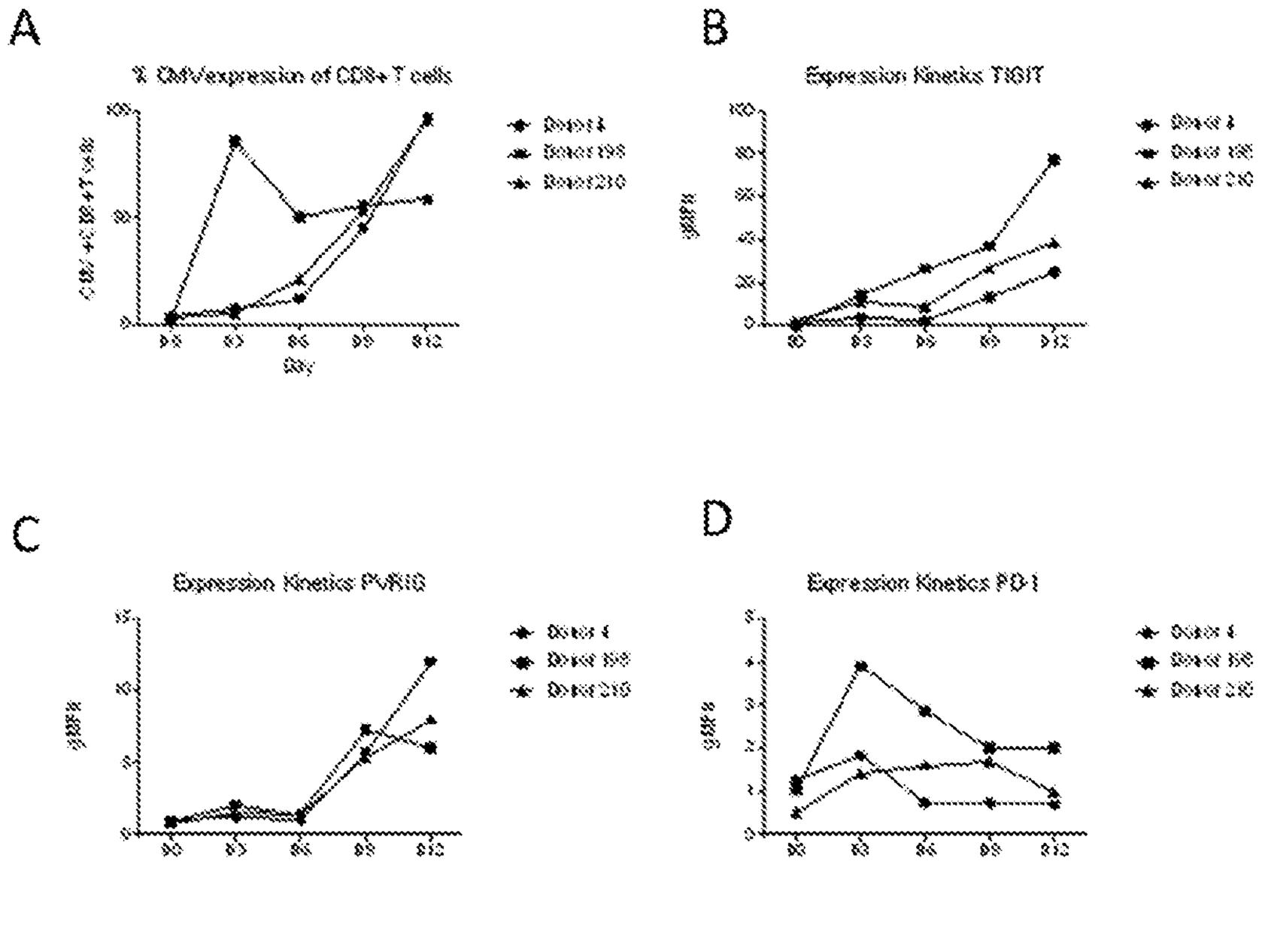

A
B
C
D
Expression Kinetics TIGIT
Expression Kinetics PVRIG
Expression Kinetics PD-1
Day

FIGURE 10

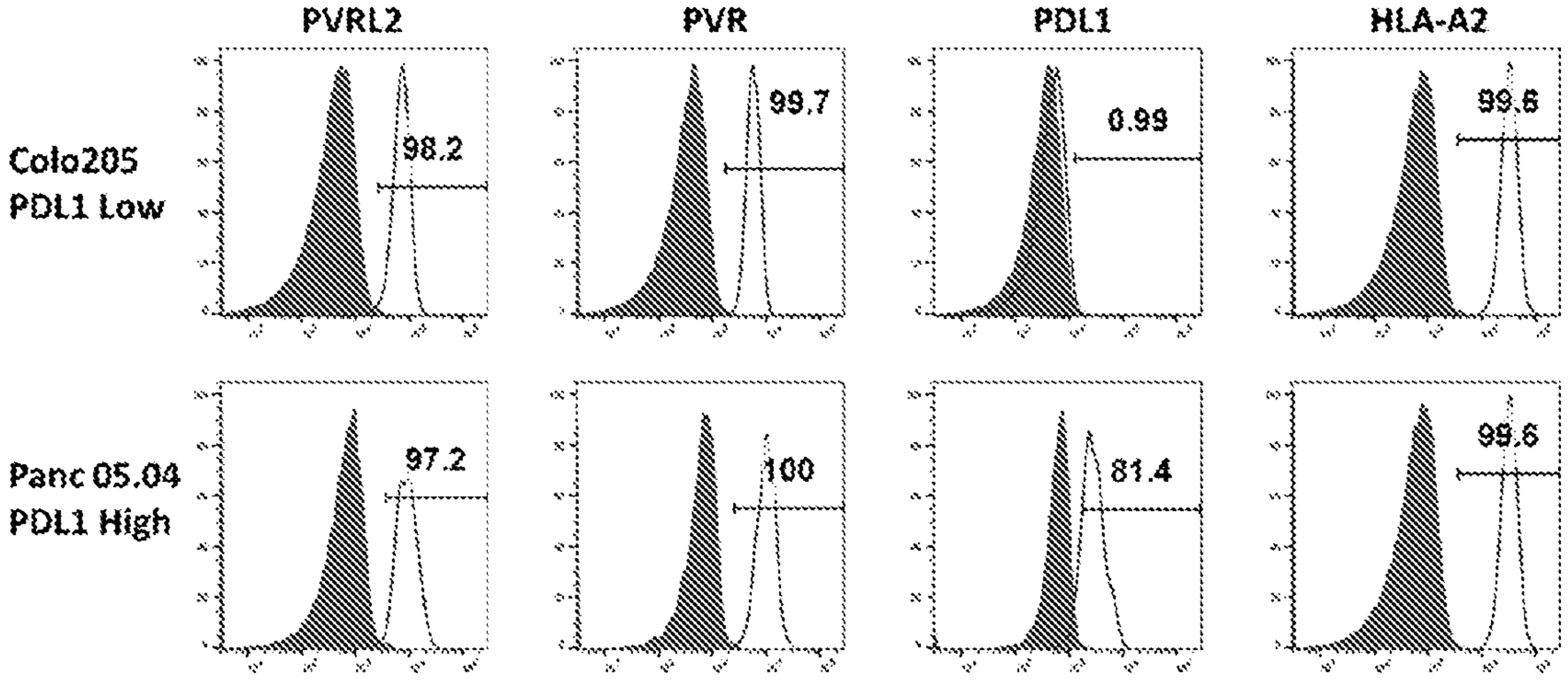

PVRL2
PVR
PDL1
HLA-A2
Colo205
PDL1 Low
98.2
99.7
0.99
99.6
Panc 05.04
PDL1 High
97.2
100
81.4
99.6

FIGURE 11A

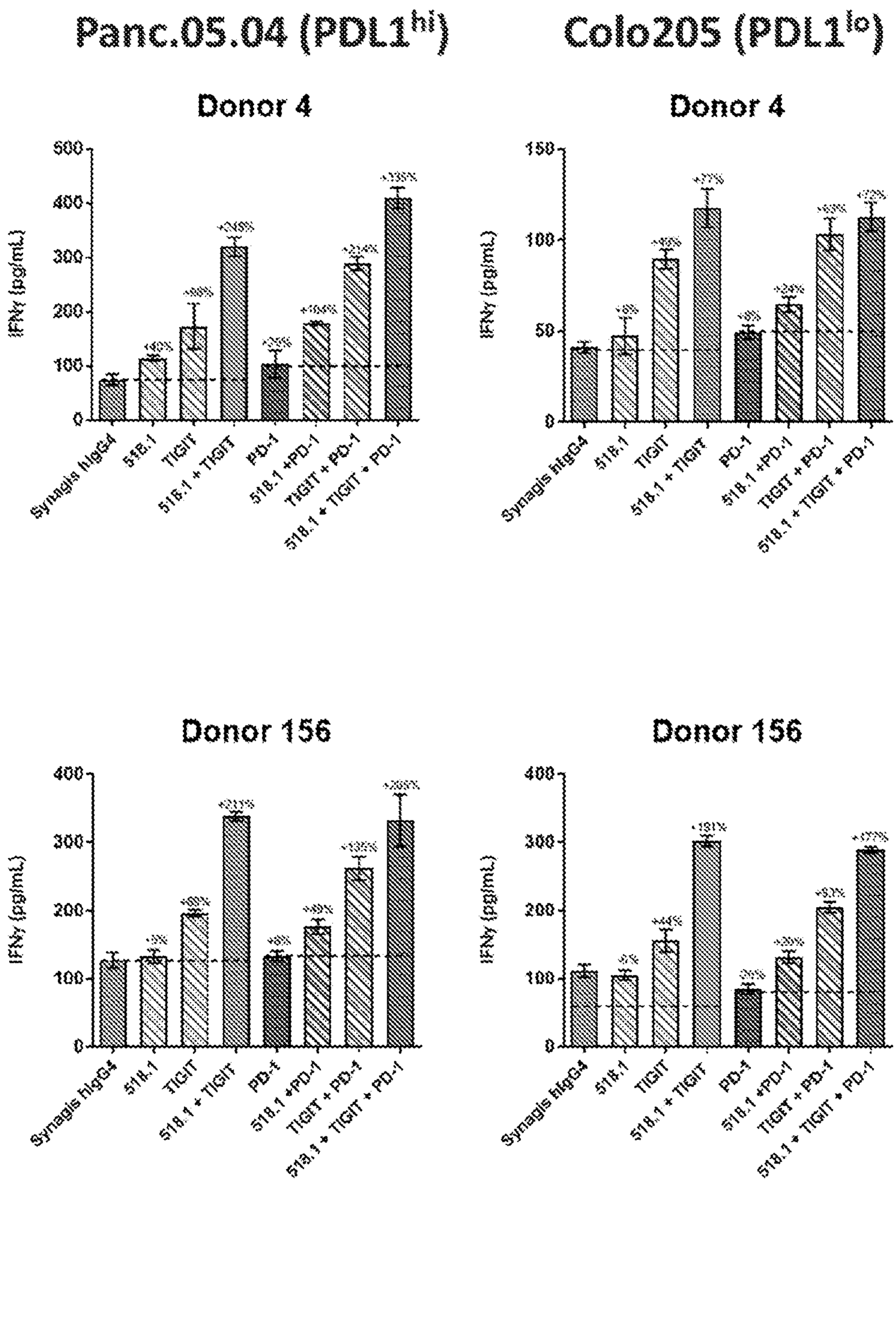

Panc.05.04 (PDL1hi)
Colo205 (PDL1lo)
Donor 4
Donor 4
IFNγ (pg/mL)
Synagis hIgG4
518.1
TIGIT
518.1 + TIGIT
PD-1
518.1 +PD-1
TIGIT + PD-1
518.1 + TIGIT + PD-1
Donor 156
Donor 156

Figure 11B

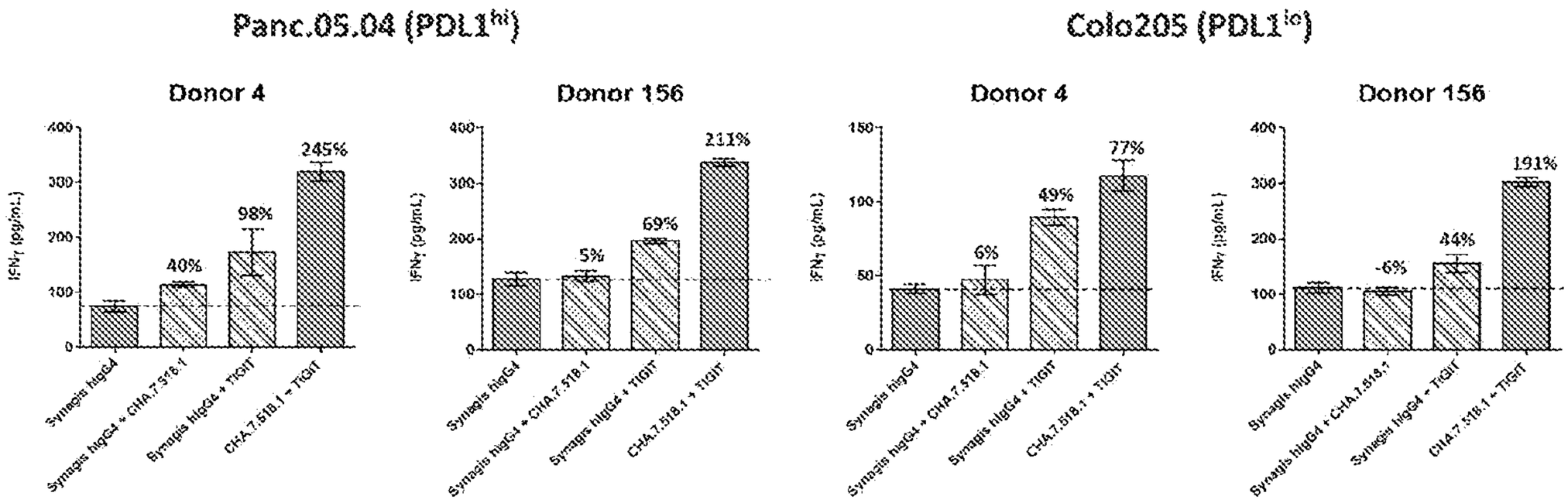

Panc.05.04 (PDL1hi)
Colo205 (PDL1lo)
Donor 4
Donor 156
Donor 4
Donor 156
IFNγ (pg/mL)
400
300
200
100
0
150
100
50
40%
98%
245%
5%
69%
211%
6%
49%
77%
-6%
44%
191%
Synagis hIgG4
Synagis hIgG4 + CHA.7.518.1
Synagis hIgG4 + TIGIT
CHA.7.518.1 + TIGIT

Figure 11C

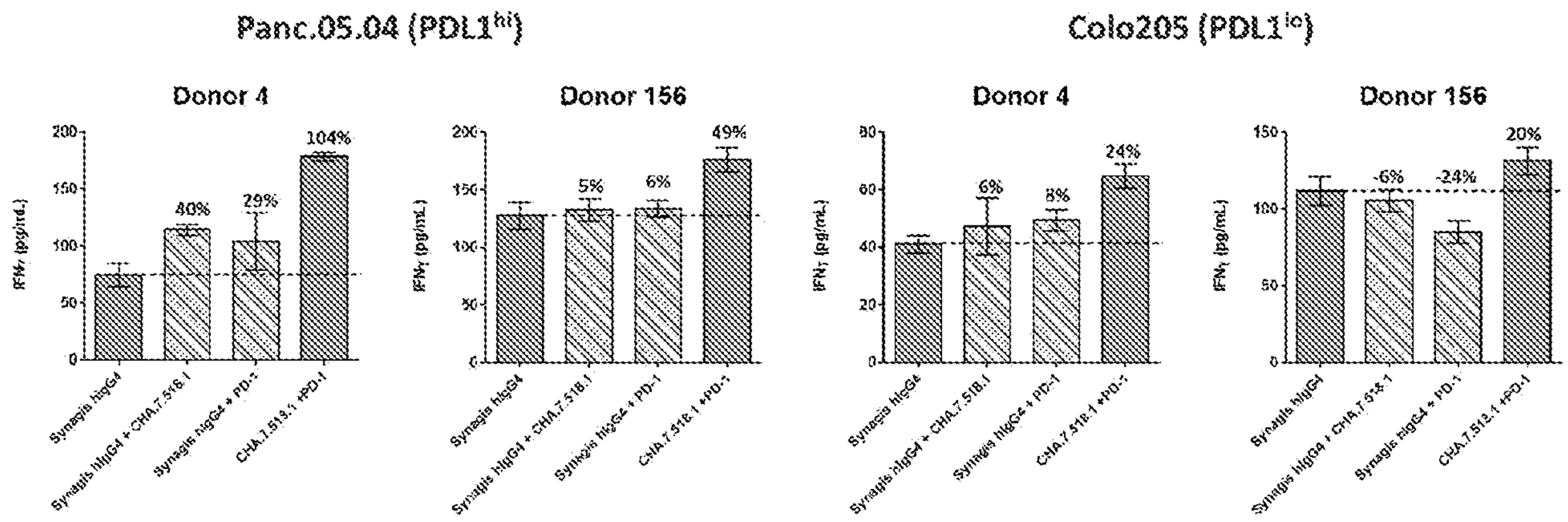

Panc.05.04 (PDL1hi)
Colo205 (PDL1lo)
Donor 4
Donor 156
Donor 4
Donor 156
IFNγ (pg/mL)
40%
29%
104%
5%
6%
49%
6%
8%
24%
-6%
-24%
20%
Synagis hIgG4
Synagis hIgG4 + CHA.7.518.1
Synagis hIgG4 + PD-1
CHA.7.518.1 +PD-1

Figure 11D

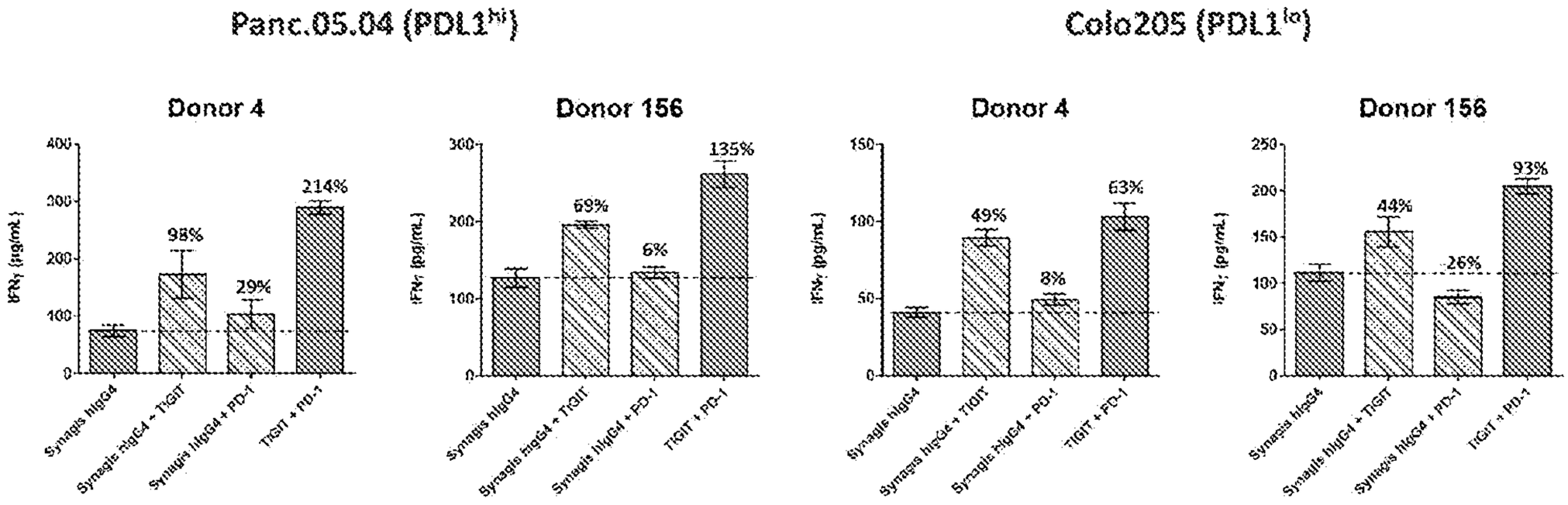

Panc.05.04 (PDL1hi)
Colo205 (PDL1lo)
Donor 4
Donor 156
Donor 4
Donor 156
IFNγ (pg/mL)
98%
29%
214%
69%
6%
135%
49%
8%
63%
44%
26%
93%
Synagis hIgG4
Synagis hIgG4 + TIGIT
Synagis hIgG4 + PD-1
TIGIT + PD-1

Figure 12

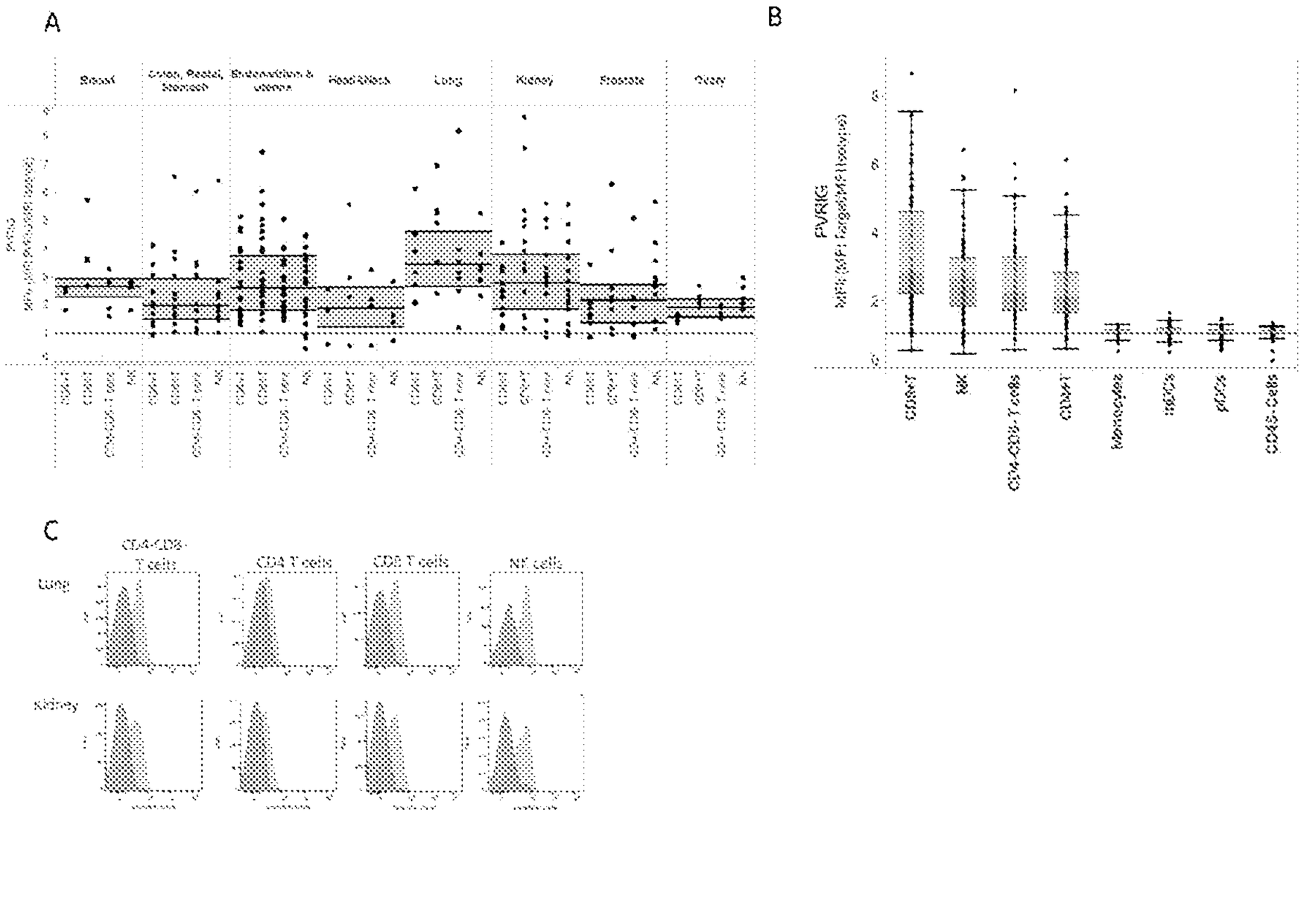
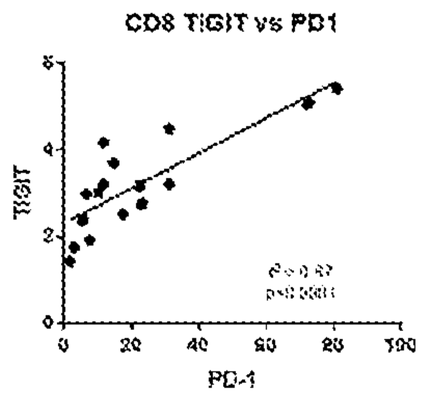
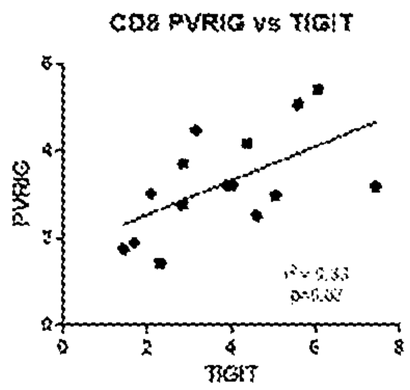
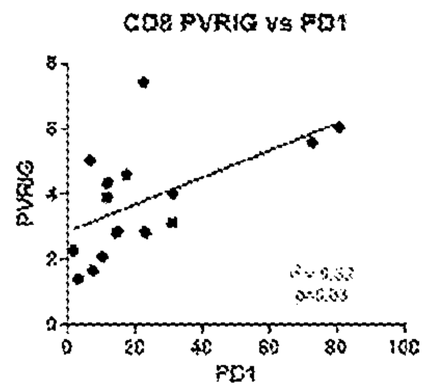
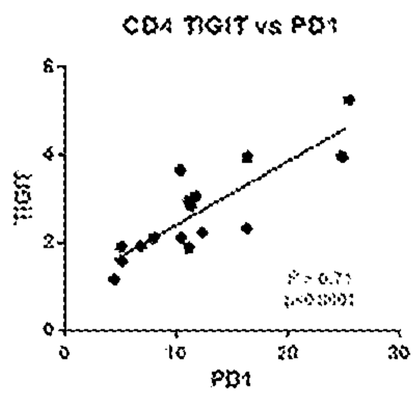

A
B
C
Breast
Colon, Rectal, Stomach
Endometrium & uterine
Head&Neck
Lung
Kidney
Prostate
Ovary
CD4+CD8+ T cells
CD4 T cells
CD8 T cells
NK cells
Lung
Kidney
PVRIG
Monocytes
iNKTs
γδTs
CD45-Cells

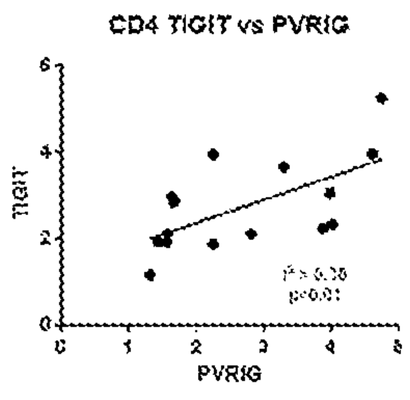
Figure 13


CD8 TIGIT vs PD1
TIGIT
PD-1


CD8 PVRIG vs TIGIT
PVRIG
TIGIT


CD8 PVRIG vs PD1
PVRIG
PD1


CD4 TIGIT vs PD1
TIGIT
PD1


CD4 TIGIT vs PVRIG
TIGIT
PVRIG

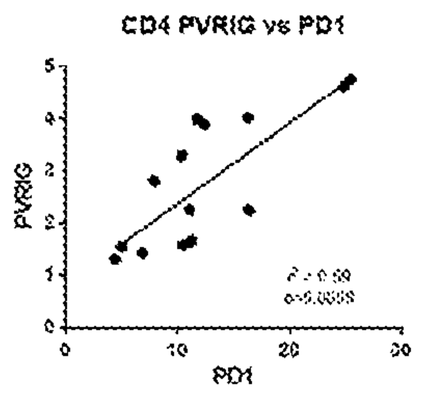

CD4 PVRIG vs PD1
PVRIG
PD1

Figure 14

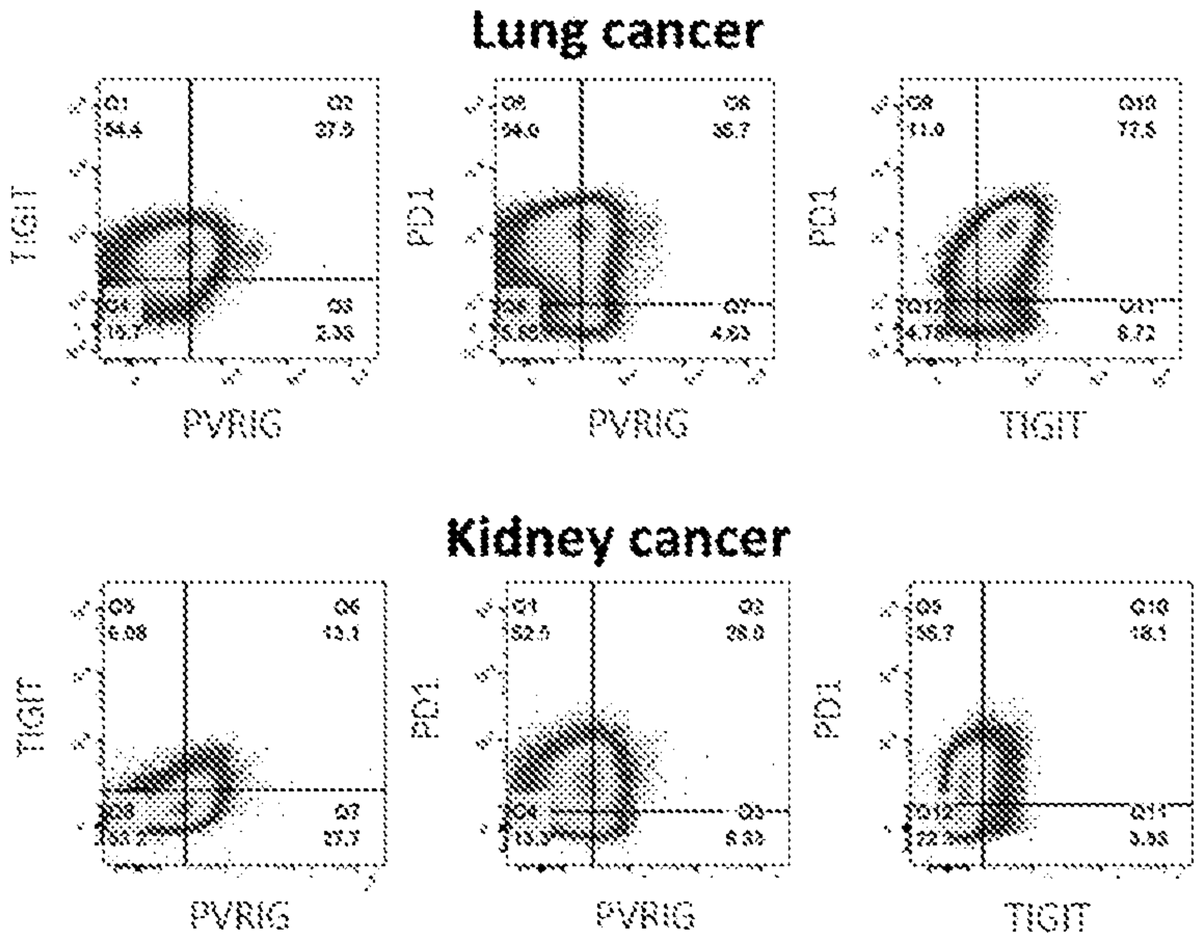
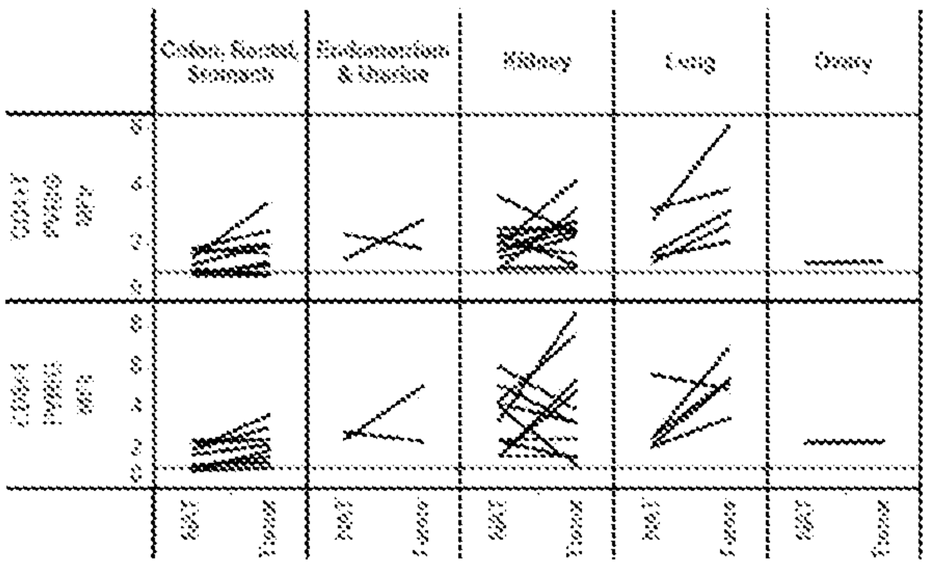
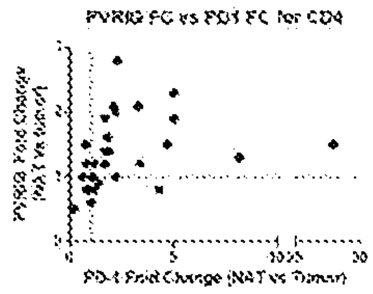

Lung cancer
TIGIT
PVRIG
PD1
PVRIG
PD1
TIGIT
Kidney cancer
TIGIT
PVRIG
PD1
PVRIG
PD1
TIGIT

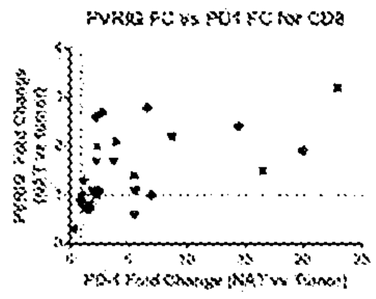
Figure 15

A



B





PVRIG Expression

CD4 T cells	NAT vs Tumor	0.3049	
CD8 T cells	NAT vs Tumor	0.025	

CD4 T cells	PVRIG FC vs PD1 FC	0.5333	0.0035
CD8 T cells	PVRIG FC vs PD1 FC	0.6253	0.0004

Figure 16

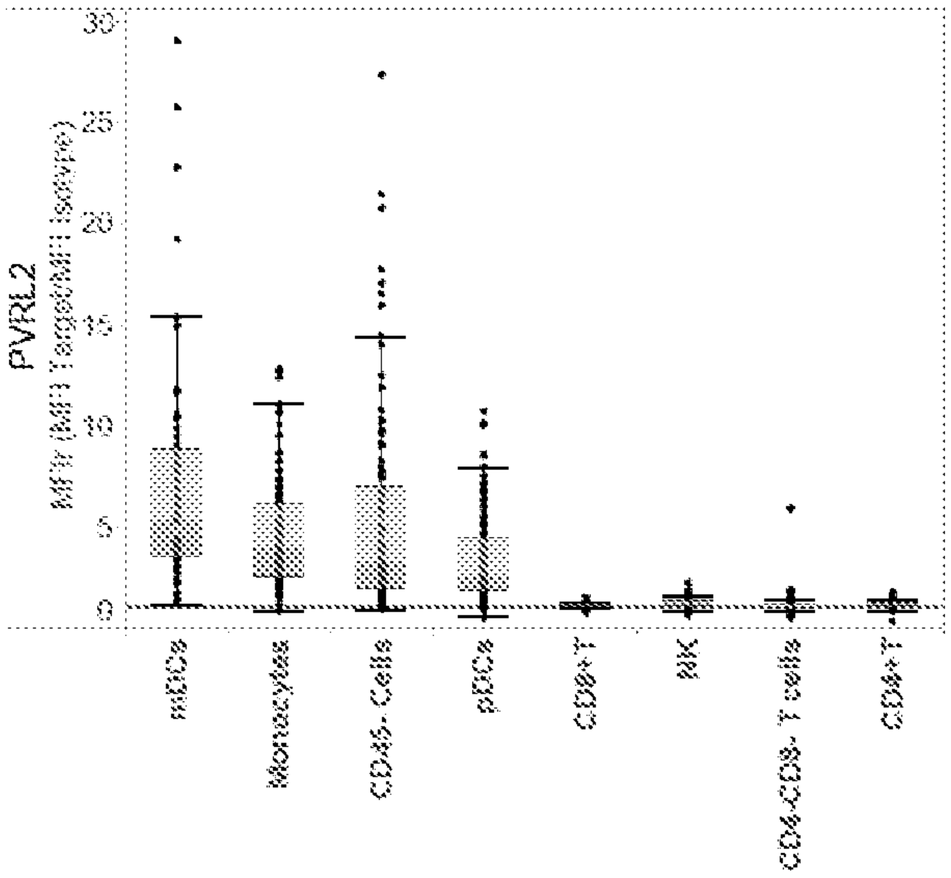

PVRL2
MFI (MFI Target/MFI
0
5
10
15
20
25
30
mDCs
Monocytes
CD45- Cells
pDCs
CD8+T
NK
CD4-CD8- T cells
CD4+T

Figure 17

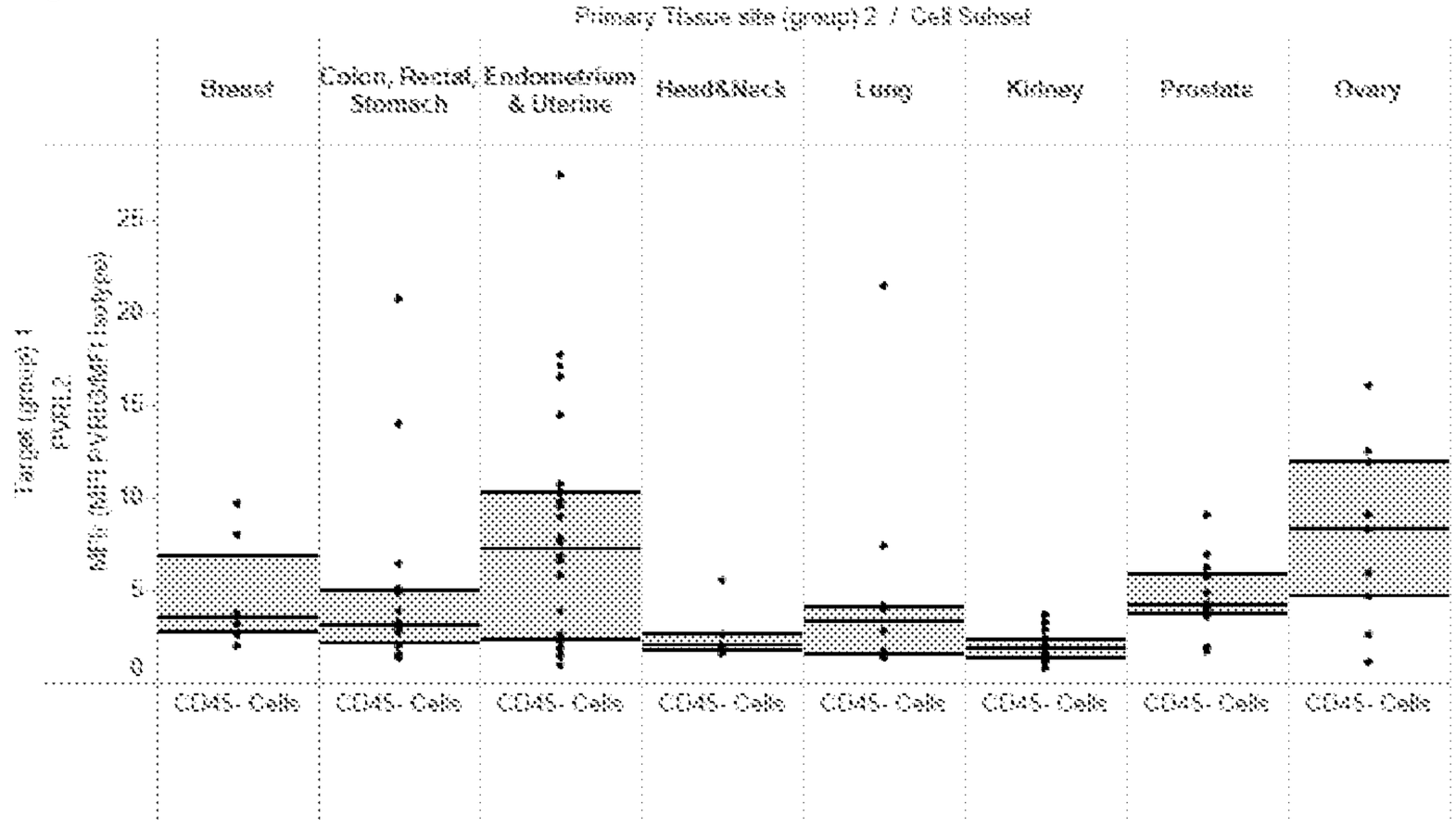

Primary Tissue site (group) 2 / Cell Subset
Breast
Colon, Rectal, Stomach
Endometrium & Uterine
Head&Neck
Lung
Kidney
Prostate
Ovary
MFI: (MHC-I (pan) FVB/NJ-PMEL-1 Tetramer (group) 2 (Isotype))
0
5
10
15
20
25
CD45- Cells

Figure 18

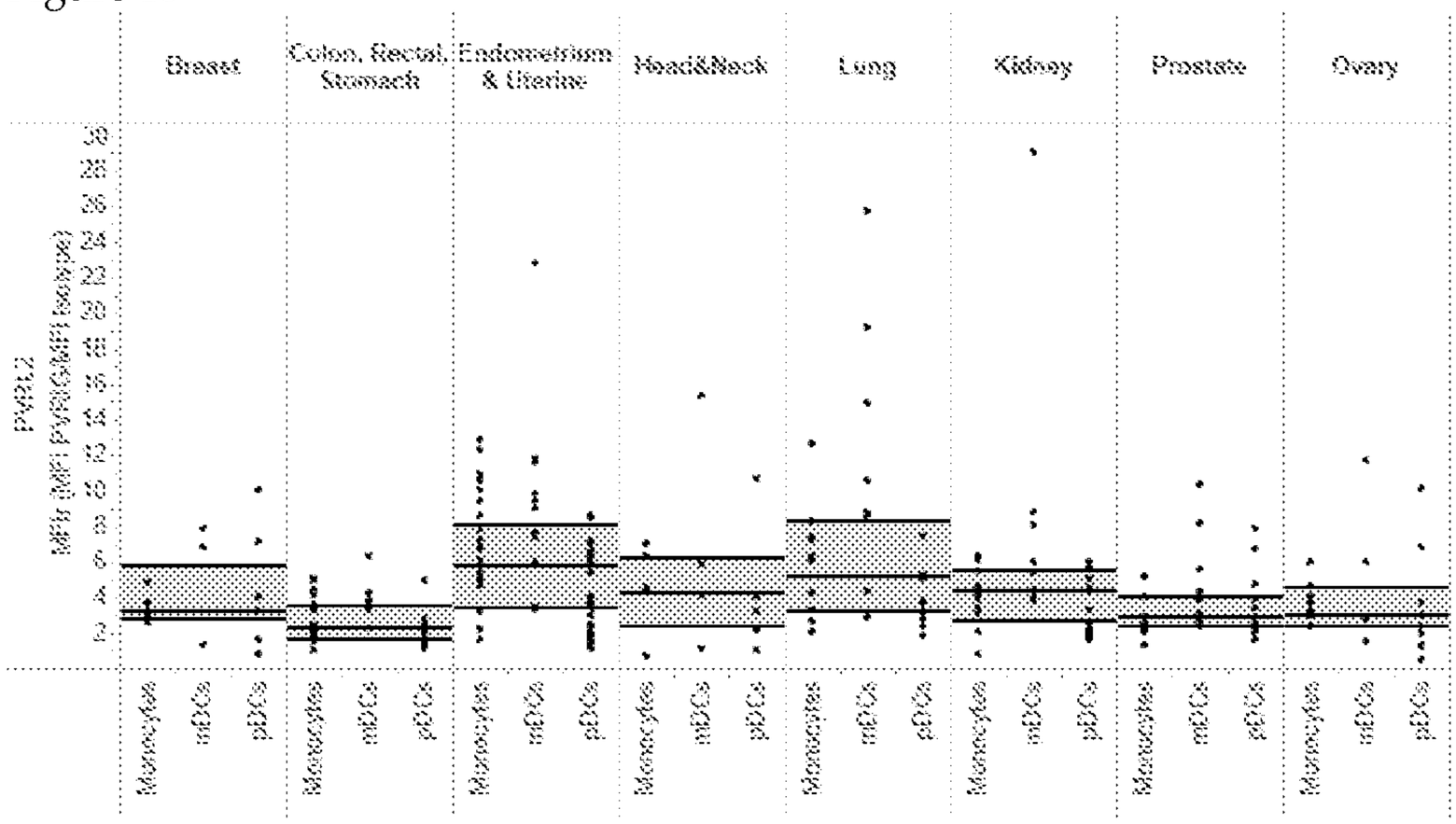
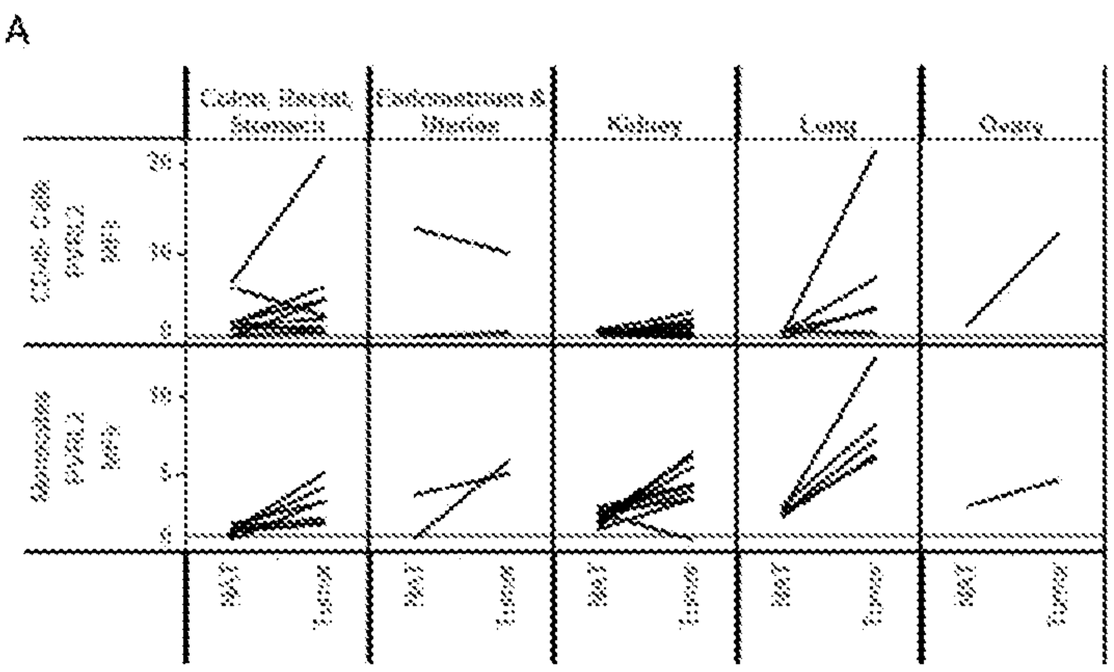
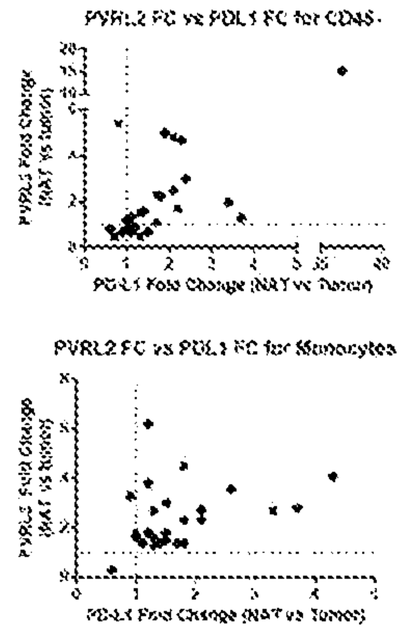

Breast
Colon, Rectal, Stomach
Endometrium & Uterine
Head&Neck
Lung
Kidney
Prostate
Ovary
MSI-H/dMMR (ng/mg)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs
pdcs
mdcs
sdcs

Figure 19





PVRL2 Expression

CD45-	NAT vs Tumor	0.02
Monocytes	NAT vs Tumor	<0.0001

Spearman Correlation

CD45- cells	PVRL2 FC vs PDL1 FC	0.83	0.0003
Monocytes	PVRL2 FC vs PDL1 FC	0.34	0.09

Figure 20

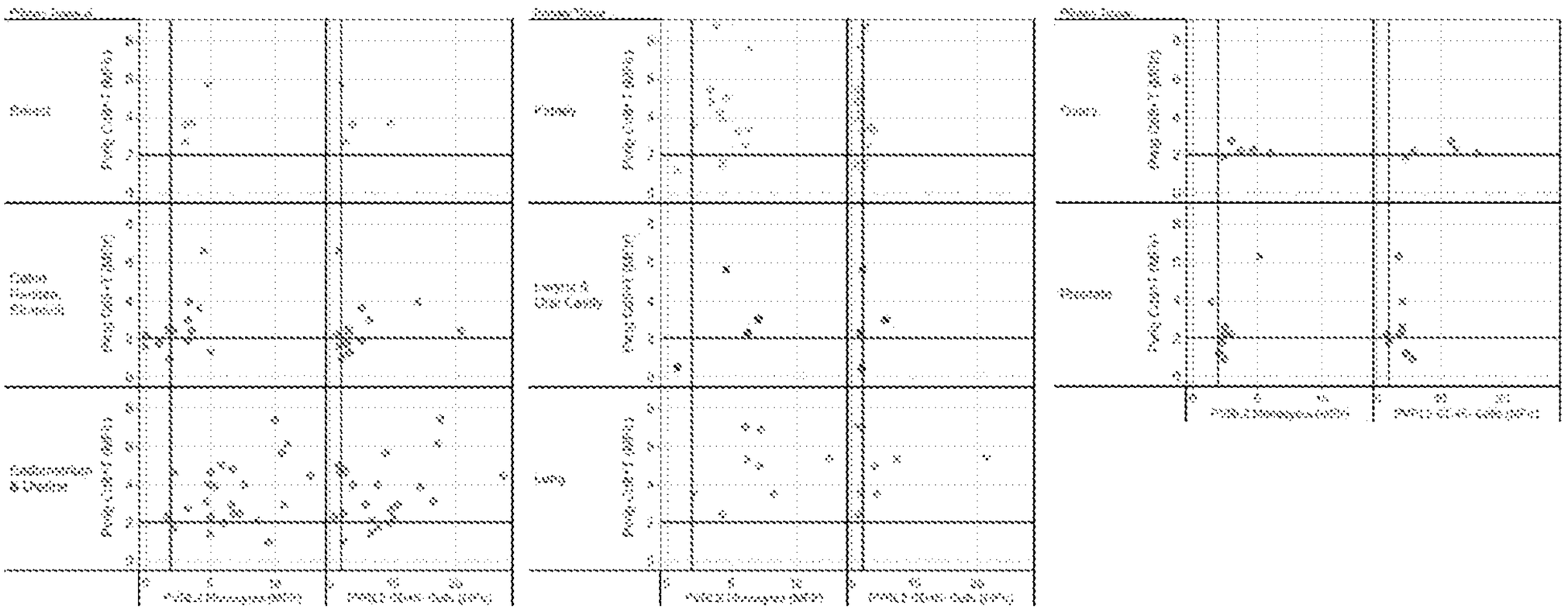

Colon Cancer Cell Line
Endometrial Cancer Cell Line
Lung Cancer Cell Line
Prostate Cancer Cell Line
PMEL Expression (log2RPKM)
PMEL Copy Number (log2CN)

Figure 21A

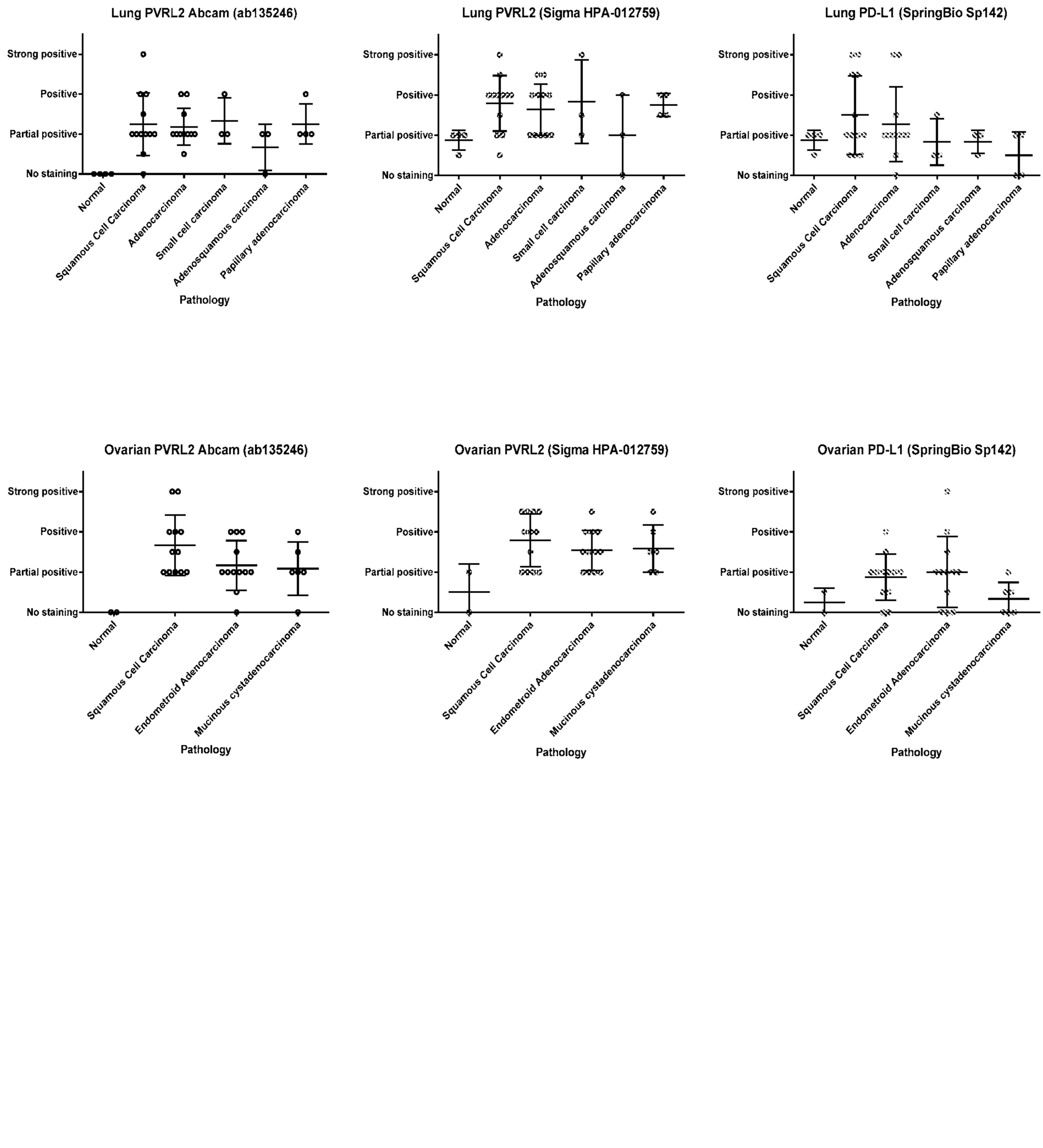
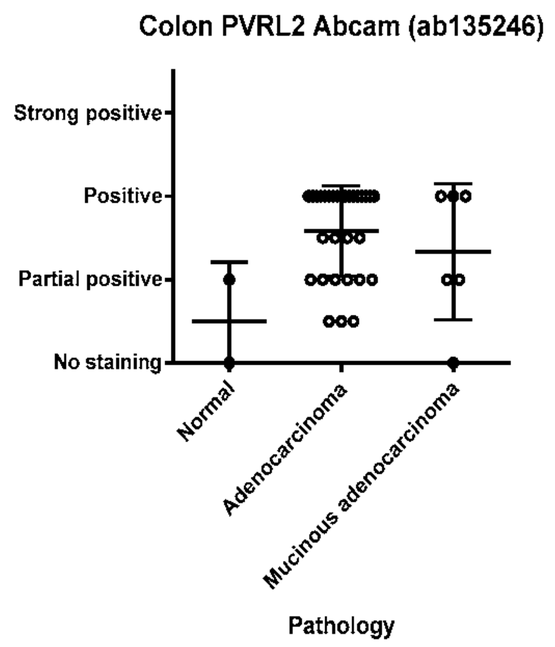
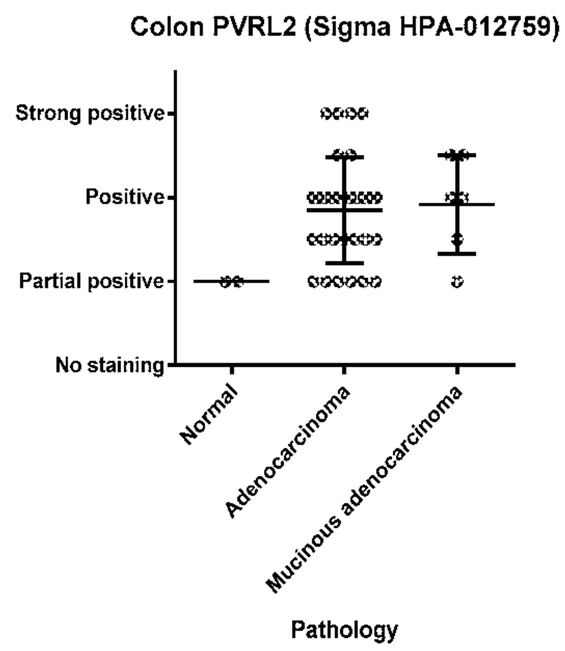
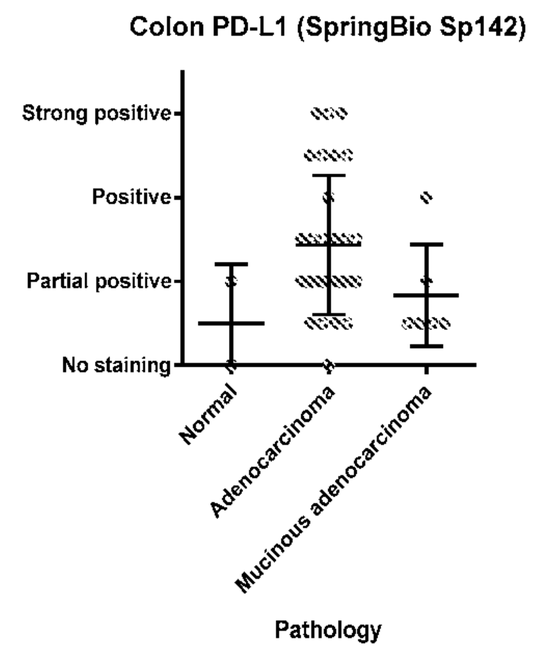
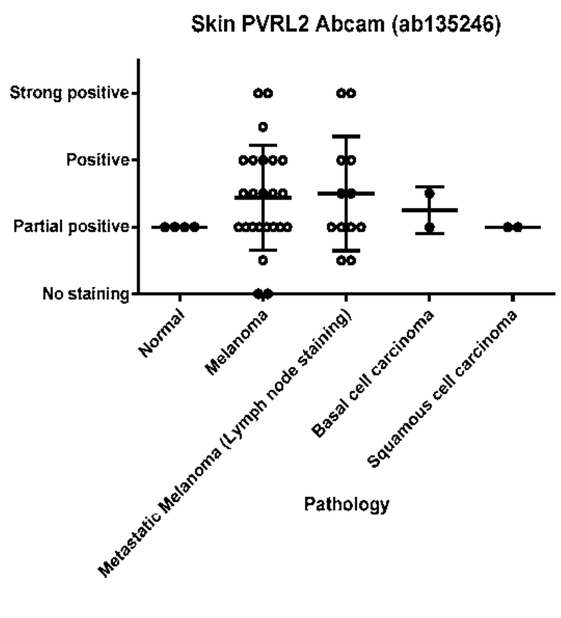

Lung PVRL2 Abcam (ab135246)
Lung PVRL2 (Sigma HPA-012759)
Lung PD-L1 (SpringBio Sp142)
Strong positive
Positive
Partial positive
No staining
Normal
Squamous Cell Carcinoma
Adenocarcinoma
Small cell carcinoma
Adenosquamous carcinoma
Papillary adenocarcinoma
Pathology
Ovarian PVRL2 Abcam (ab135246)
Ovarian PVRL2 (Sigma HPA-012759)
Ovarian PD-L1 (SpringBio Sp142)
Normal
Squamous Cell Carcinoma
Endometroid Adenocarcinoma
Mucinous cystadenocarcinoma
Pathology

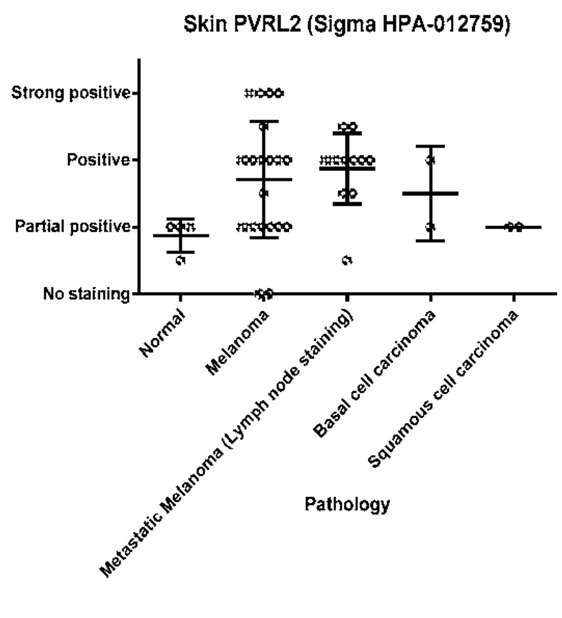
Figure 21B

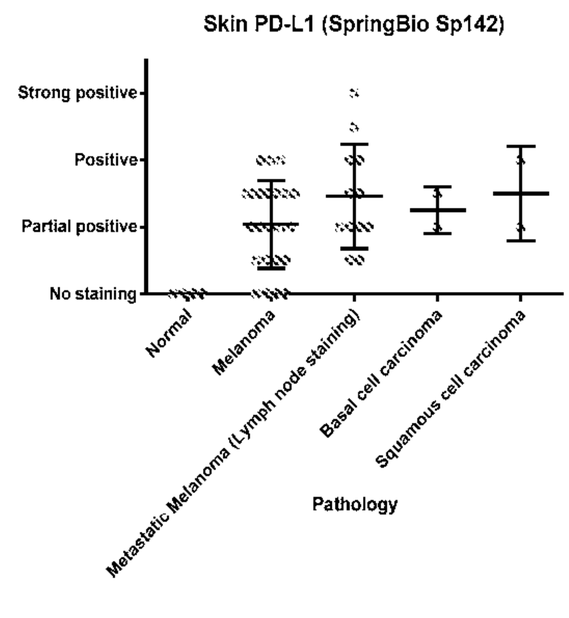

Colon PVRL2 Abcam (ab135246)
Strong positive
Positive
Partial positive
No staining
Normal
Adenocarcinoma
Mucinous adenocarcinoma
Pathology

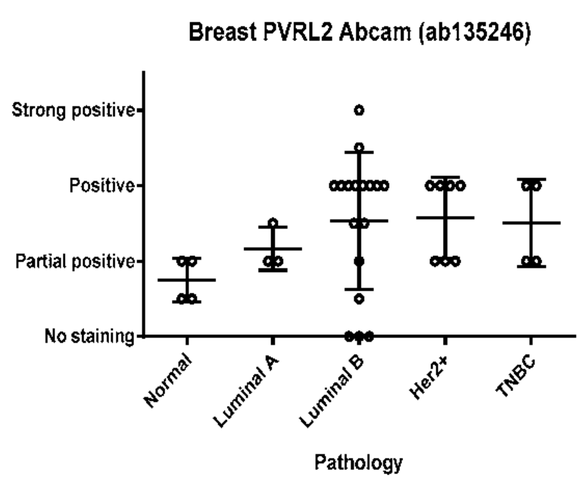

Colon PVRL2 (Sigma HPA-012759)
Strong positive
Positive
Partial positive
No staining
Normal
Adenocarcinoma
Mucinous adenocarcinoma
Pathology

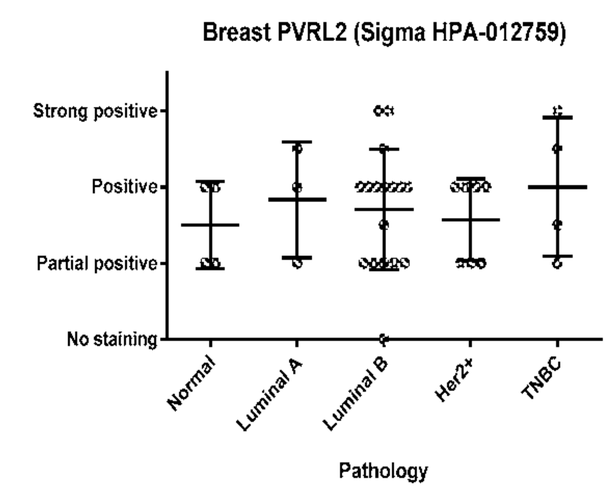

Colon PD-L1 (SpringBio Sp142)
Strong positive
Positive
Partial positive
No staining
Normal
Adenocarcinoma
Mucinous adenocarcinoma
Pathology


Skin PVRL2 Abcam (ab135246)
Strong positive
Positive
Partial positive
No staining
Normal
Melanoma
Metastatic Melanoma (Lymph node staining)
Basal cell carcinoma
Squamous cell carcinoma
Pathology


Skin PVRL2 (Sigma HPA-012759)
Strong positive
Positive
Partial positive
No staining
Normal
Melanoma
Metastatic Melanoma (Lymph node staining)
Basal cell carcinoma
Squamous cell carcinoma
Pathology


Skin PD-L1 (SpringBio Sp142)
Strong positive
Positive
Partial positive
No staining
Normal
Melanoma
Metastatic Melanoma (Lymph node staining)
Basal cell carcinoma
Squamous cell carcinoma
Pathology


Breast PVRL2 Abcam (ab135246)
Strong positive
Positive
Partial positive
No staining
Normal
Luminal A
Luminal B
Her2+
TNBC
Pathology


Breast PVRL2 (Sigma HPA-012759)
Strong positive
Positive
Partial positive
No staining
Normal
Luminal A
Luminal B
Her2+
TNBC
Pathology

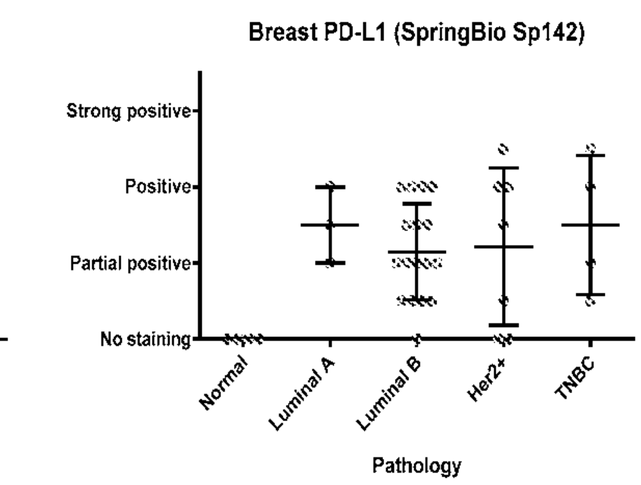
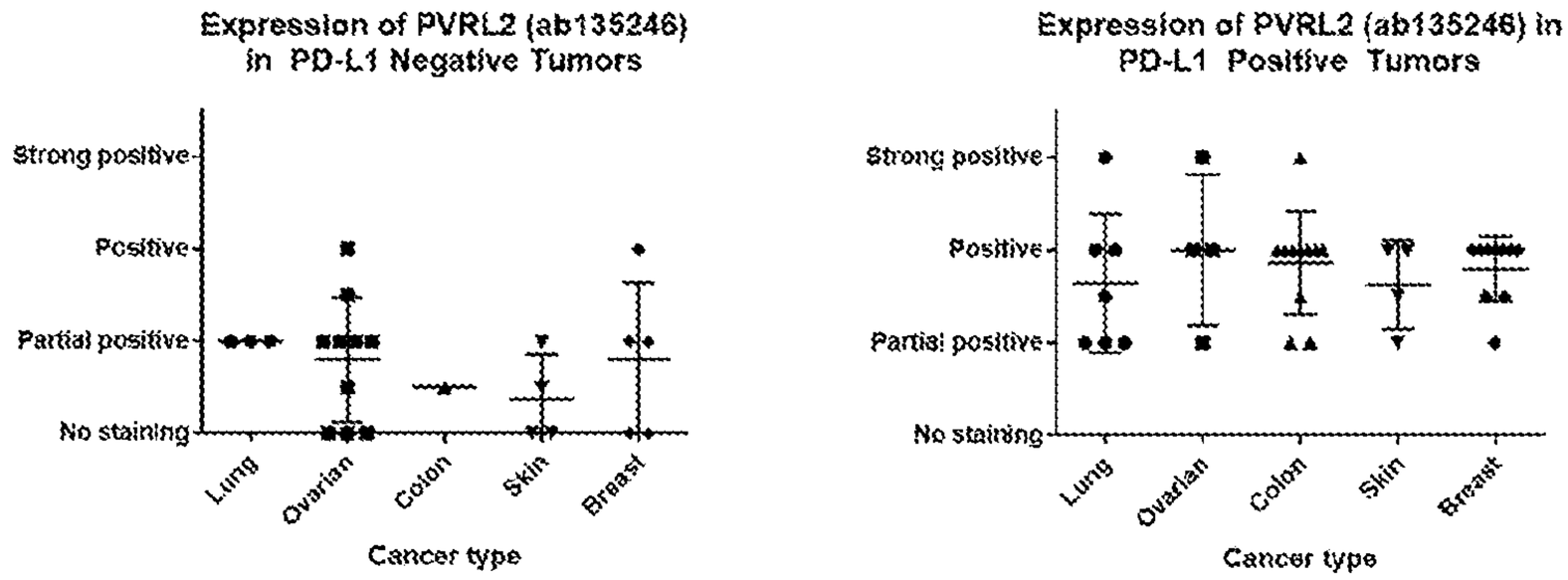
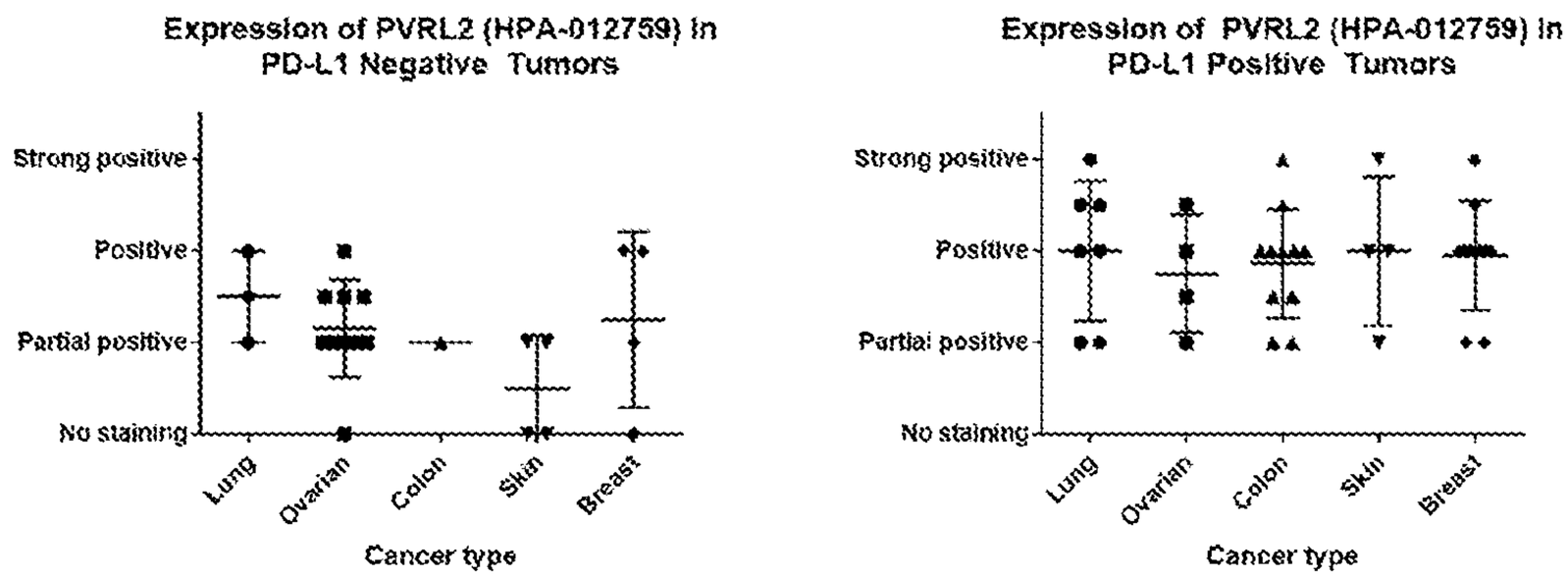

Breast PD-L1 (SpringBio Sp142)
Strong positive
Positive
Partial positive
No staining
Normal
Luminal A
Luminal B
Her2+
TNBC
Pathology

Figure 22

A





B

Expression of PVRL2 in PD-L1 negative tumors

	Lung	Ovarian	Colon	Skin	Breast
PVRL2 (ab135246)	3/3	6/10	0/1	1/4	3/5
PVRL2 (HPA-012759)	3/3	9/10	1/1	2/4	3/4

Figure 23

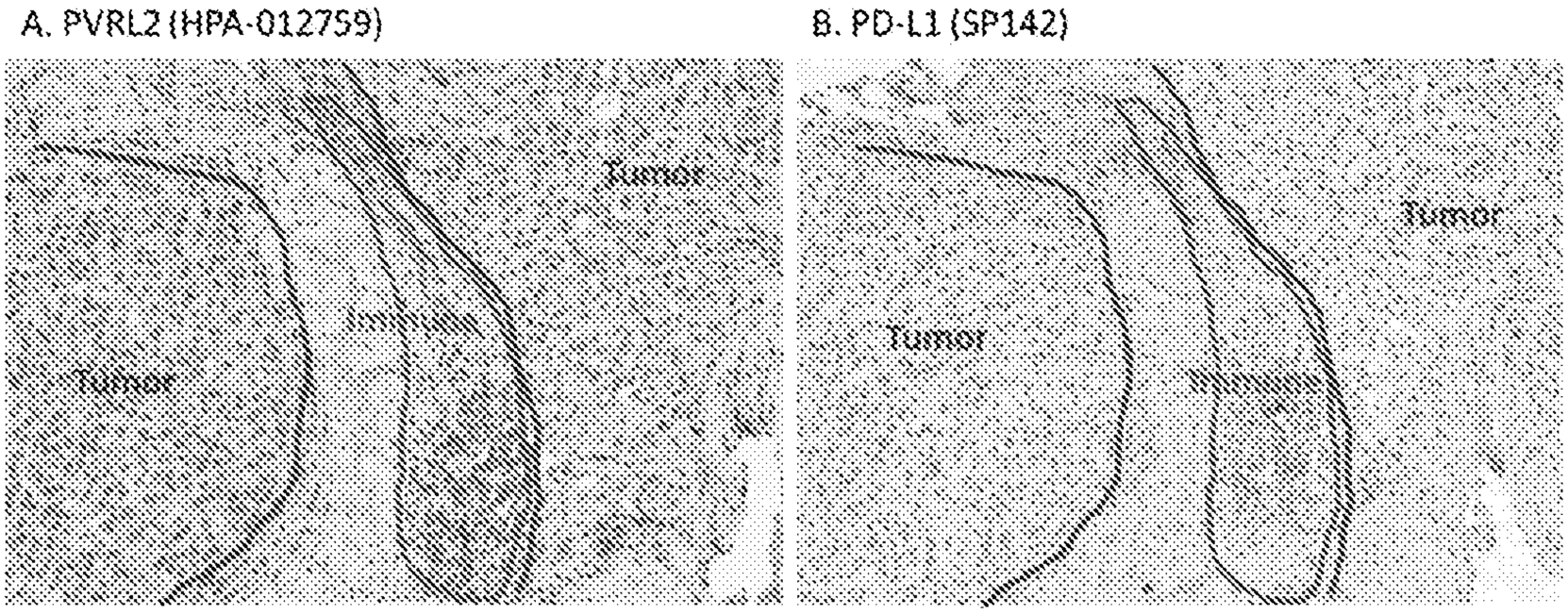
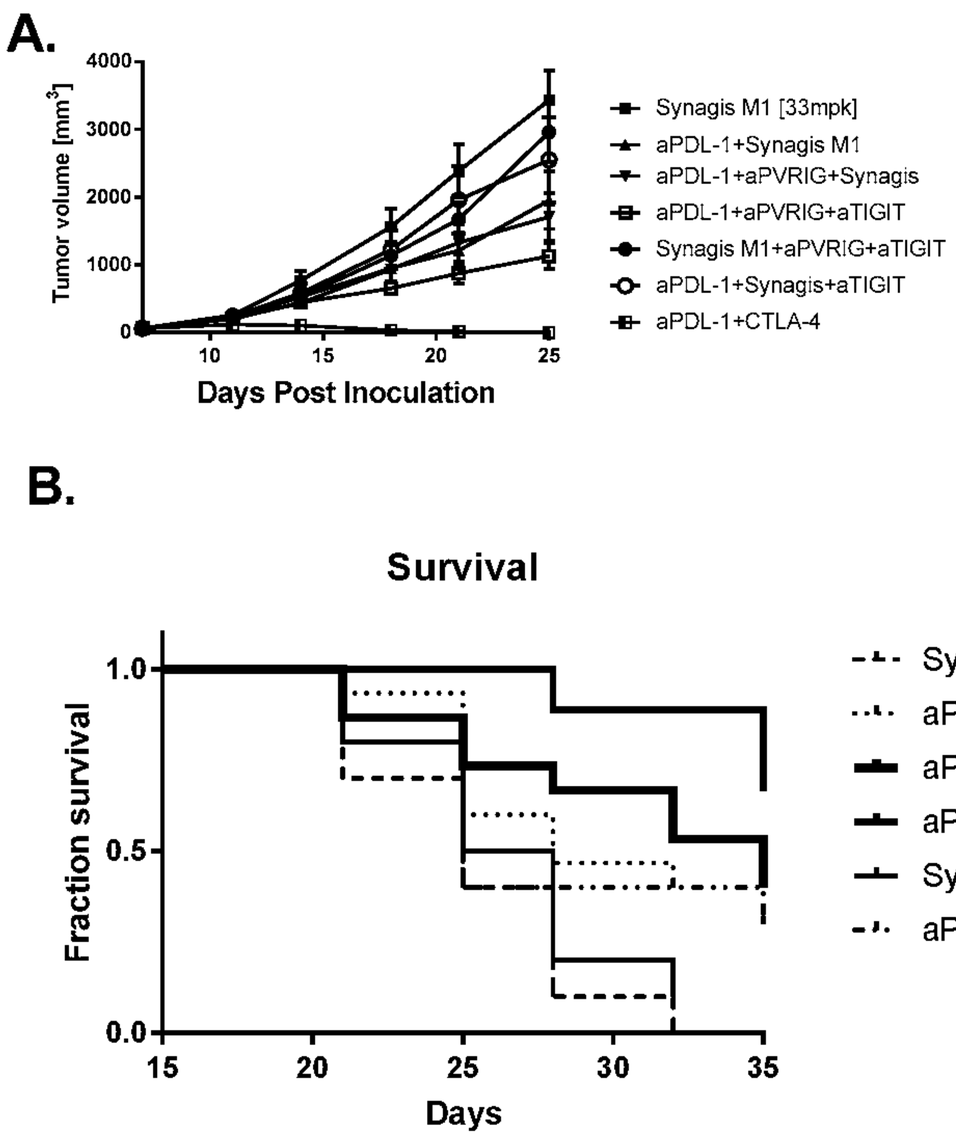
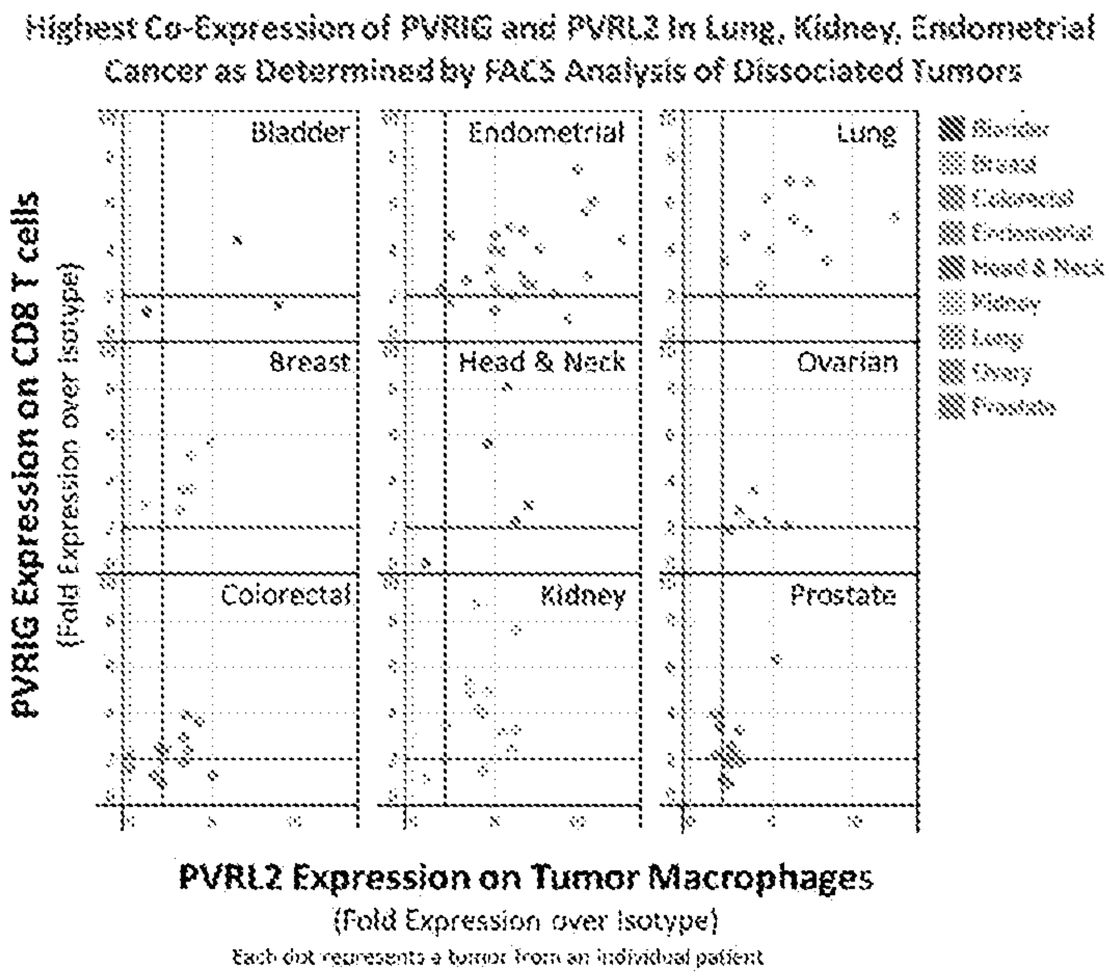

A. PVRL2 (HPA-012759)
Tumor
Tumor
Tumor
B. PD-L1 (SP142)
Tumor
Tumor

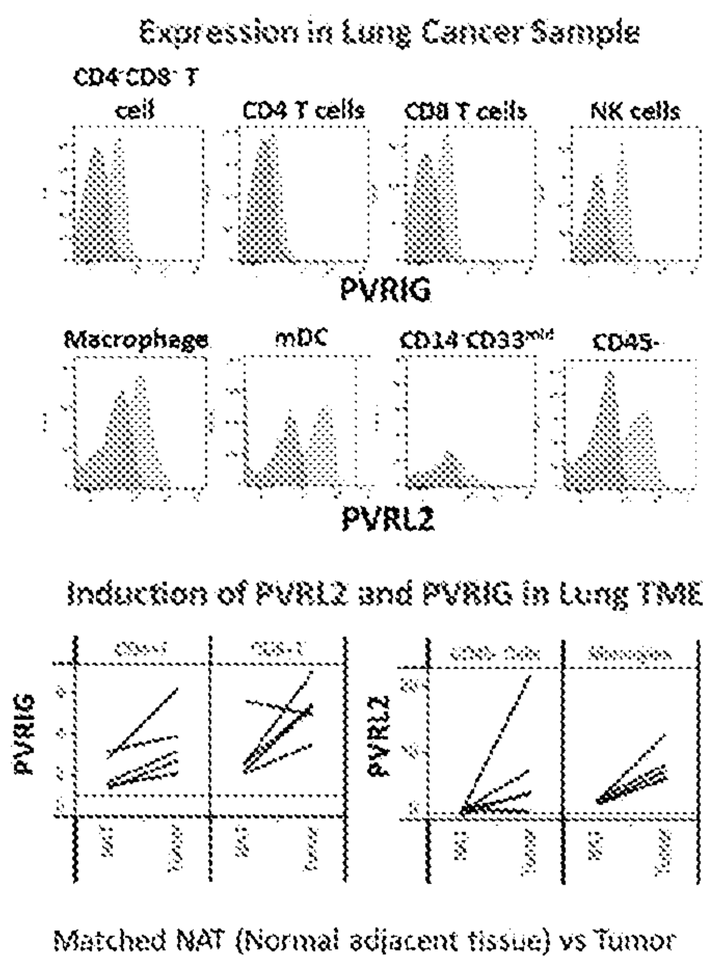
Figure 24

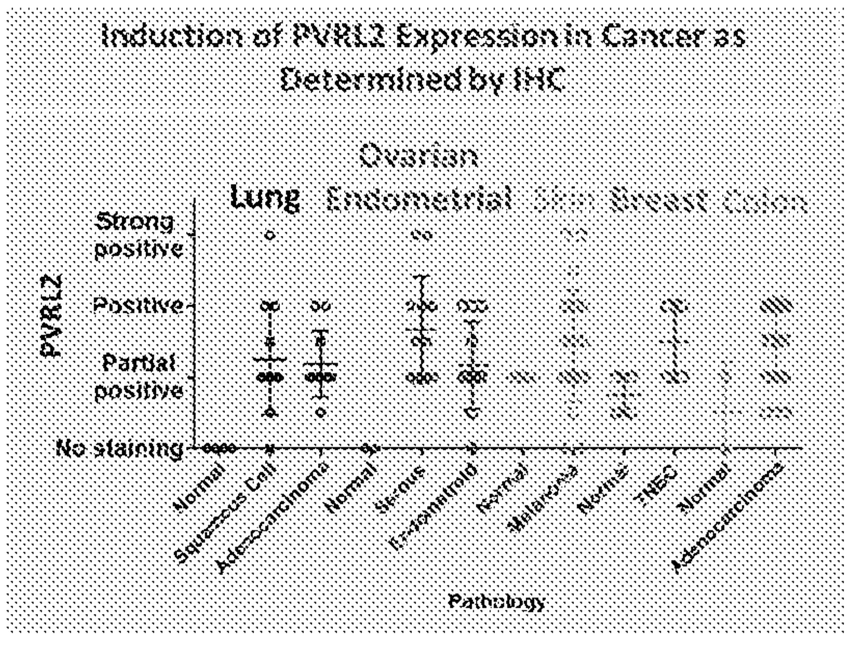


	aPDL-1+Synagis	aPDL-1+aPVRIG+Synagis	aPVRIG+aTIGIT+Synagis	aPDL-1+aTIGIT+Synagis
TGI (triple combo)	31%	29%	61%	55%
p-value	0.26	0.35	0.008	0.037
p-value (slope)	0.0074	0.0084	<0.0001	<0.0001

Figure 25


Highest Co-Expression of PVRIG and PVRL2 in Lung, Kidney, Endometrial Cancer as Determined by FACS Analysis of Dissociated Tumors
PVRIG Expression on CD8 T cells
(Fold Expression over isotype)
Bladder
Endometrial
Lung
Breast
Head & Neck
Ovarian
Colorectal
Kidney
Prostate
Bladder
Breast
Colorectal
Endometrial
Head & Neck
Kidney
Lung
Ovary
Prostate
PVRL2 Expression on Tumor Macrophages
(Fold Expression over Isotype)
Each dot represents a tumor from an individual patient


Expression in Lung Cancer Sample
CD4-CD8- T cell
CD4 T cells
CD8 T cells
NK cells
PVRIG
Macrophage
mDC
CD14-CD33mid
CD45-
PVRL2
Induction of PVRL2 and PVRIG in Lung TME
PVRIG
PVRL2
Matched NAT (Normal adjacent tissue) vs Tumor


Induction of PVRL2 Expression in Cancer as Determined by IHC
Ovarian
Lung
Endometrial
Skin
Breast
Colon
Strong positive
Positive
Partial positive
No staining
PVRL2
Normal
Squamous Cell
Adenocarcinoma
Normal
Serous
Endometrioid
Normal
Melanoma
Nevus
TNBC
Normal
Adenocarcinoma
Pathology

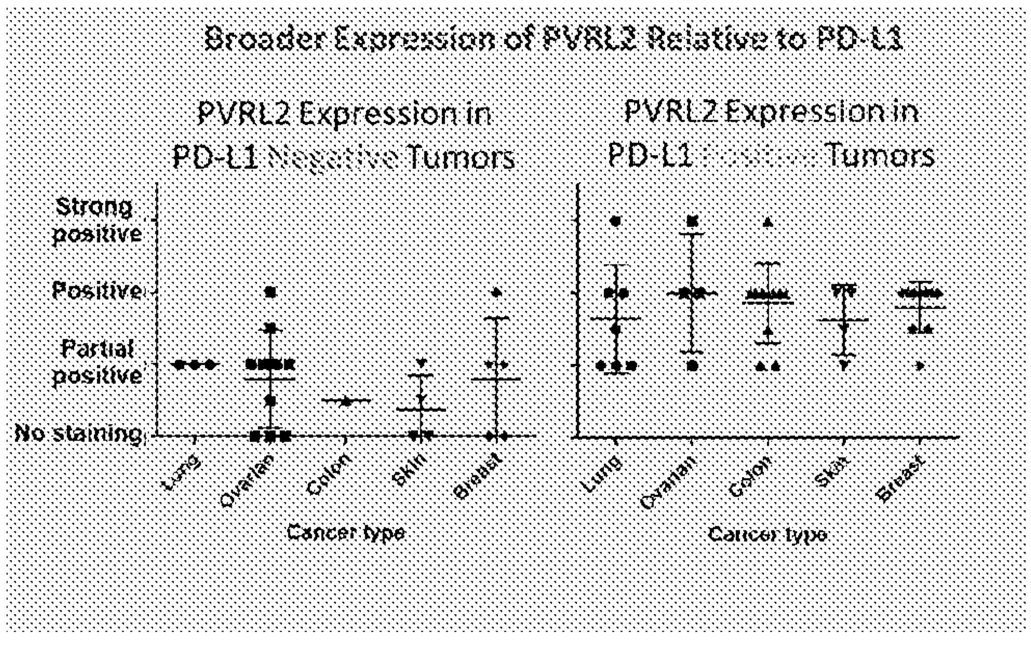
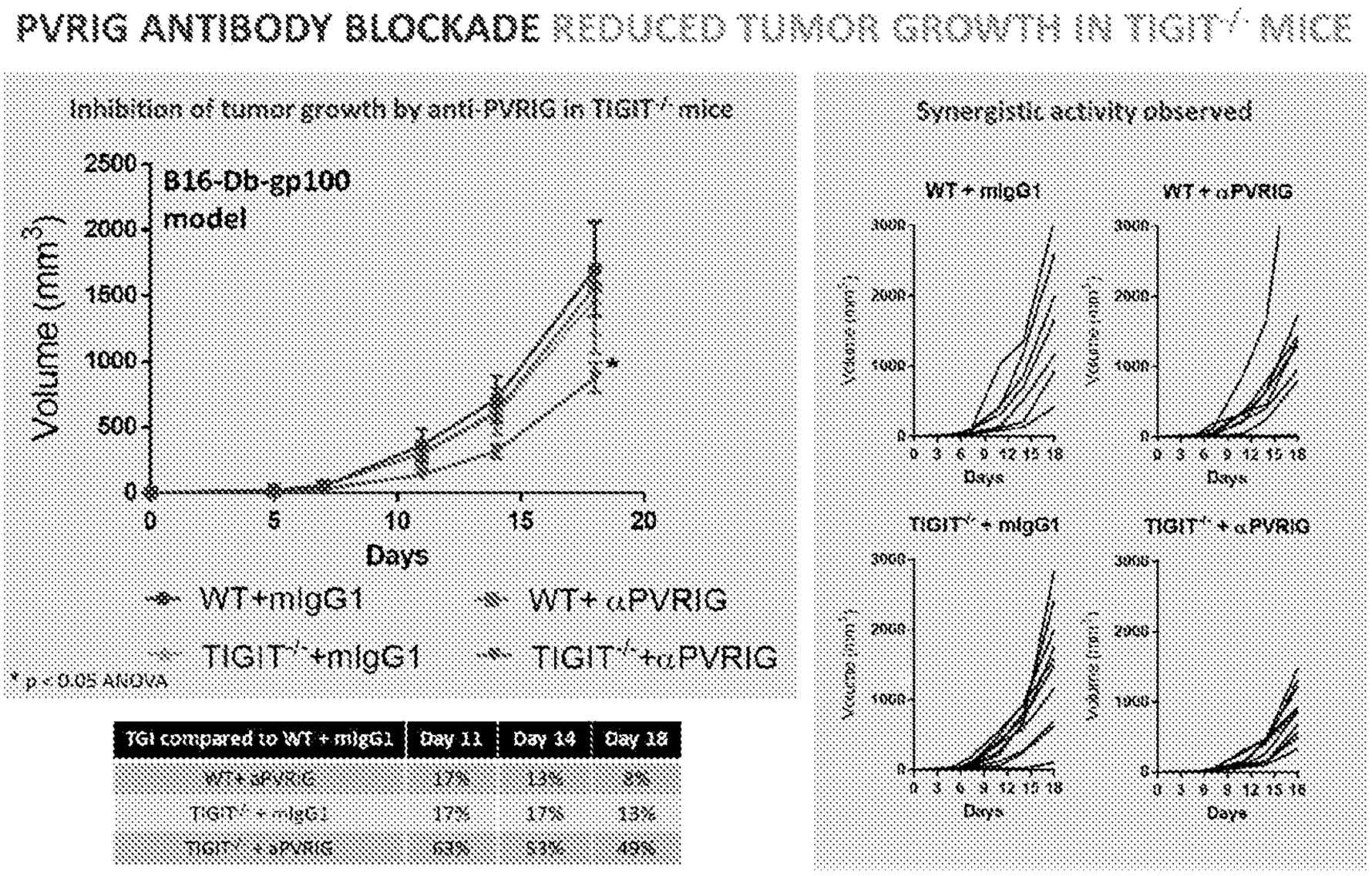
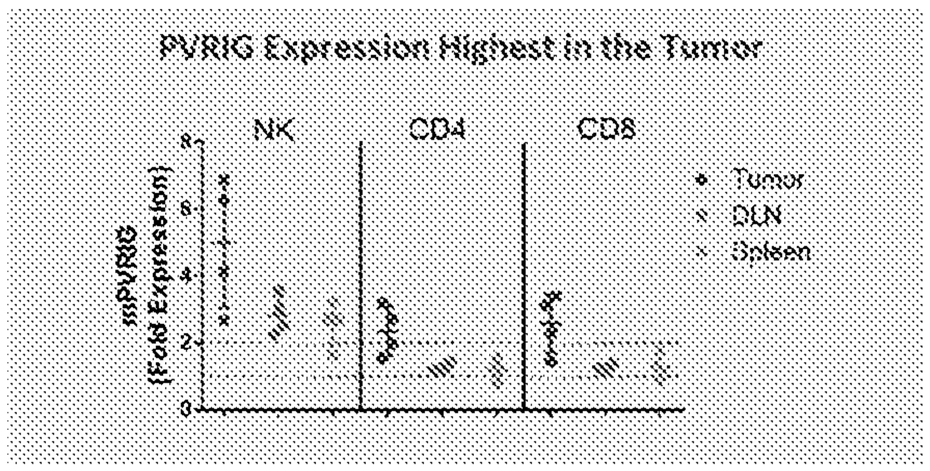
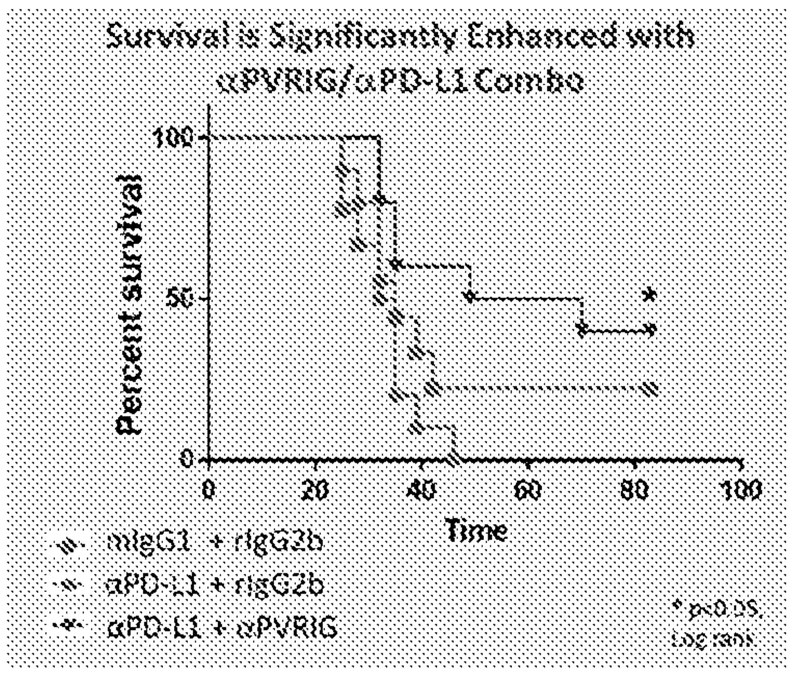
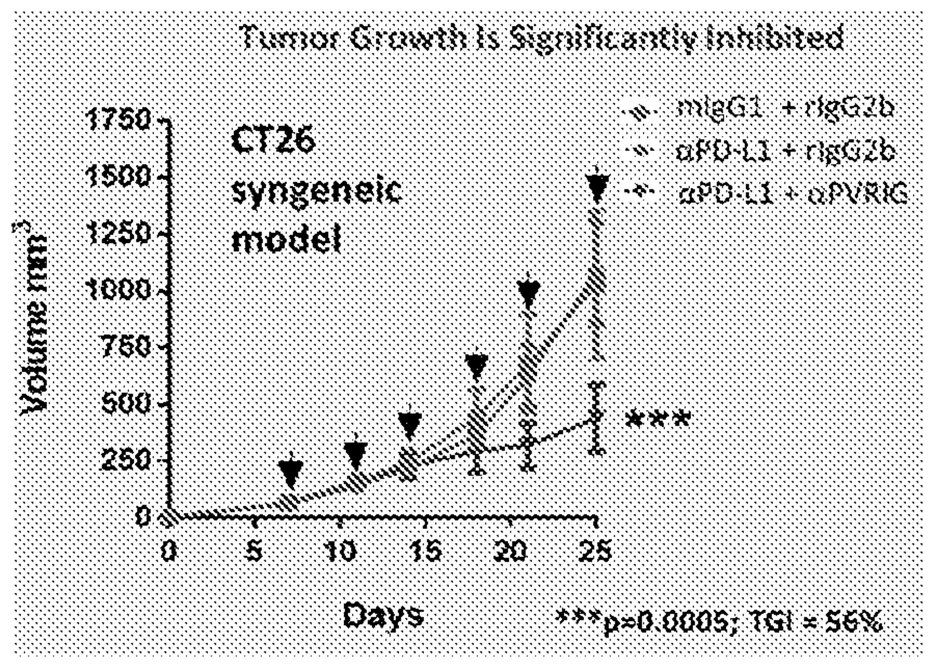

Broader Expression of PVRL2 Relative to PD-L1
PVRL2 Expression in PD-L1 Negative Tumors
PVRL2 Expression in PD-L1 Positive Tumors
Strong positive
Positive
Partial positive
No staining
Lung
Ovarian
Colon
Skin
Breast
Cancer type

Figure 26


PVRIG ANTIBODY BLOCKADE REDUCED TUMOR GROWTH IN TIGIT-/- MICE
Inhibition of tumor growth by anti-PVRIG in TIGIT-/- mice
B16-Db-gp100 model
Volume (mm3)
Days
WT+mIgG1
WT+ αPVRIG
TIGIT-/-+mIgG1
TIGIT-/-+αPVRIG
* p < 0.05 ANOVA
TGI compared to WT + mIgG1 | Day 11 | Day 14 | Day 18
WT + αPVRIG | 17% | 13% | 3%
TIGIT-/- + mIgG1 | 17% | 17% | 13%
TIGIT-/- + αPVRIG | 63% | 53% | 49%
Synergistic activity observed
WT + mIgG1
WT + αPVRIG
TIGIT-/- + mIgG1
TIGIT-/- + αPVRIG
Days


PVRIG Expression Highest in the Tumor
NK
CD4
CD8
Tumor
DLN
Spleen


Survival is Significantly Enhanced with αPVRIG/αPD-L1 Combo
Percent survival
Time
mIgG1 + rIgG2b
αPD-L1 + rIgG2b
αPD-L1 + αPVRIG
* p<0.05, Log rank


Tumor Growth is Significantly Inhibited
CT26 syngeneic model
Volume mm3
Days
mIgG1 + rIgG2b
αPD-L1 + rIgG2b
αPD-L1 + αPVRIG
***
***p=0.0005; TGI = 56%

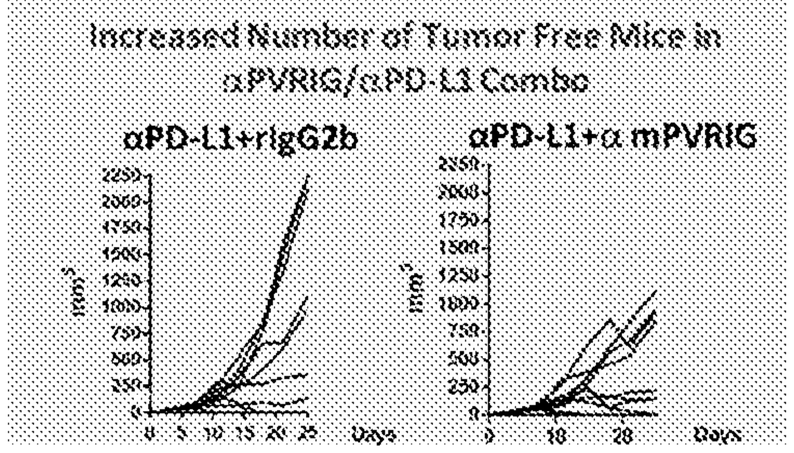
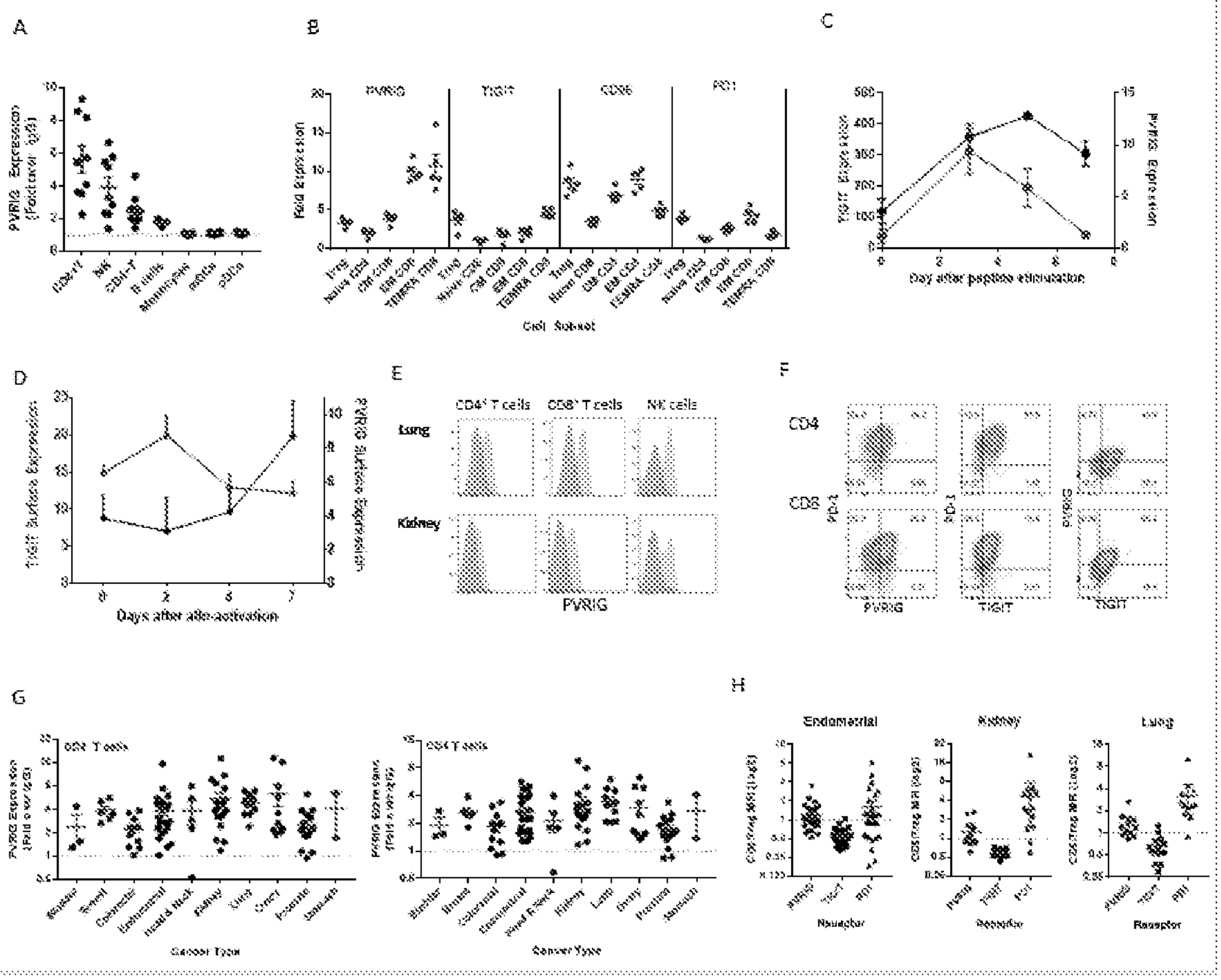

Increased Number of Tumor Free Mice in αPVRIG/αPD-L1 Combo
αPD-L1+rIgG2b
αPD-L1+α mPVRIG
Days

Figure 27


A
B
C
D
E
F
G
H
CD8+ T cells
CD4+ T cells
Lung
Kidney
PVRIG
TIGIT
CD4
CD8
Endometrial
Kidney
Lung
Day after peptide stimulation
Days after allo-activation
Cancer Type
Receptor

Fgiure 28A

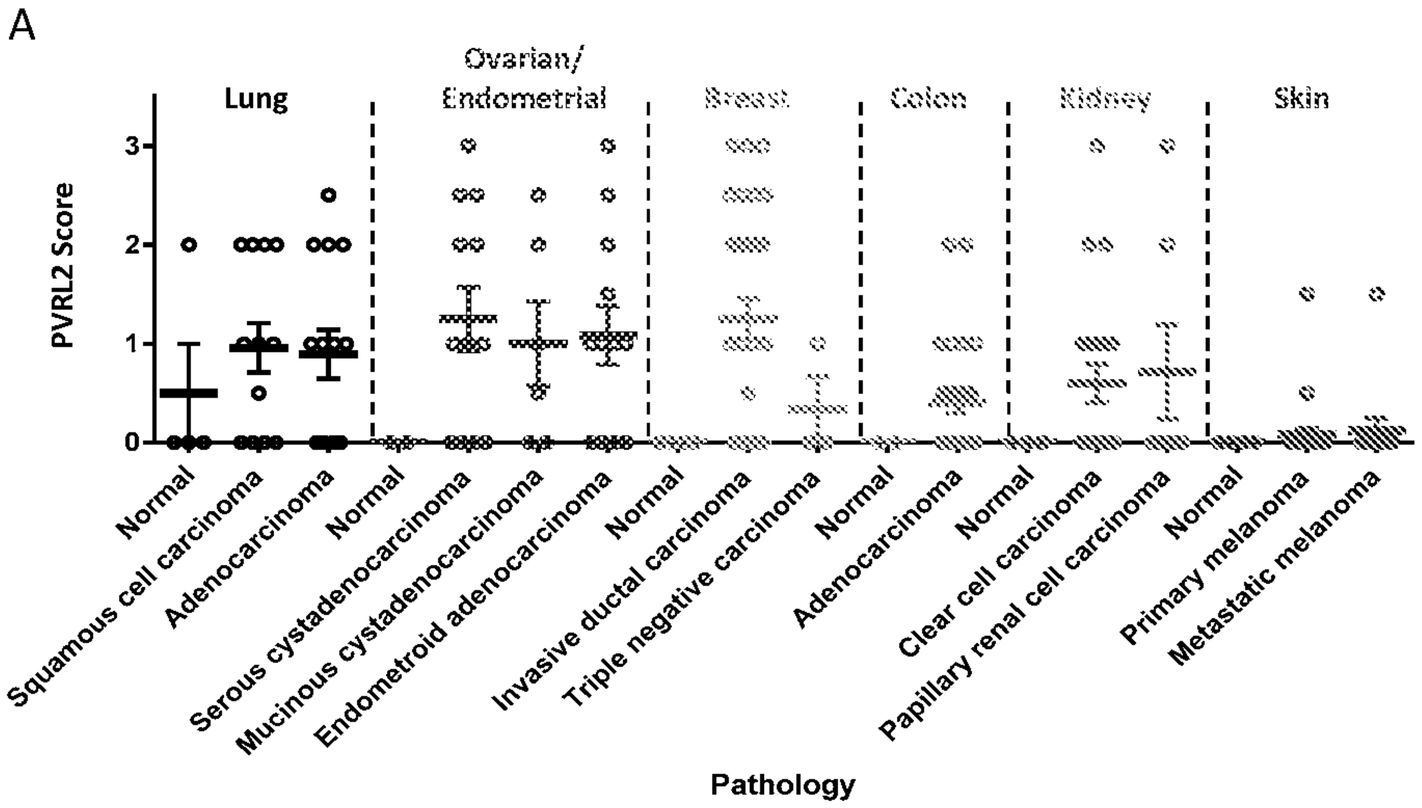


Figure 28B

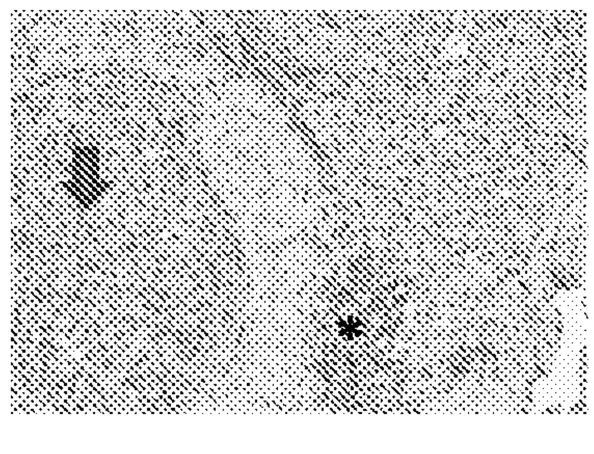


Figure 28C

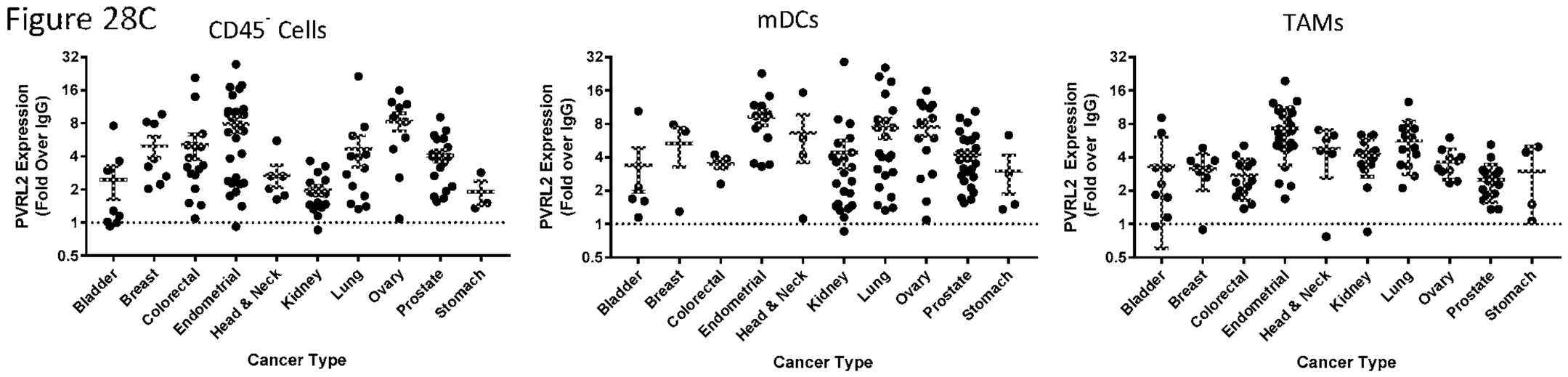


Figure 28D

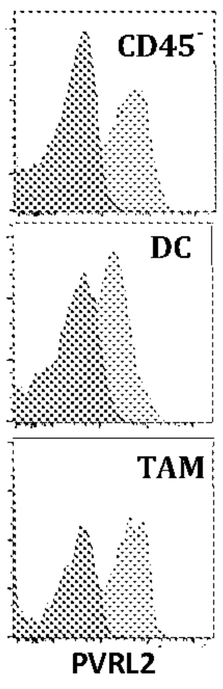


Figure 28 E

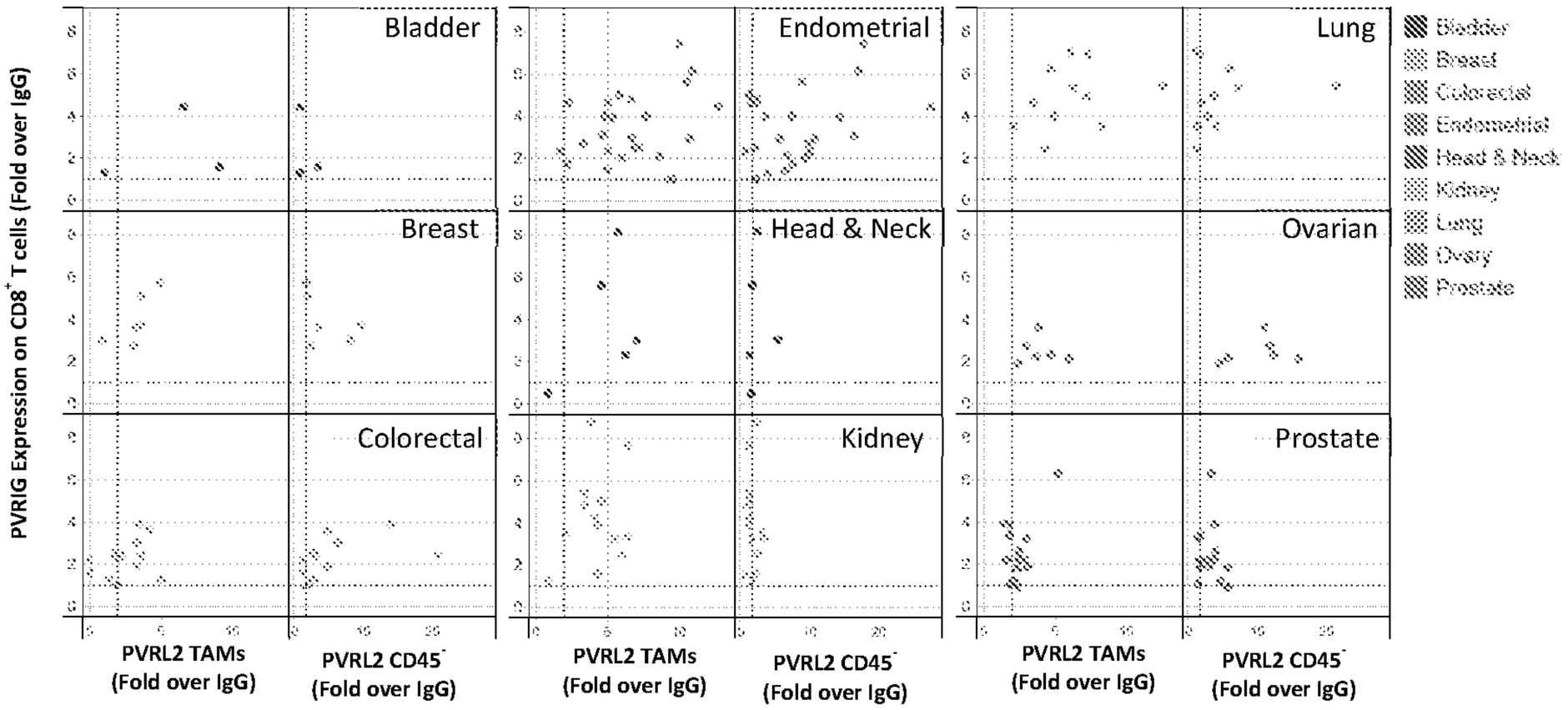


Figure 28F

	All Tumors				PD-L1+				PD-L1-		
Tissue Type	**PVRL2+**	**Total**	**% Positive**		**PVRL2+**	**Total**	**% Positive**		**PVRL2+**	**Total**	**% Positive**
Lung											
Normal	1	4	25		N/A	N/A	N/A		N/A	N/A	N/A
Adenocarcinoma	8	14	57		3	5	60		5	9	56
Squamous cell carcinoma	8	13	62		5	7	71		3	6	50
Ovarian											
Normal	0	2	0		N/A	N/A	N/A		N/A	N/A	N/A
Serous cystadenocarcinoma	8	12	67		2	3	67		6	9	67
Mucinous cystadenocarcinoma	4	6	67		1	1	100		3	5	60
Endometrioid adenocarcinoma	8	12	67		3	4	75		5	8	63
Colon											
Normal	0	2	0		N/A	N/A	N/A		N/A	N/A	N/A
Adenocarcinoma	16	30	53		8	14	57		7	16	44
Skin											
Normal	0	4	0		N/A	N/A	N/A		N/A	N/A	N/A
Melanoma-Primary	3	24	13		1	4	25		2	20	10
Metastatic melanoma	1	12	8		1	4	25		0	8	0
Renal											
Normal	0	3	0		N/A	N/A	N/A		N/A	N/A	N/A
Clear cell carcinoma	8	20	40		0	0	N/A		8	20	40
Papillary renal cell carcinoma	2	7	29		1	1	100		1	6	17
Breast											
TNBC	1	3	33		0	0	N/A		1	3	33
Invasive ductal carcinoma	19	30	63		6	10	60		13	20	65

Figure 29

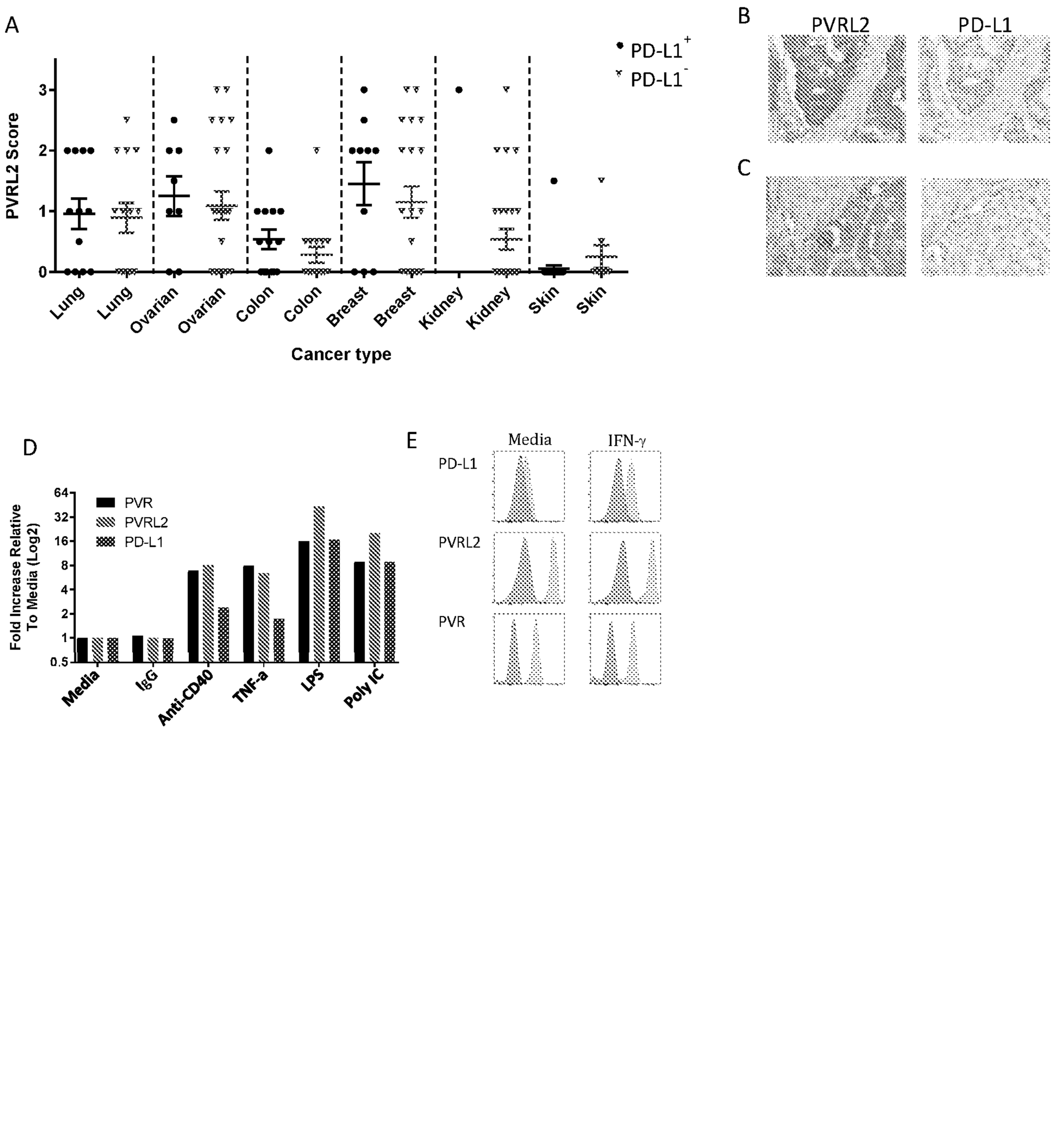

A
PD-L1+
PD-L1-
PVRL2 Score
3
2
1
0
Lung
Lung
Ovarian
Ovarian
Colon
Colon
Breast
Breast
Kidney
Kidney
Skin
Skin
Cancer type
B
PVRL2
PD-L1
C
D
PVR
PVRL2
PD-L1
Fold Increase Relative To Media (Log2)
64
32
16
8
4
2
1
0.5
Media
IgG
Anti-CD40
TNF-a
LPS
Poly IC
E
Media
IFN-γ
PD-L1
PVRL2
PVR

Figure 30

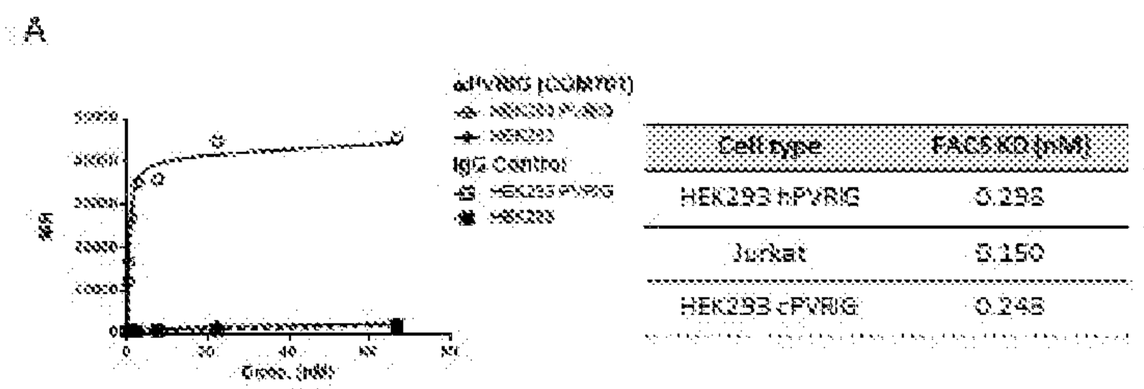

A
Cell type
FACS KD (nM)
HEK293 hPVRIG
0.298
Jurkat
0.150
HEK293 cPVRIG
0.248
B
C
D
E
TIL-209 TIL-463
+33%
+46%
+54%
+20%
F
Mel624
TIL-209
Colo205
TIL-463
Panc 05.04
CMVpp65 specific T cells
PD-L1
PVR
PVRL2
PVRIG
TIGIT
PD-1
G
TIL-209
TIL-463
+63%
+35%
+20%
+47%
H
I

Figure 31

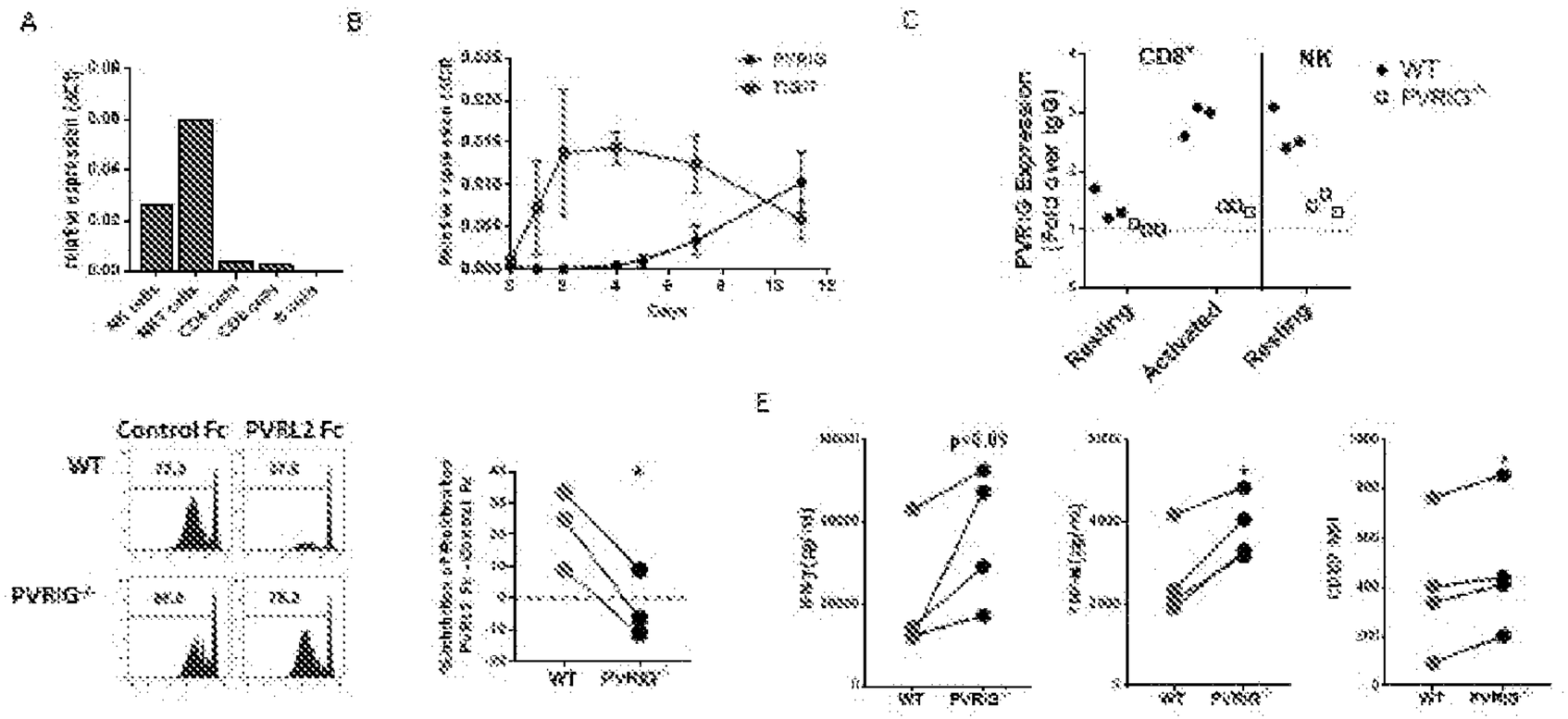

A
B
C
D
E
Control Fc
PVRL2 Fc
WT
PVRIG-/-
CD8+
NK
Resting
Activated
Resting
WT
PVRL2
PVRIG
Days
p<0.05

Figure 32

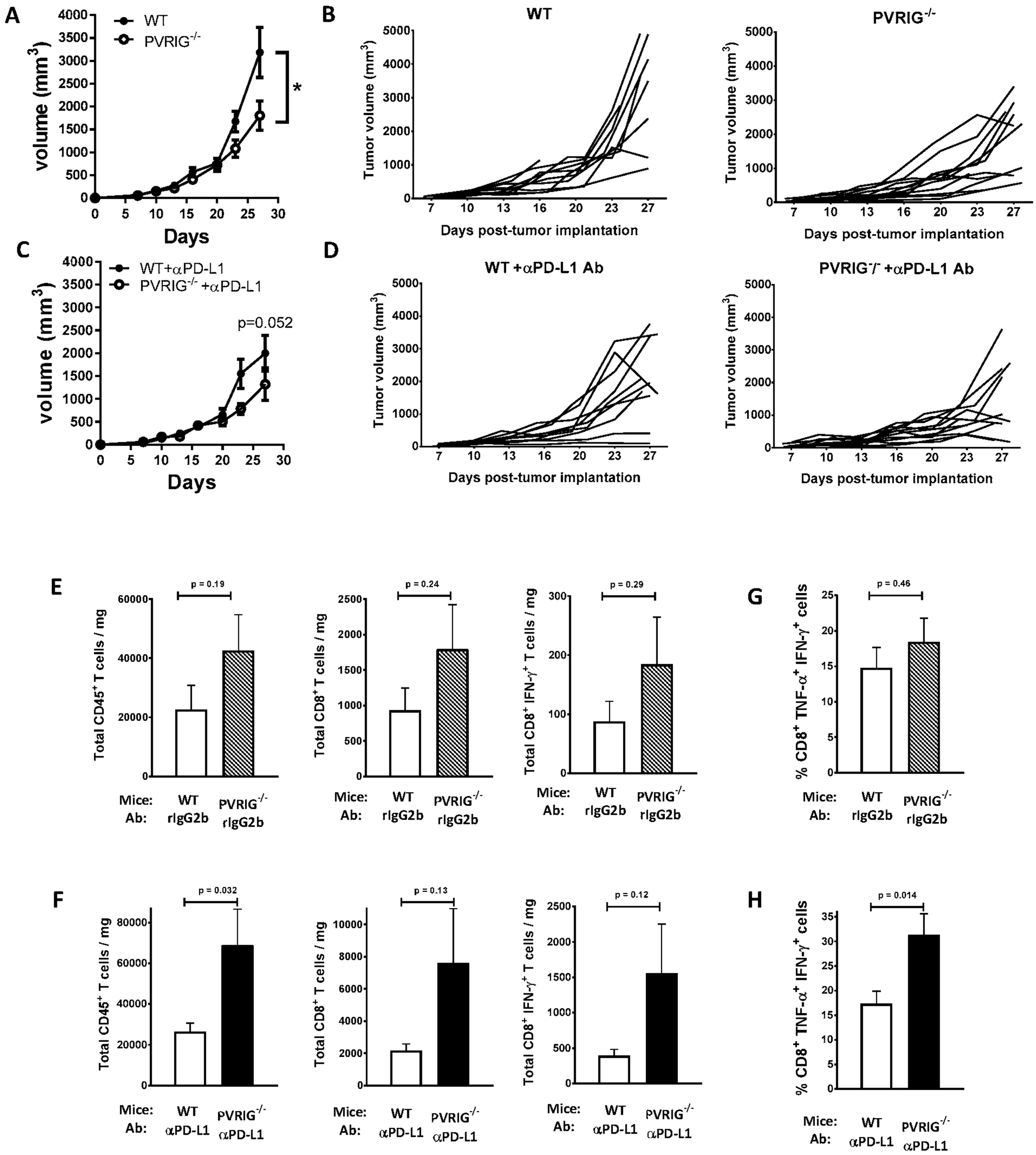

A
WT
PVRIG-/-
volume (mm3)
Days
*
B
WT
PVRIG-/-
Tumor volume (mm3)
Days post-tumor implantation
C
WT+αPD-L1
PVRIG-/- +αPD-L1
p=0.052
D
WT +αPD-L1 Ab
PVRIG-/- +αPD-L1 Ab
E
F
G
H
Total CD45+ T cells / mg
Total CD8+ T cells / mg
Total CD8+ IFN-γ+ T cells / mg
% CD8+ TNF-α+ IFN-γ+ cells
p = 0.19
p = 0.24
p = 0.29
p = 0.46
p = 0.032
p = 0.13
p = 0.12
p = 0.014
Mice:
Ab:
WT
PVRIG-/-
rIgG2b
αPD-L1

Figure 33

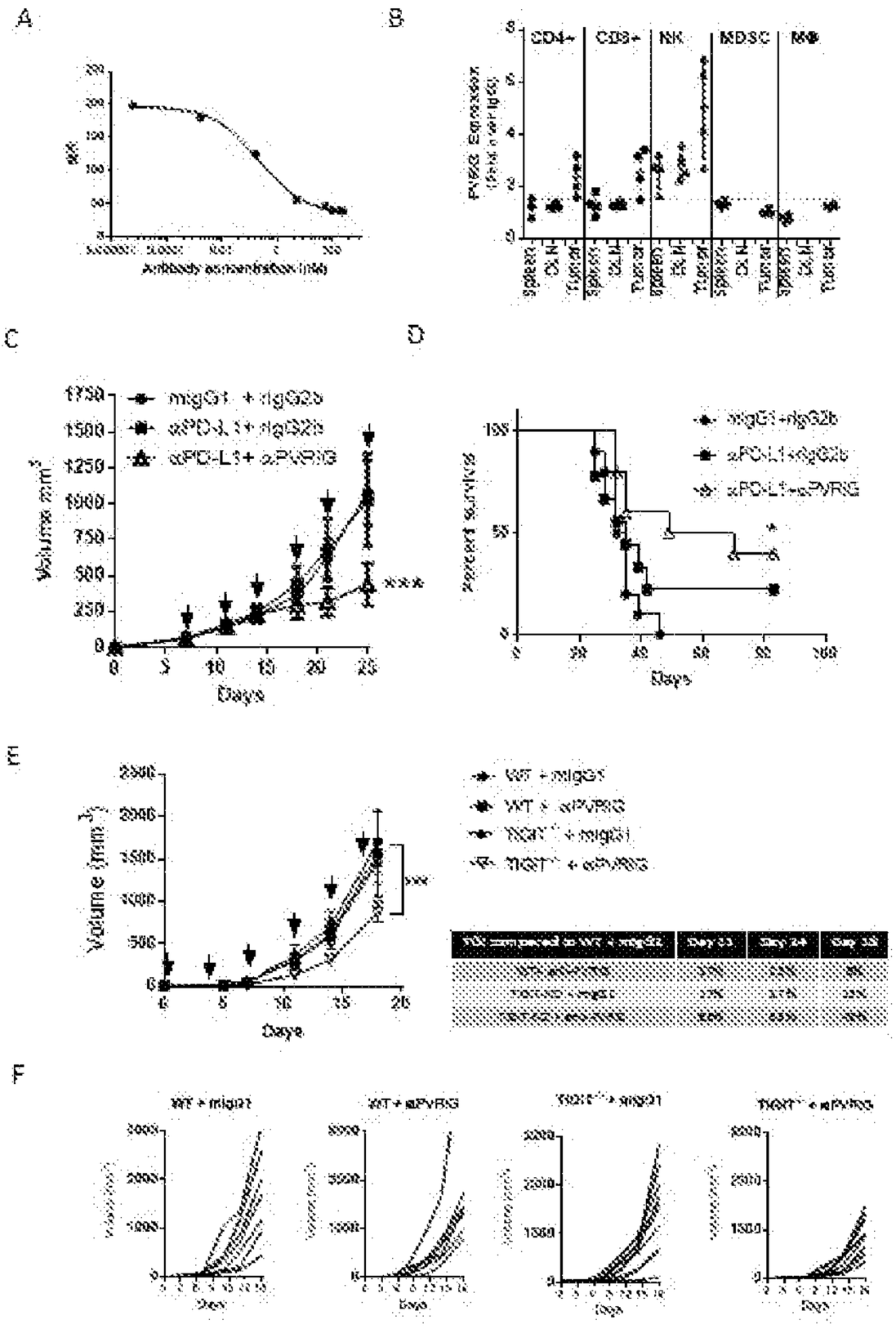

A
B
CD4+
CD8+
NK
MDSC
M
C
mIgG1 + mIgG2b
αPD-L1+ mIgG2b
αPD-L1+ αPVRIG
Volume mm3
Days
***
D
mIgG1+IgG2b
αPD-L1+IgG2b
αPD-L1+αPVRIG
Percent survival
Days
E
WT + mIgG1
WT + αPVRIG
TIGIT-/- + mIgG1
TIGIT-/- + αPVRIG
Volume (mm3)
Days
***
F
WT + mIgG1
WT + αPVRIG
TIGIT-/- + mIgG1
TIGIT-/- + αPVRIG

Figure 34

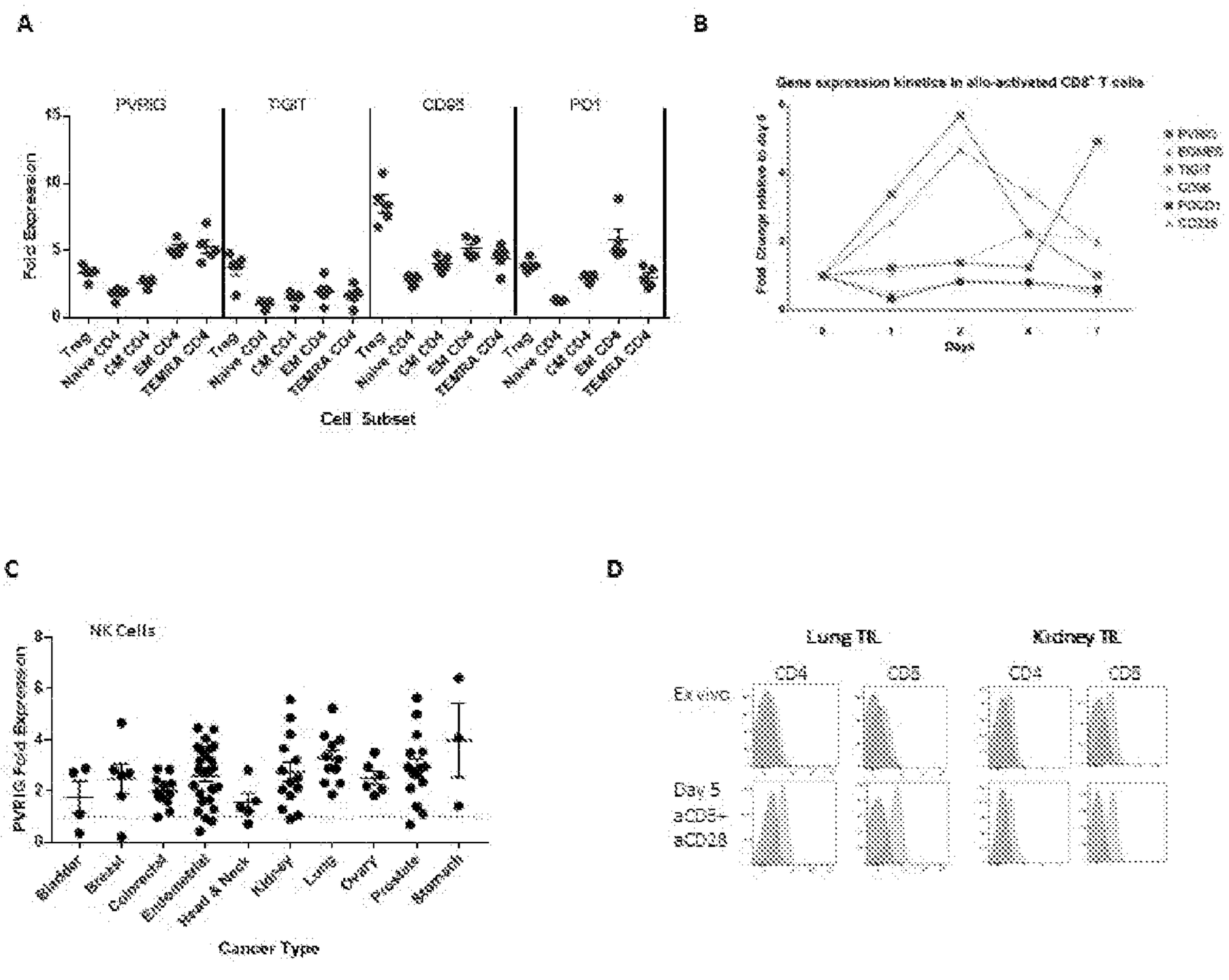
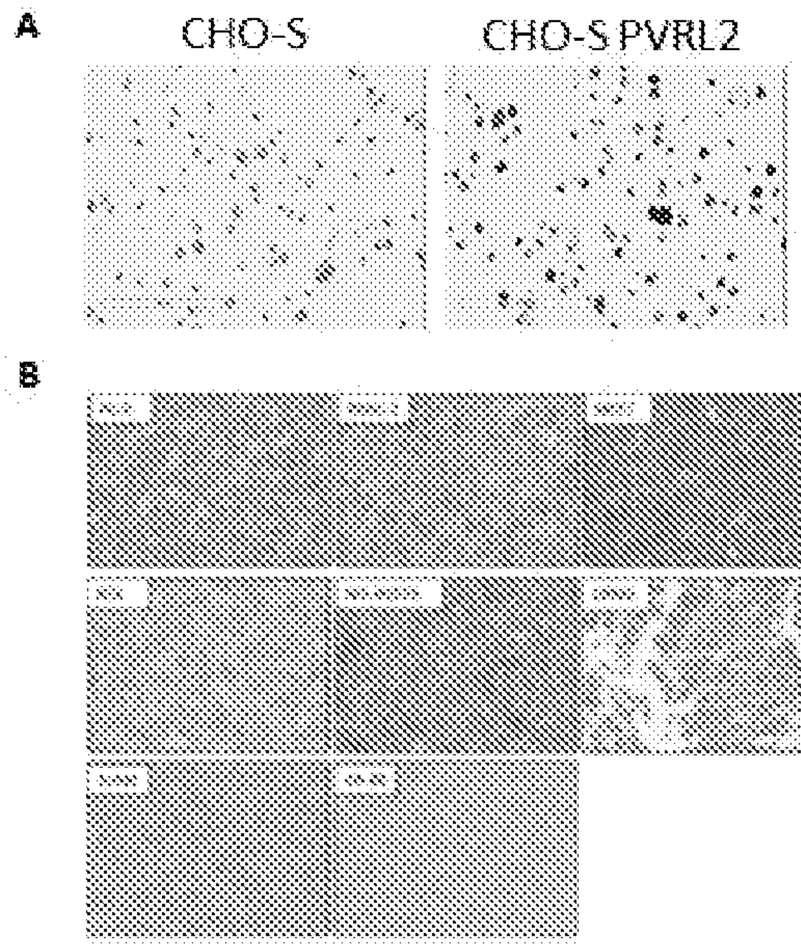
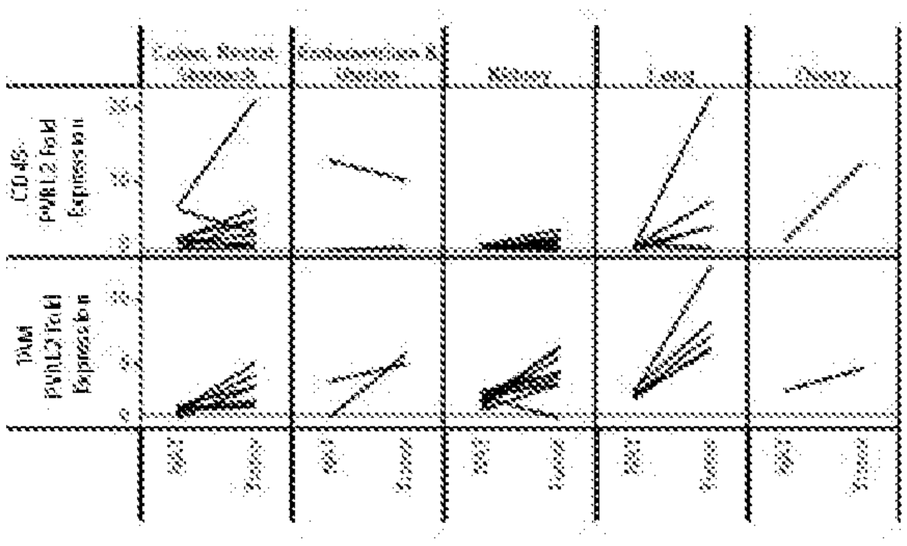

A
PVRIG
TIGIT
CD96
PD1
Fold Expression
Treg
Naive CD4
CM CD4
EM CD4
TEMRA CD4
Treg
Naive CD4
CM CD4
EM CD8
TEMRA CD4
Treg
Naive CD4
CM CD4
EM CD8
TEMRA CD4
Treg
Naive CD4
CM CD4
EM CD8
TEMRA CD4
Cell Subset
B
Gene expression kinetics in allo-activated CD8+ T cells
Fold Change relative to day 0
PVRIG
TIGIT
CD96
PDCD1
CD226
C
NK Cells
PVRIG Fold Expression
Bladder
Breast
Colorectal
Endometrial
Head & Neck
Kidney
Lung
Ovary
Prostate
Stomach
Cancer Type
D
Lung TIL
Kidney TIL
CD4
CD8
CD4
CD8
Ex vivo
Day 5
aCD3+
aCD28
E
Colon, Rectal Cancers
Endometrial & Ovarian
Kidney
Lung
Ovary
CD4 T cells
PVRIG Fold Expression
CD8 T cells
PVRIG Fold Expression
PVRIG Expression
CD4 T cells
CD8 T cells
F

Figure 35



Cell Line	PVRL2 Expression by FACS
KC-2	+
PANC-1	+
MCF7	+
HT-29	+
RT-4	+
NCI-H1573	+
GPM2	-
Daudi	-
Jurkat	-
C4-46	-

Figure 36



PVRL2 Expression

CD45+	NAT vs Tumor	0.02
Monocytes	NAT vs Tumor	<0.0001

Figure 37

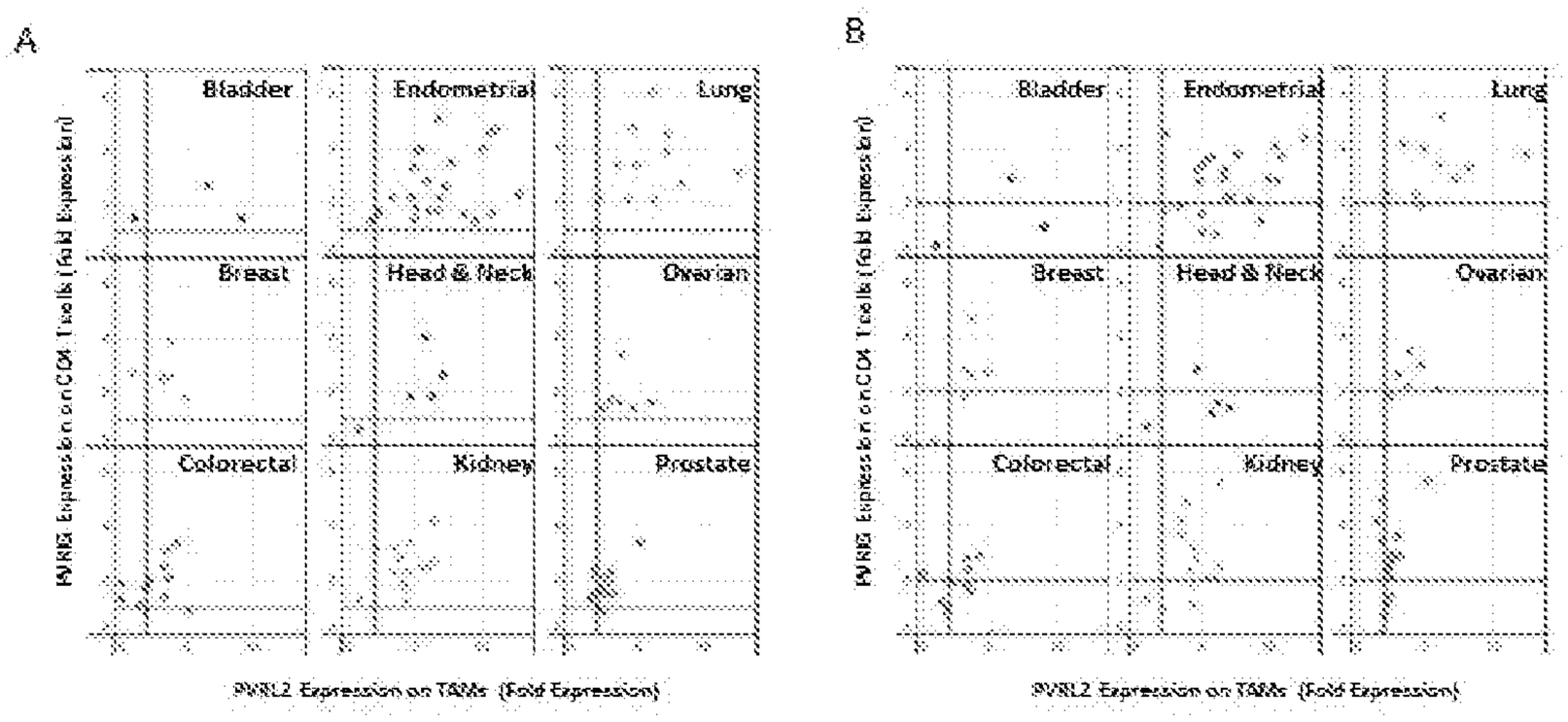

A
Bladder
Endometrial
Lung
Breast
Head & Neck
Ovarian
Colorectal
Kidney
Prostate
PVRIG Expression on CD4 T cells (Fold Expression)
PVRL2 Expression on TAMs (Fold Expression)
B
Bladder
Endometrial
Lung
Breast
Head & Neck
Ovarian
Colorectal
Kidney
Prostate
PVRL2 Expression on TAMs (Fold Expression)

Figure 38

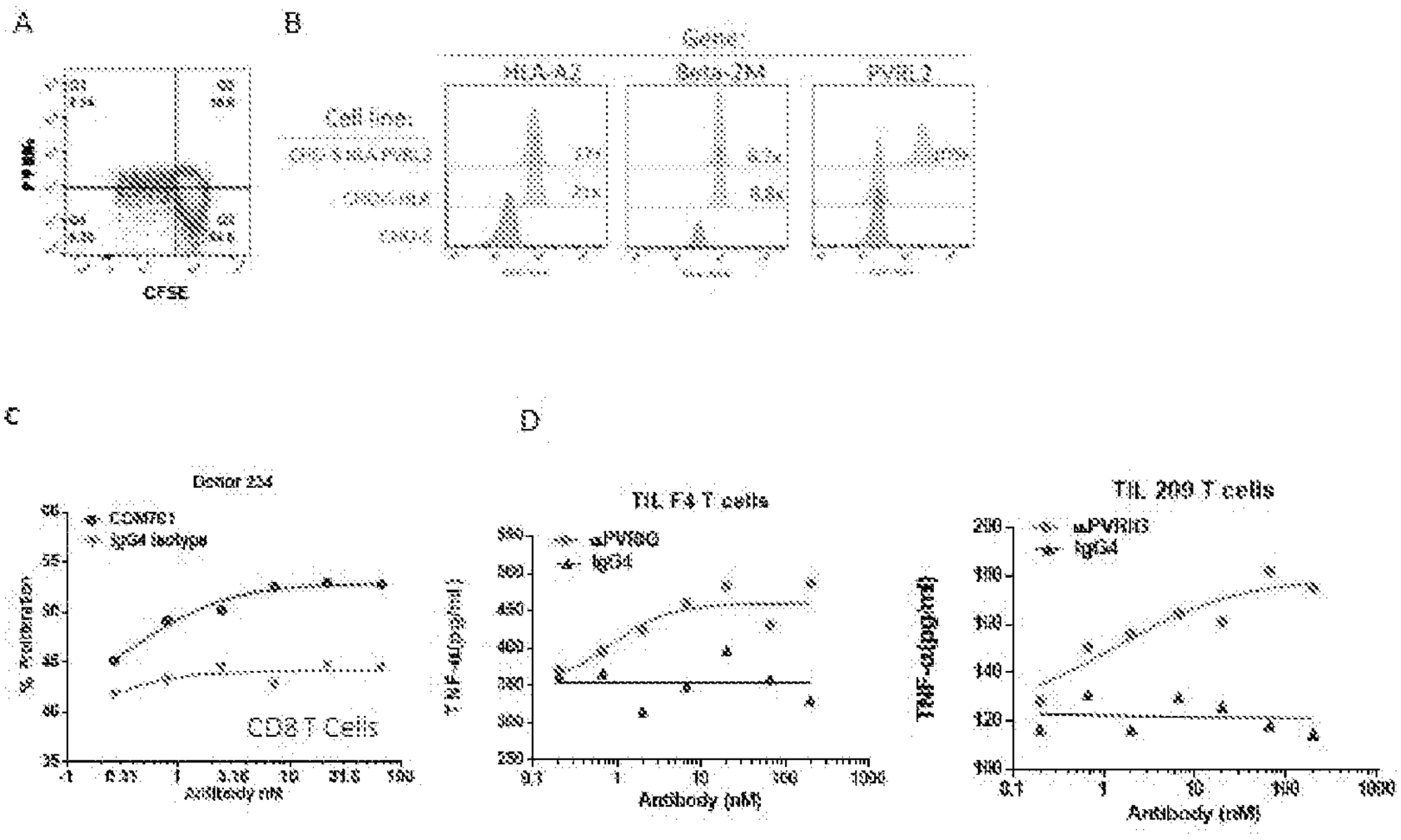

A
B
Gene:
HLA-A2
Beta-2M
PVRL2
Cell line:
CFSE
C
Donor 234
CD8 T Cells
Antibody nM
D
TIL F4 T cells
TIL 209 T cells
Antibody (nM)
TNF-alpha(pg/ml)

Figure 39

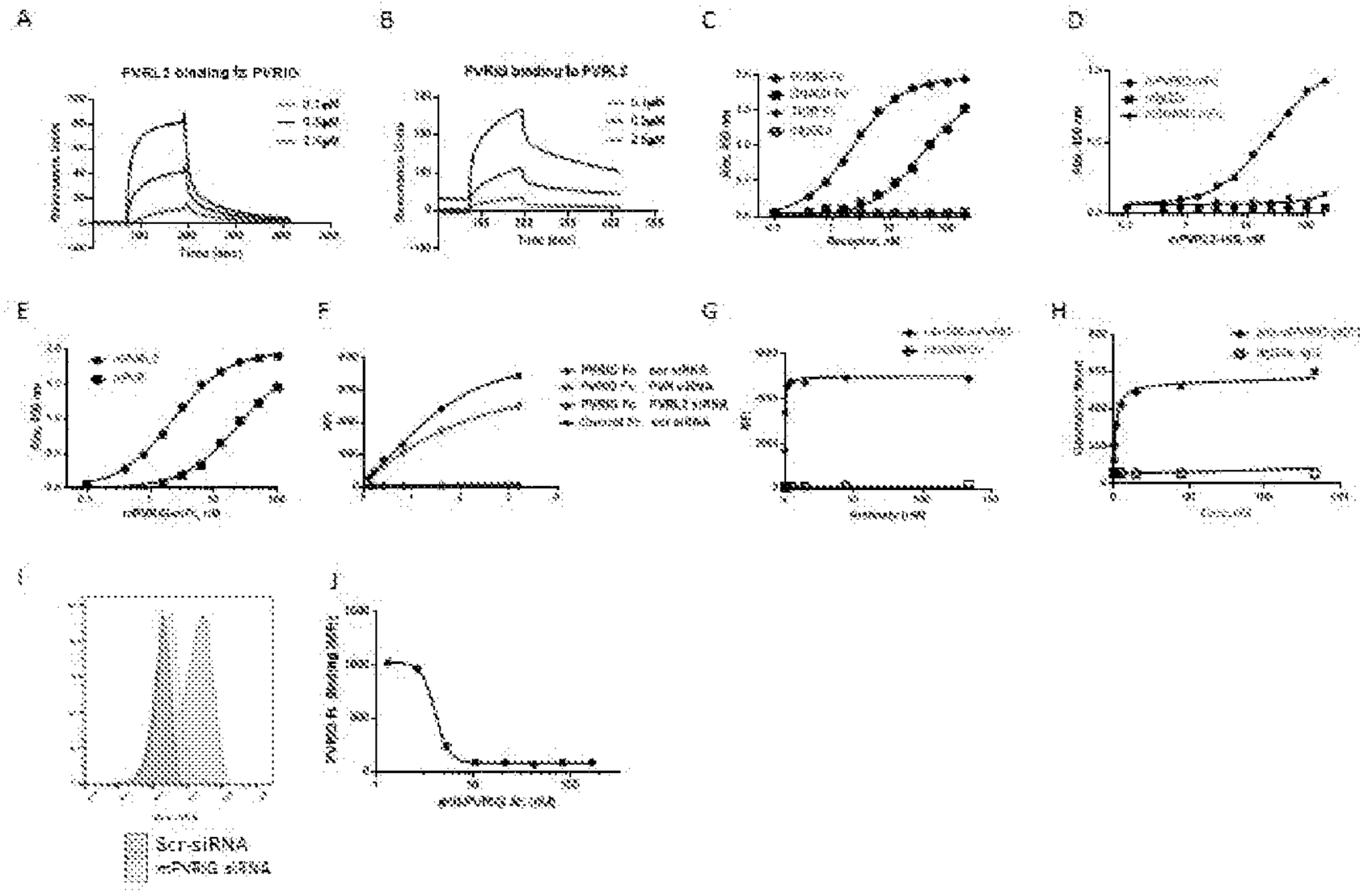


Figure 40

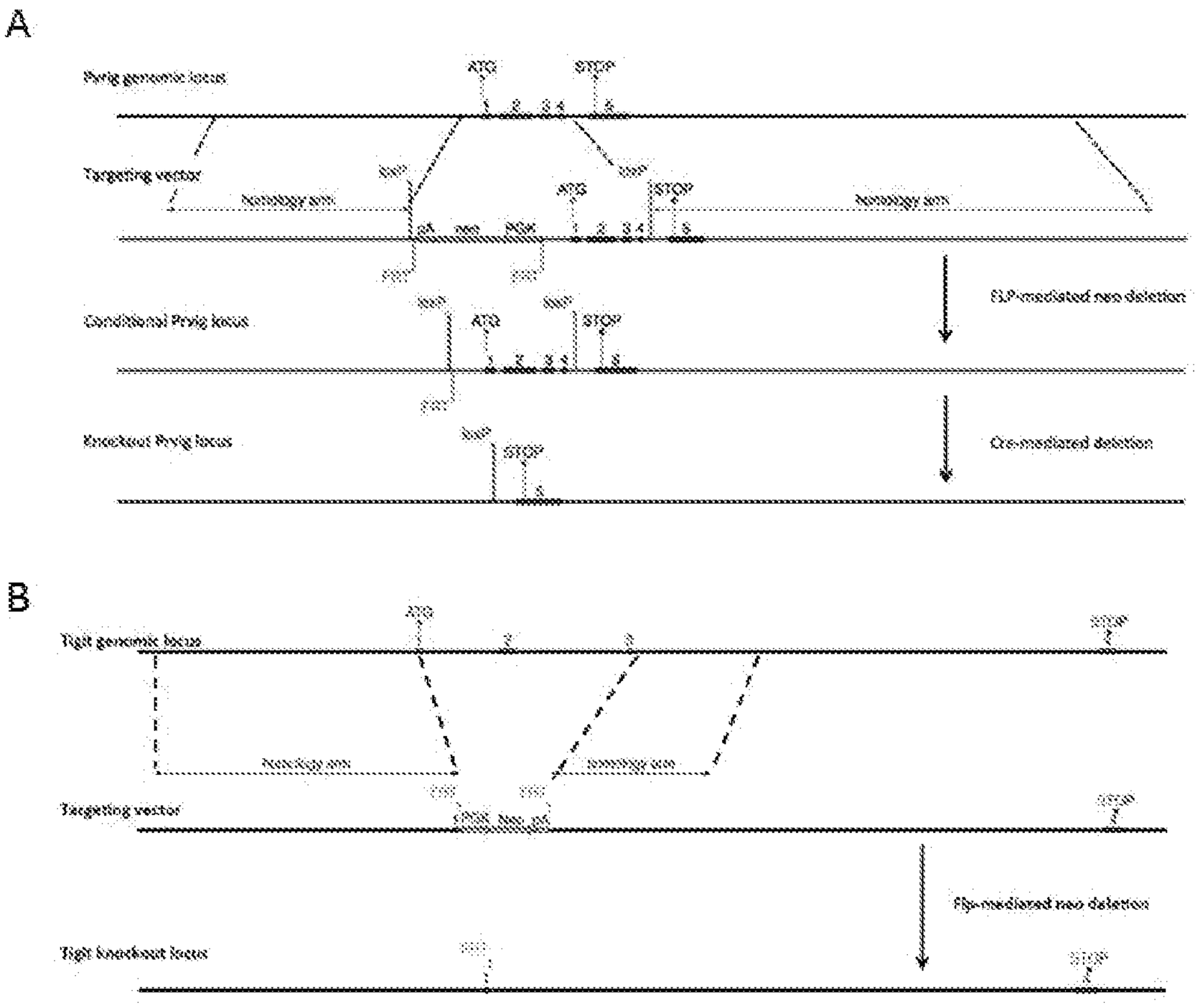

A
Flp-mediated neo deletion
Cre-mediated deletion
B
Flp-mediated neo deletion

Figure 41

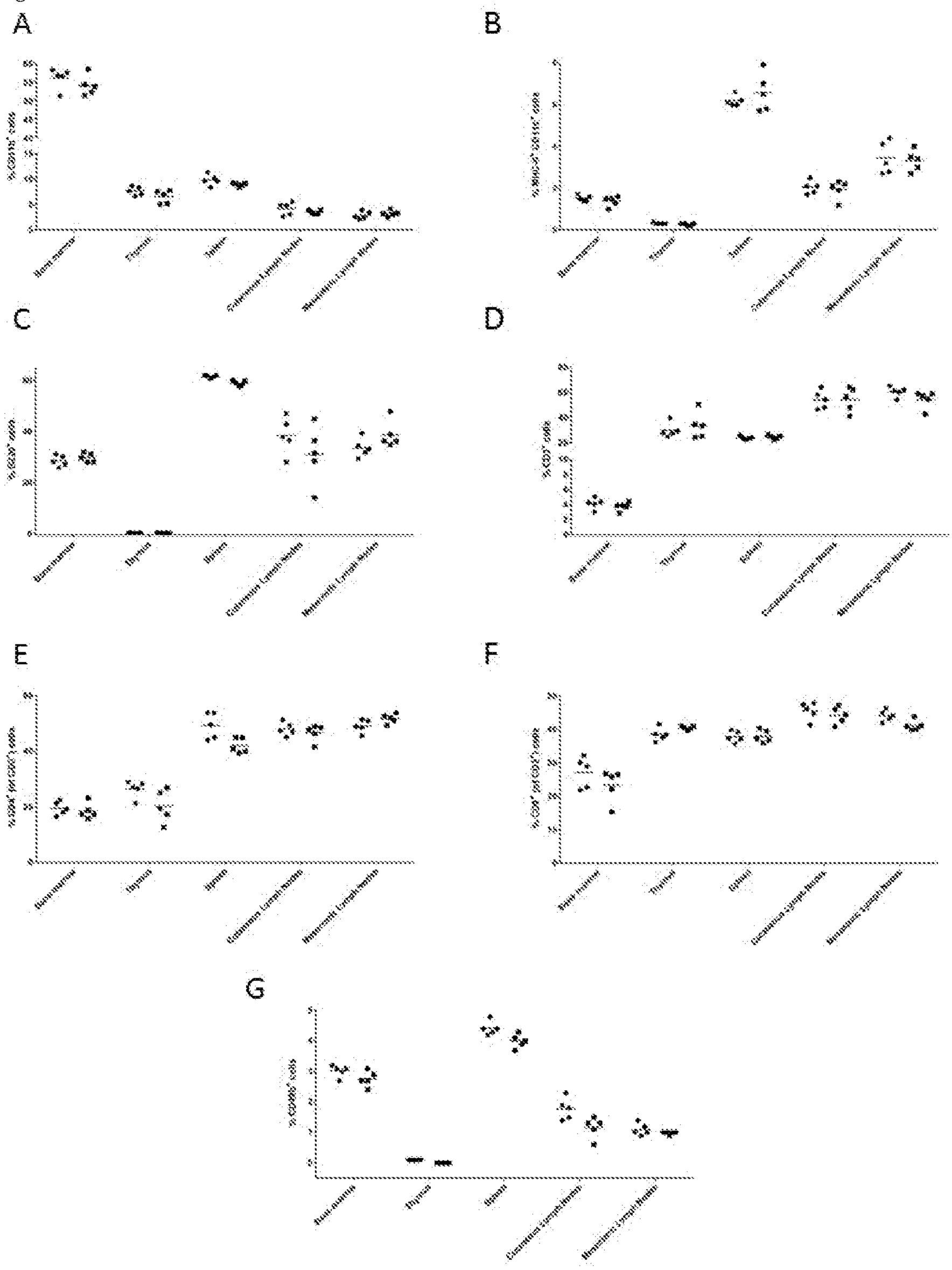


Figure 41 (cont.)

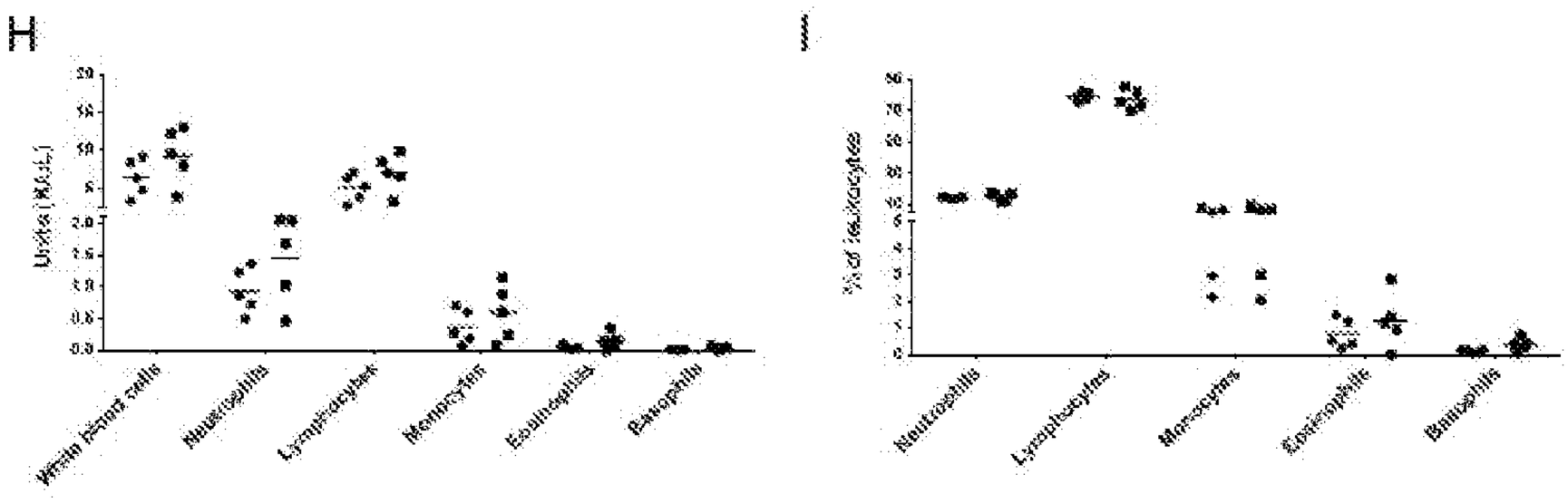


Figure 42

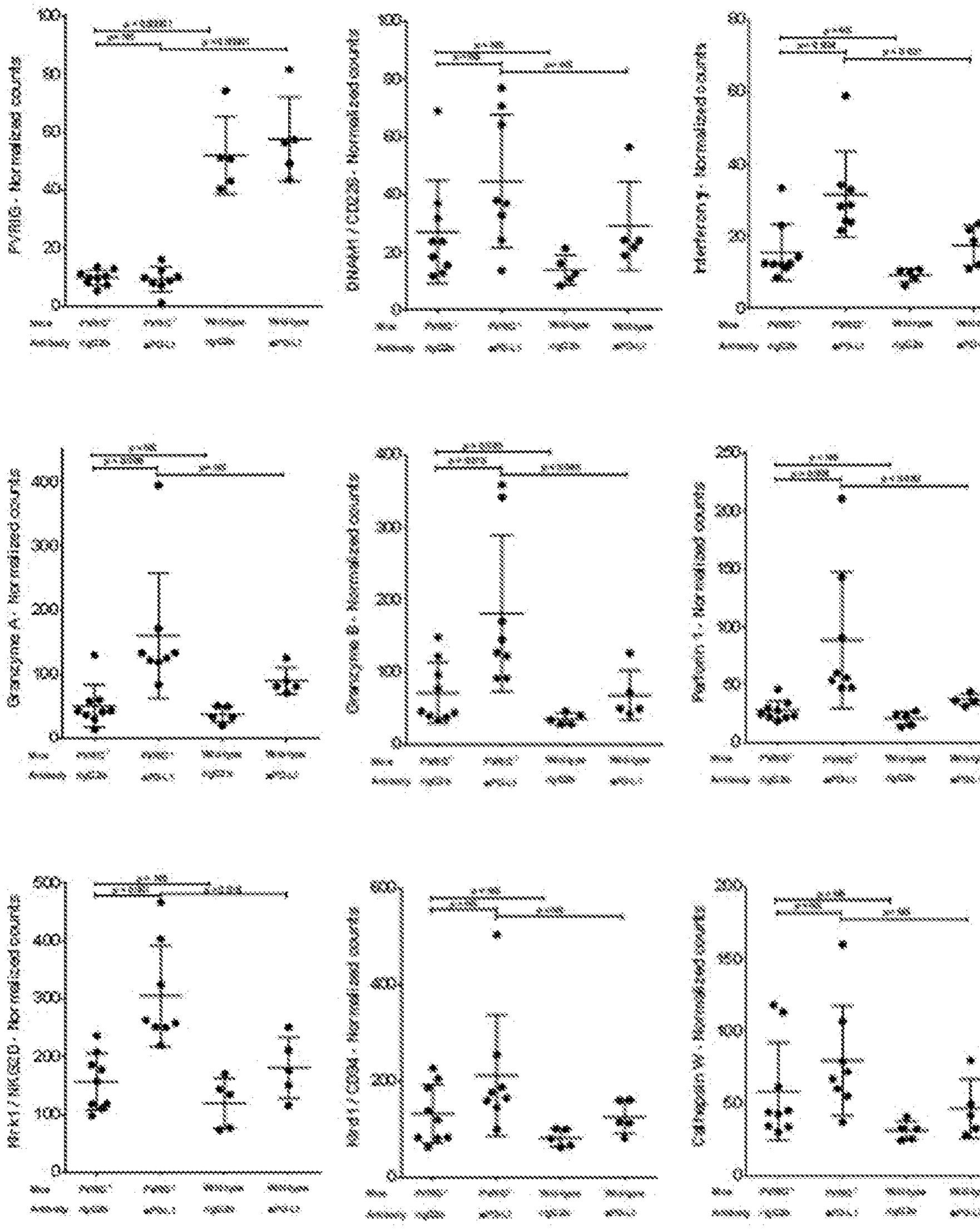

PVRIG - Normalized counts
CD226 - Normalized counts
Interferon γ - Normalized counts
Granzyme A - Normalized counts
Granzyme B - Normalized counts
Perforin 1 - Normalized counts
KIR3DL1 / KIR3DS1 - Normalized counts
TIGIT / CD226 - Normalized counts
CD96 - Normalized counts

Figure 43

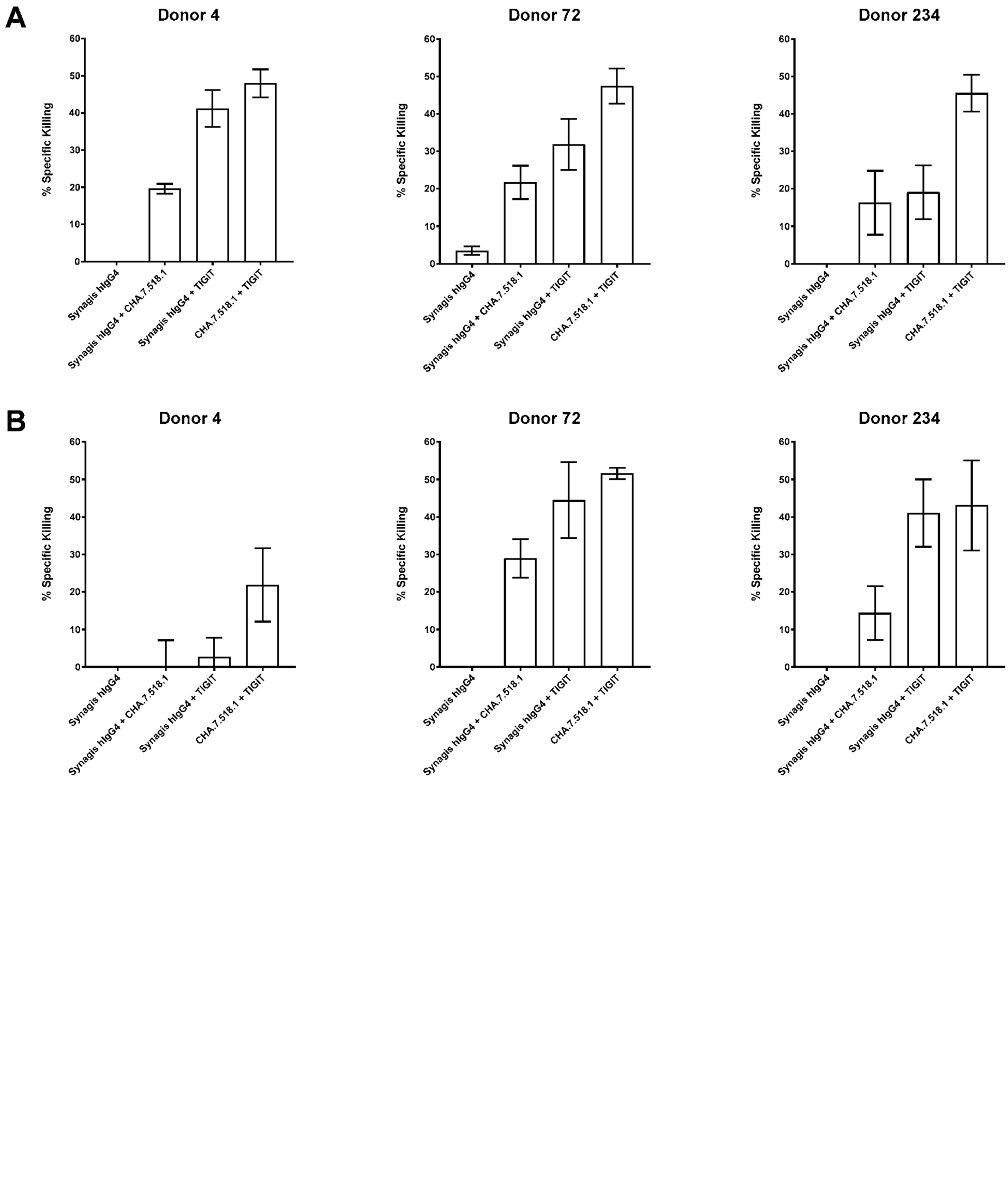

A
Donor 4
Donor 72
Donor 234
% Specific Killing
0
10
20
30
40
50
60
Synagis hIgG4
Synagis hIgG4 + CHA.7.518.1
Synagis hIgG4 + TIGIT
CHA.7.518.1 + TIGIT
B
Donor 4
Donor 72
Donor 234
% Specific Killing
Synagis hIgG4
Synagis hIgG4 + CHA.7.518.1
Synagis hIgG4 + TIGIT
CHA.7.518.1 + TIGIT

Figure 44

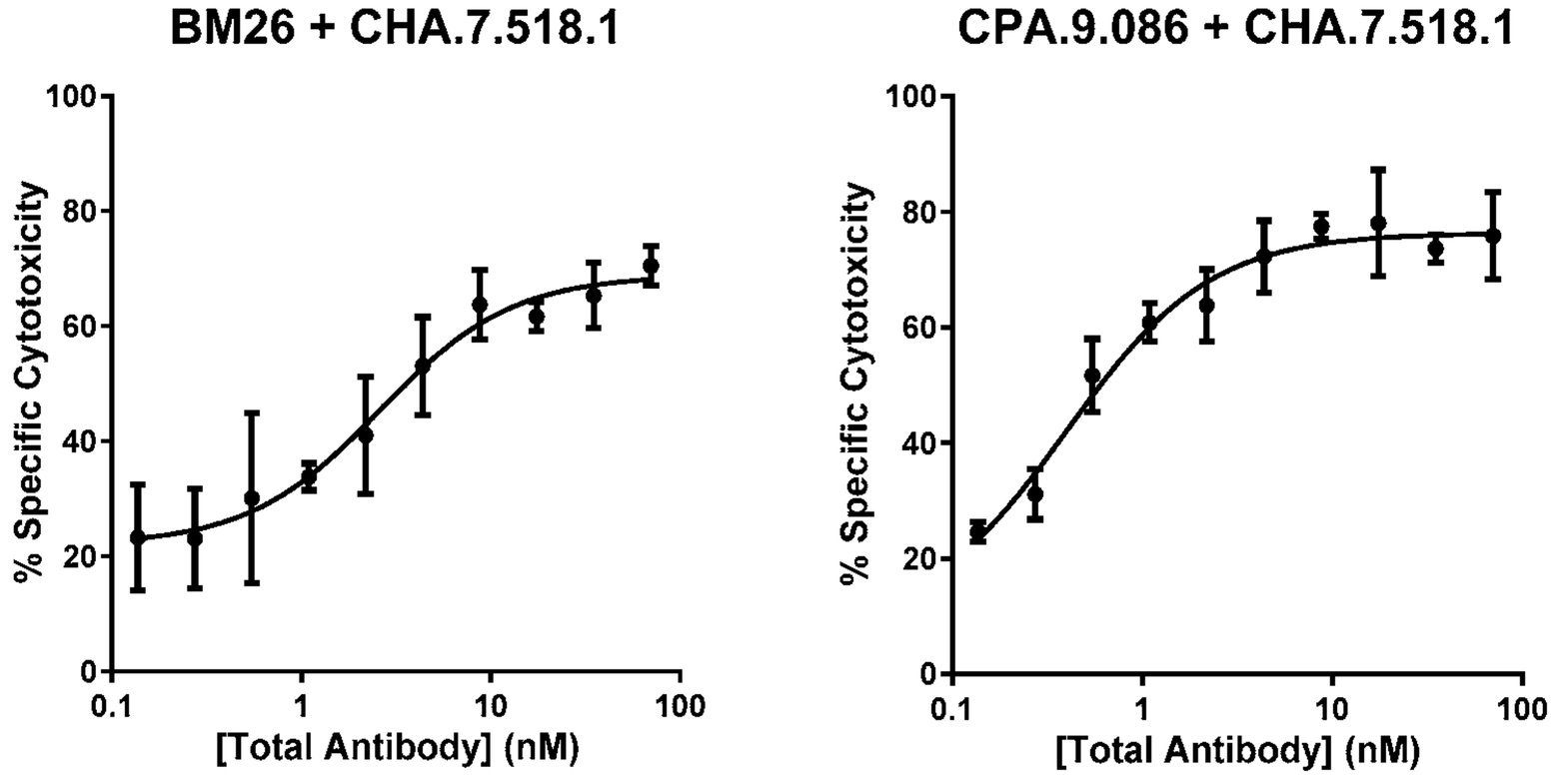

BM26 + CHA.7.518.1
CPA.9.086 + CHA.7.518.1
% Specific Cytotoxicity
[Total Antibody] (nM)
0
20
40
60
80
100
0.1
1
10
100

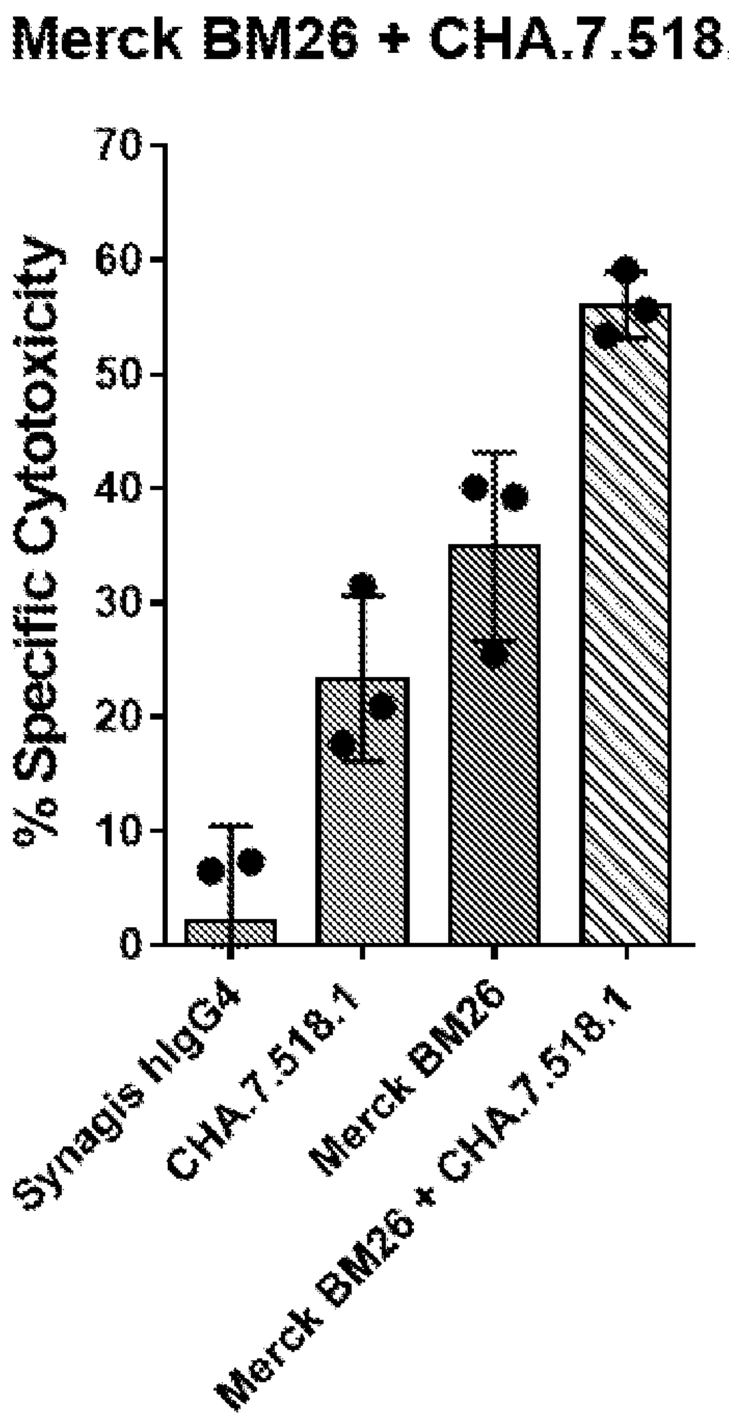
Figure 45

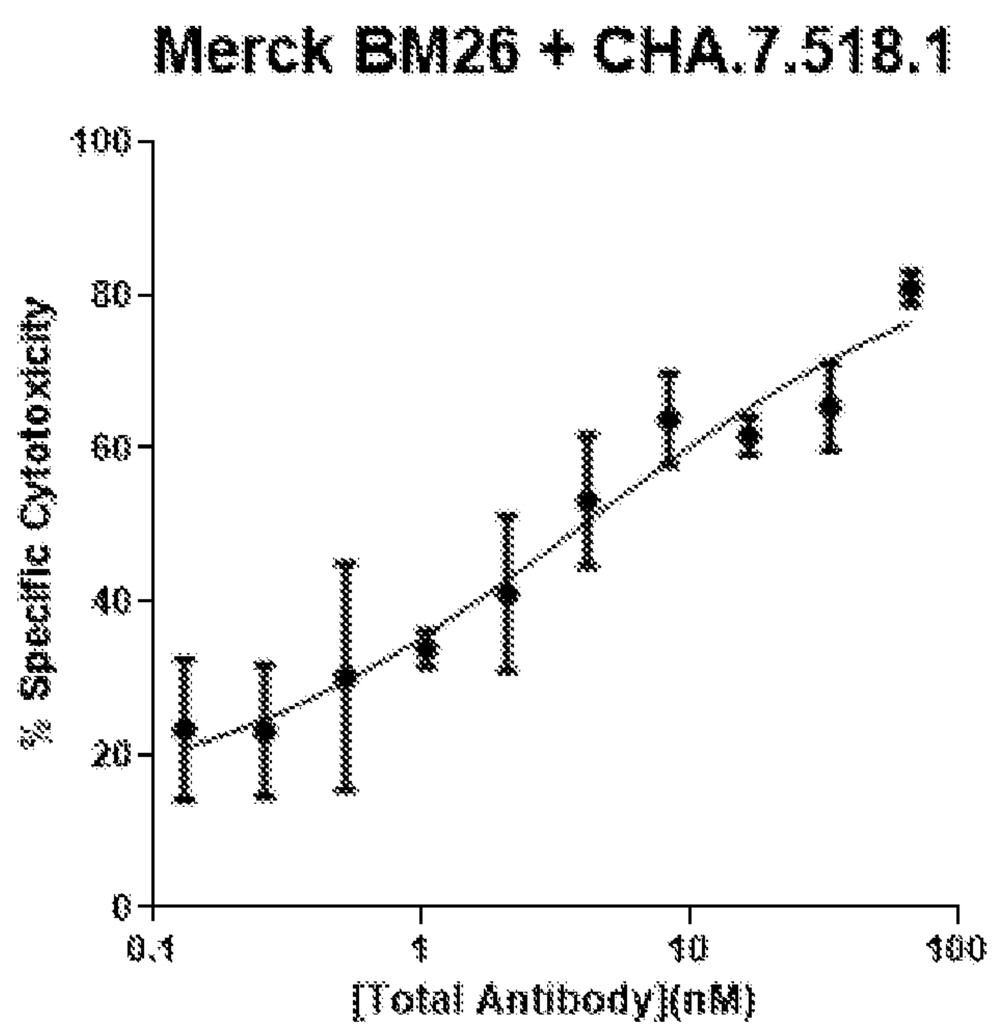
CPA9.086 CDR sequences

Definition	H-CDR1	H-CDR2	H-CDR3	L-CDR1	L-CDR2	L-CDR3
IMGT	GFTFSSYA **(SEQ ID NO:1105)**	ISYAGEVK **(SEQ ID NO:1107)**	ARDPLPLHYYGMDV **(SEQ ID NO:1109)**	SSNMGRRP **(SEQ ID NO:1111)**	SQN **(SEQ ID NO:1113)**	AVWDDIGRVLQ **(SEQ ID NO:1115)**
Kabat	SYAMH **(SEQ ID NO:1106)**	VISYAGEVKYYADSVKG **(SEQ ID NO:1108)**	DPLPLHYYGMDV **(SEQ ID NO:1110)**	SGSSSNMGRRPVN **(SEQ ID NO:1112)**	SQNQRPS **(SEQ ID NO:1114)**	AVWDDIGRVLQ **(SEQ ID NO:1116)**

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 46


Merck BM26 + CHA.7.518.1
% Specific Cytotoxicity
0
10
20
30
40
50
60
70
Synagis hIgG4
CHA.7.518.1
Merck BM26
Merck BM26 + CHA.7.518.1


Merck BM26 + CHA.7.518.1
% Specific Cytotoxicity
0
20
40
60
80
100
0.1
1
10
100
[Total Antibody](nM)

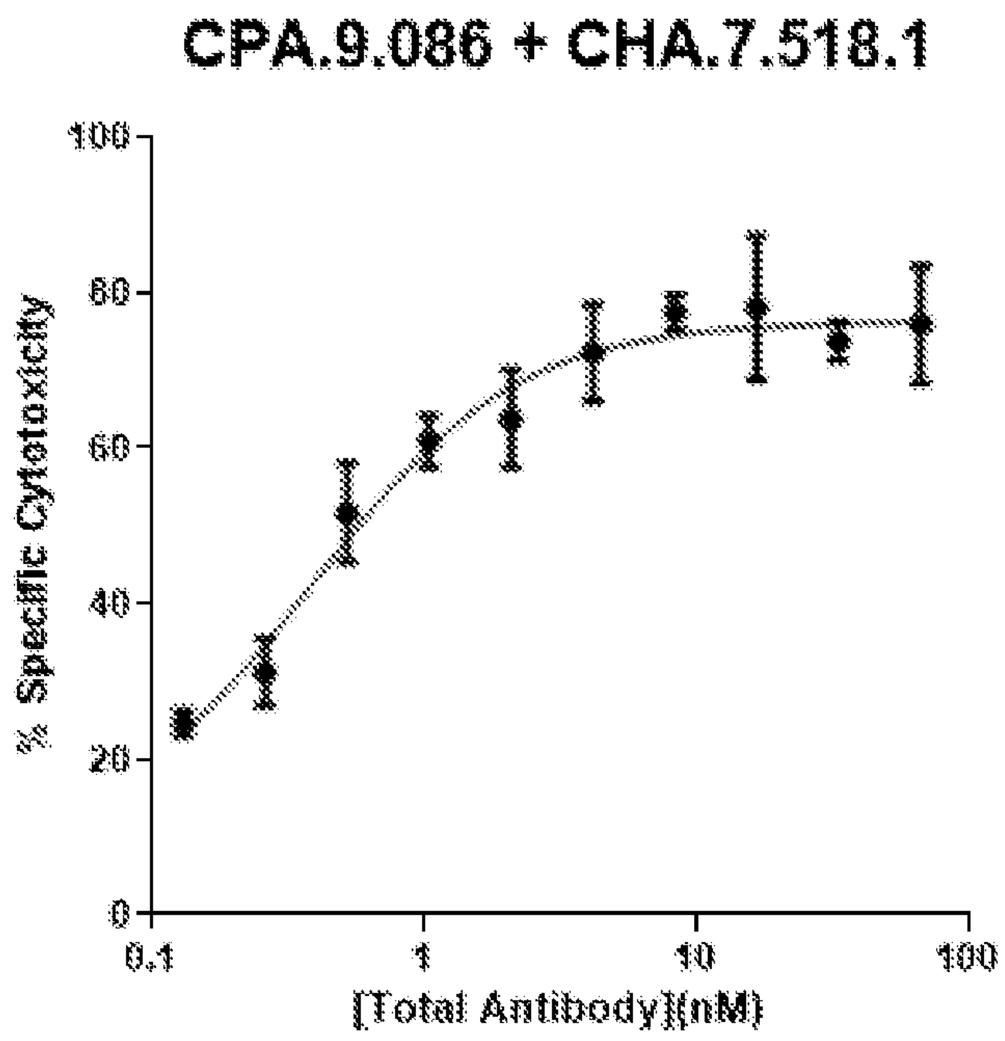
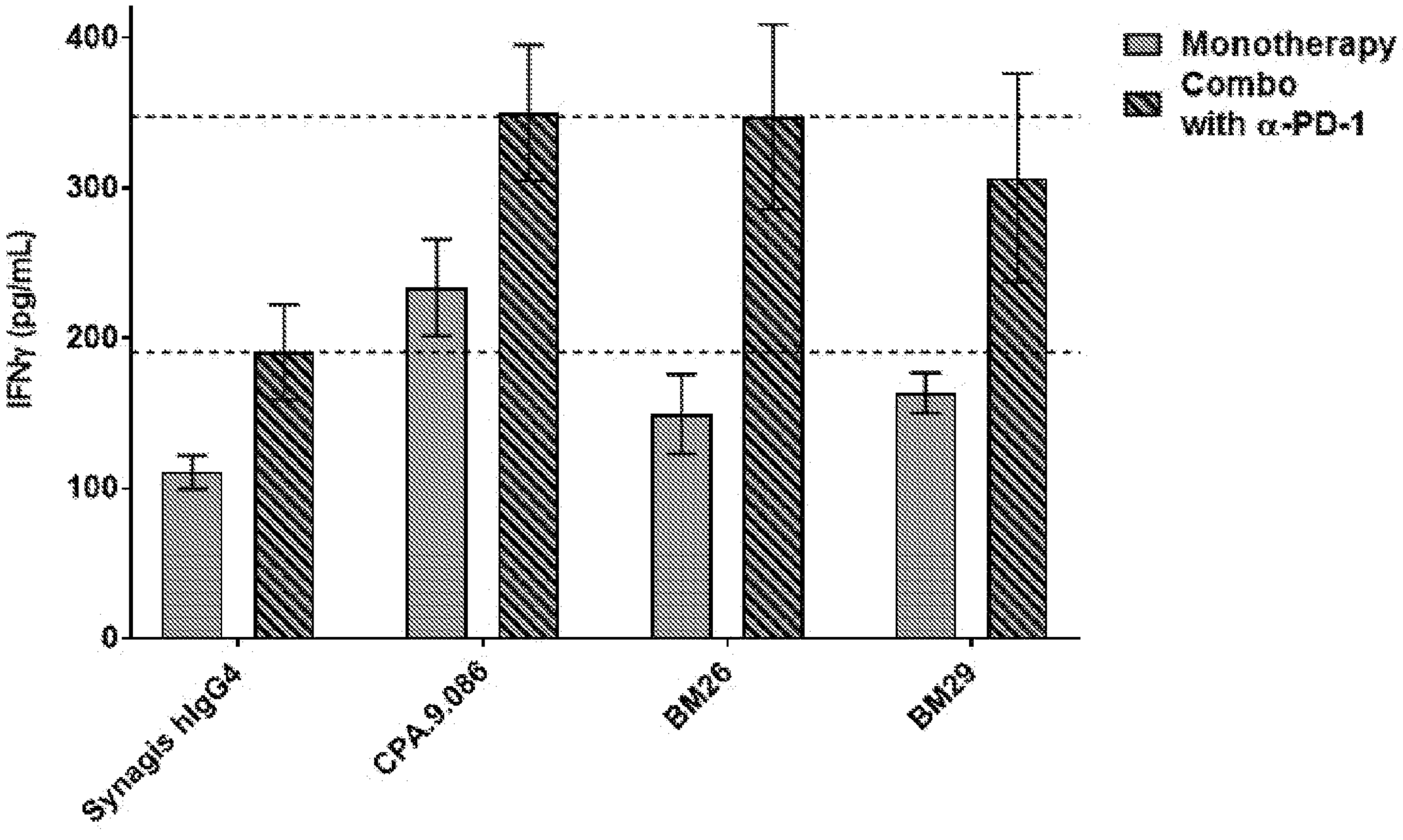

CPA.9.086 + CHA.7.518.1
% Specific Cytotoxicity
0
20
40
60
80
100
0.1
1
10
100
[Total Antibody](nM)

Figure 47


400
300
200
100
0
IFNγ (pg/mL)
Monotherapy
Combo with α-PD-1
Synagis hIgG4
CPA.9.086
BM26
BM29

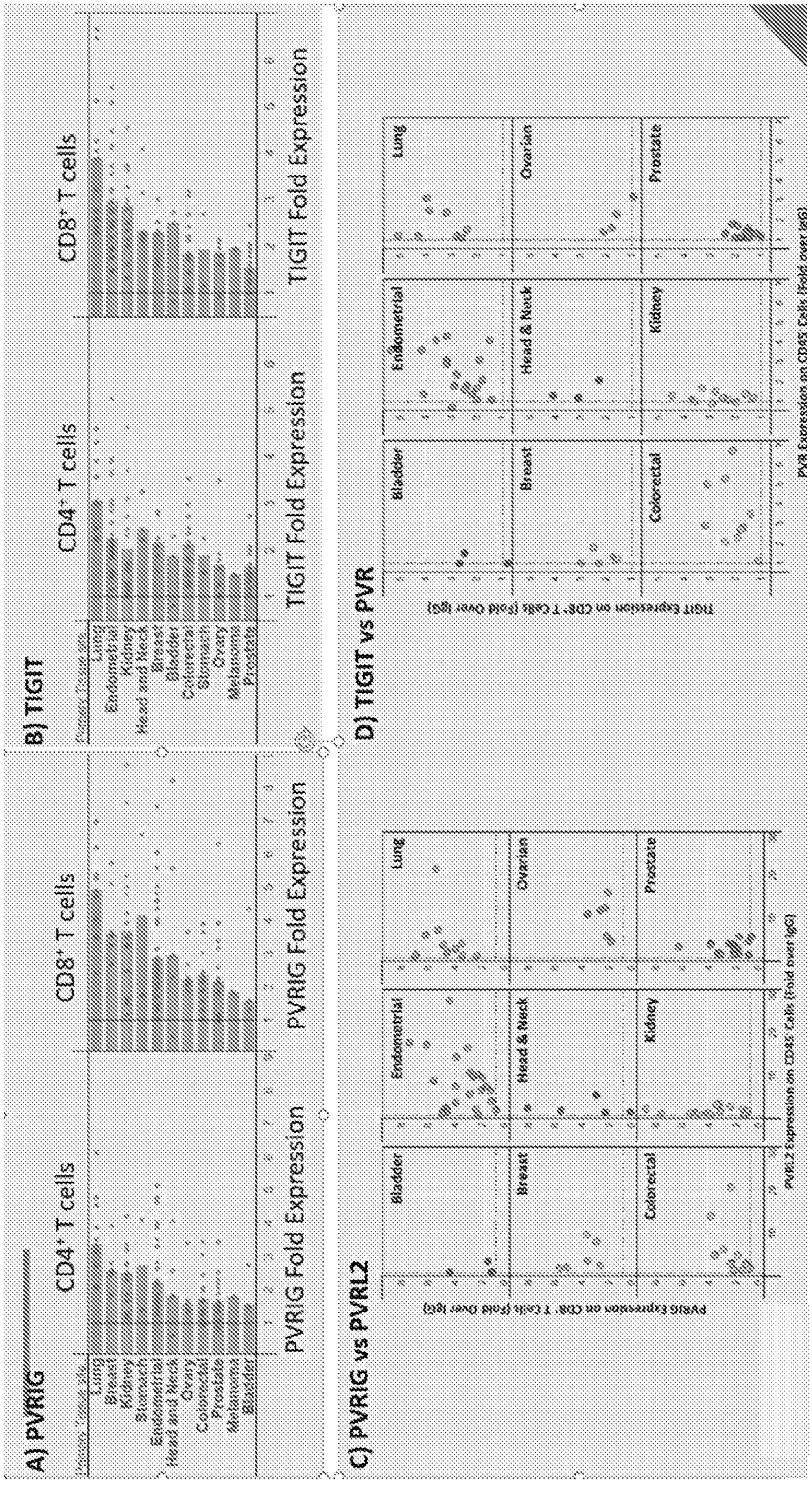
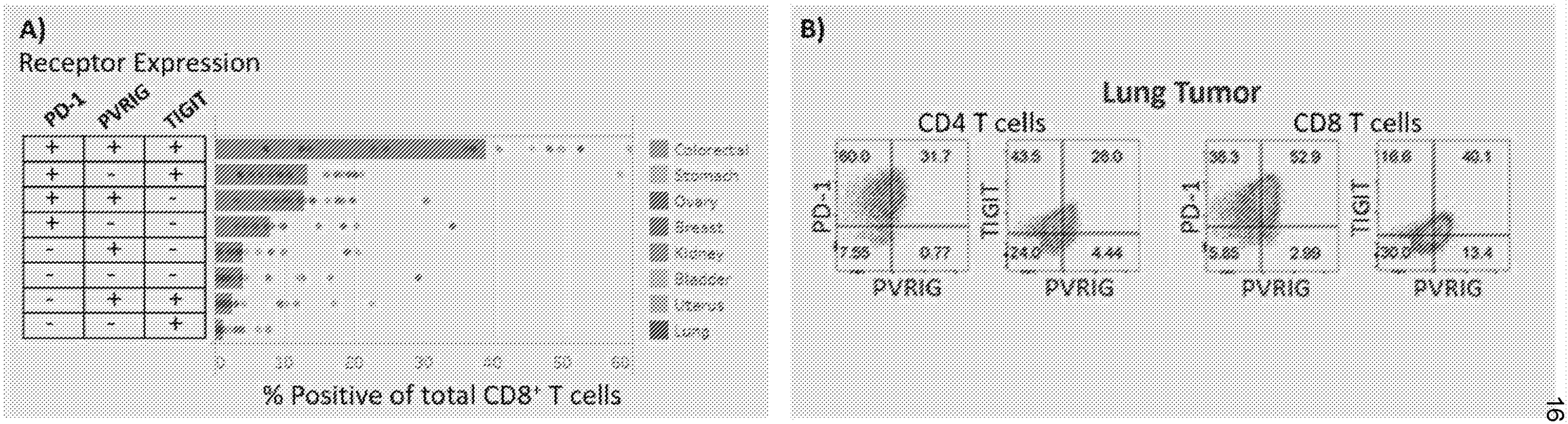
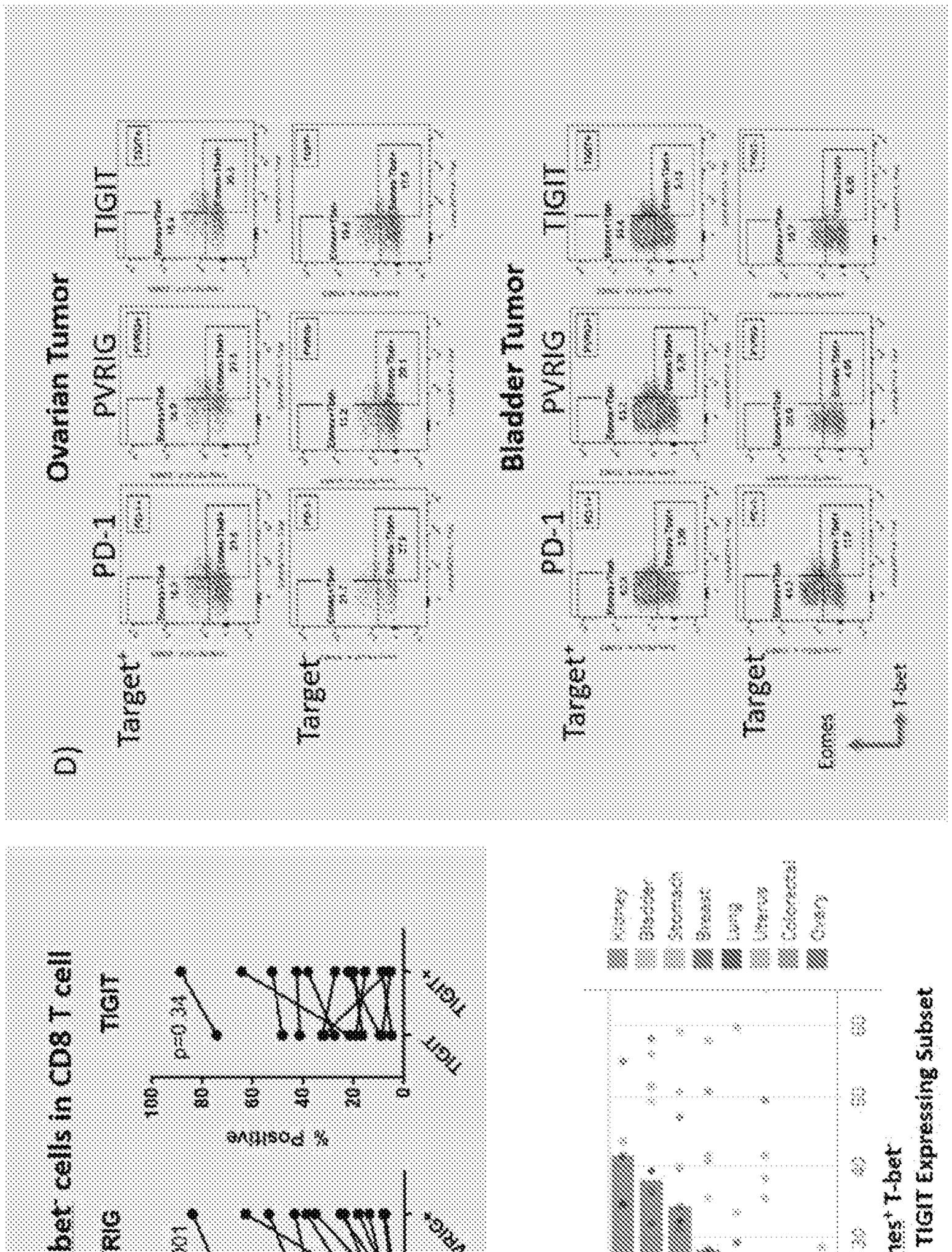
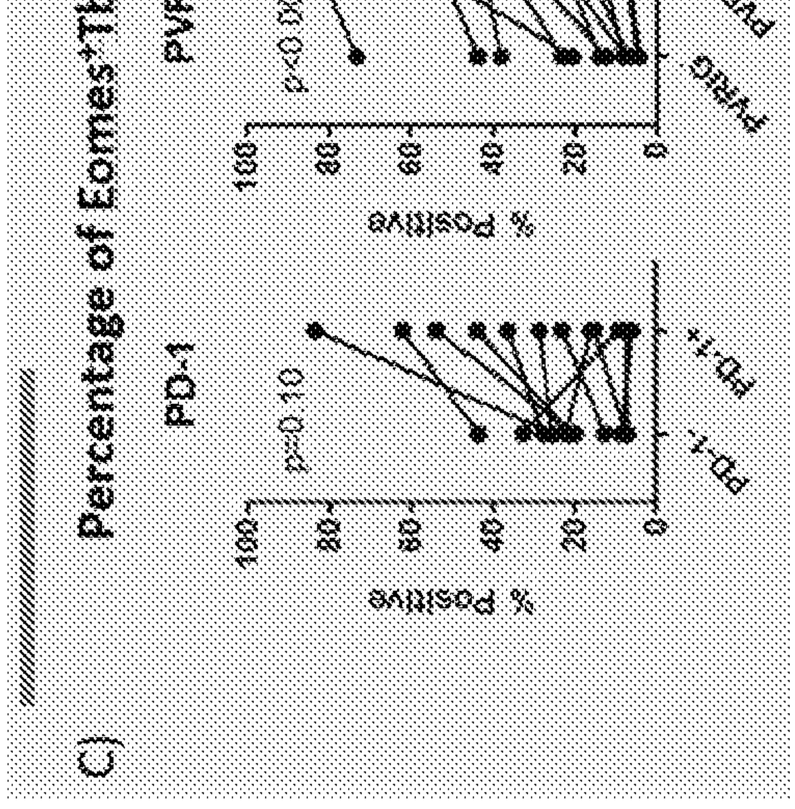

A) PVRIG
CD4+ T cells
Tumor Type
Lung
Breast
Kidney
Stomach
Endometrial
Head and Neck
Ovary
Colorectal
Prostate
Melanoma
Bladder
PVRIG Fold Expression
B) TIGIT
CD4+ T cells
CD8+ T cells
TIGIT Fold Expression
C) PVRIG vs PVRL2
Bladder
Endometrial
Lung
Breast
Head & Neck
Ovarian
Colorectal
Kidney
Prostate
PVRIG expression on CD8+ T cells (fold over IgG)
PVRL2 expression on CD8+ T cells (fold over IgG)
D) TIGIT vs PVR
TIGIT expression on CD8+ T cells (fold over IgG)
PVR expression on CD8+ T cells (fold over IgG)

Figure 48

Figure 49


A)
Receptor Expression
PD-1
PVRIG
TIGIT
% Positive of total CD8+ T cells
B)
Lung Tumor
CD4 T cells
CD8 T cells
PD-1
TIGIT
PVRIG
80.0
31.7
7.55
6.77
43.5
28.0
24.0
4.44
98.3
52.9
5.65
2.88
16.6
40.1
13.4





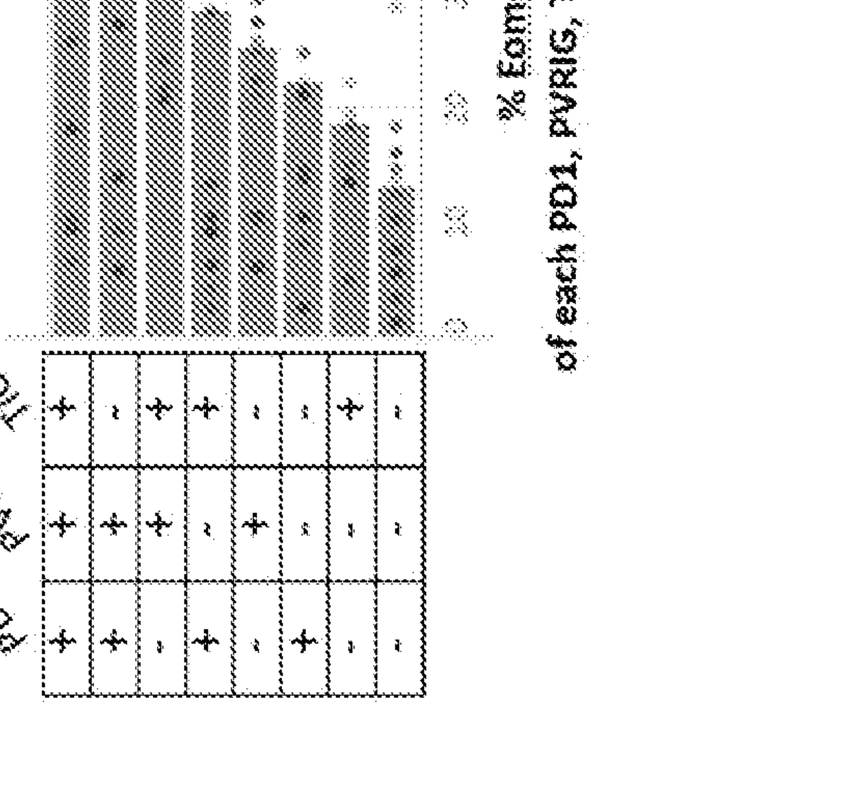
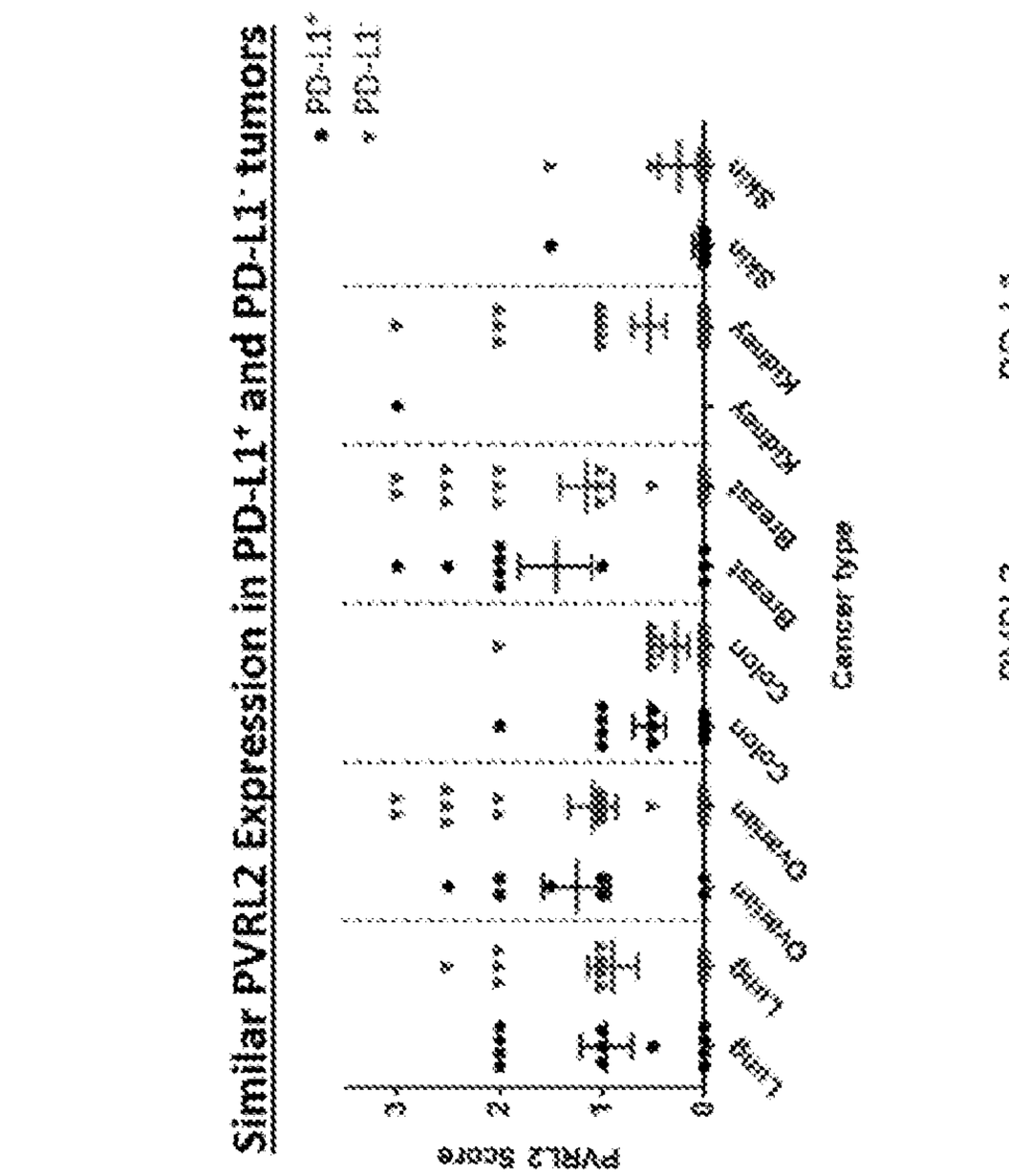


Figure 49 (cont.)


B)
Similar PVRL2 Expression in PD-L1+ and PD-L1- tumors
PD-L1+
PD-L1-
PVRL2 score
Cancer type
Lung
Ovarian
Colon
Breast
Kidney
C)
PD-L1
PVRL2
Endometrioid Cancer
Lung Adenocarcinoma

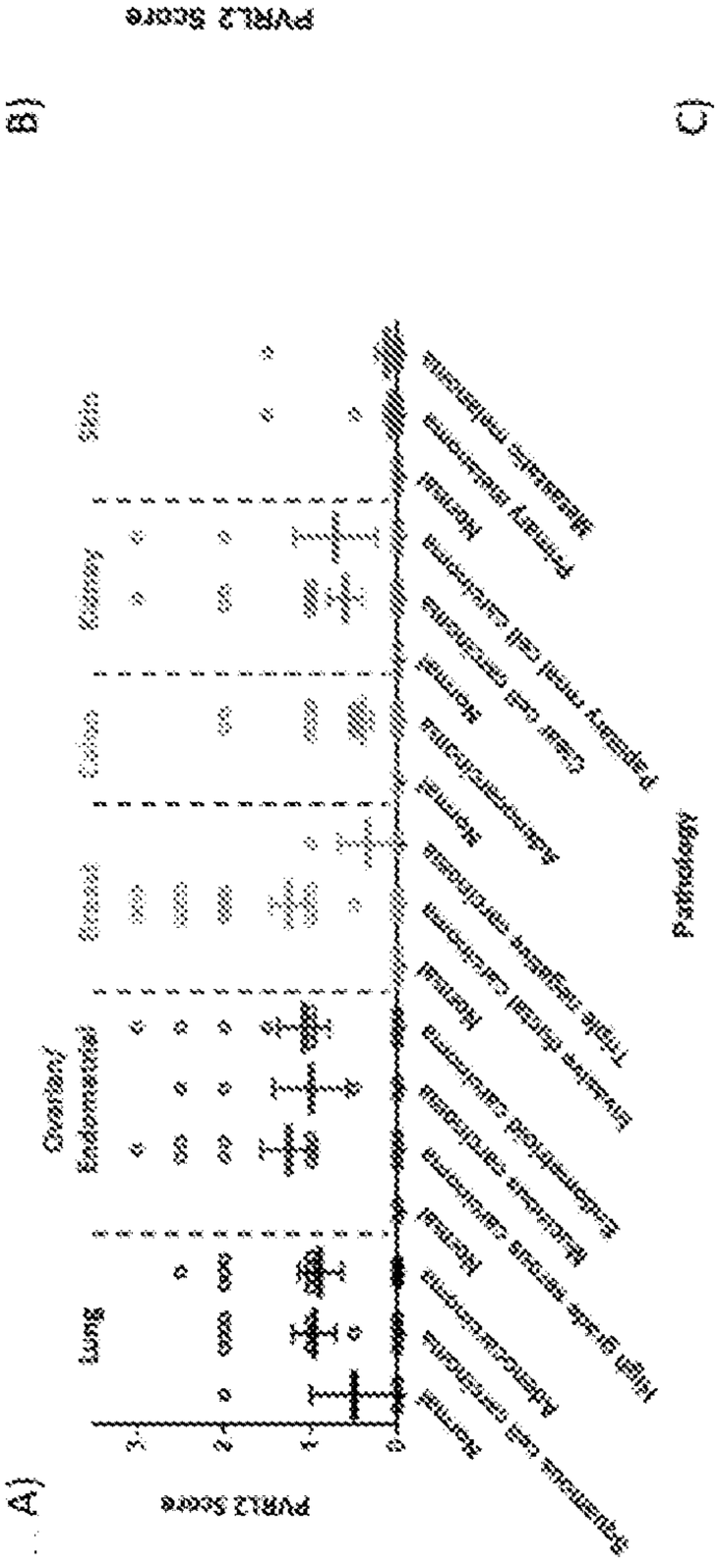
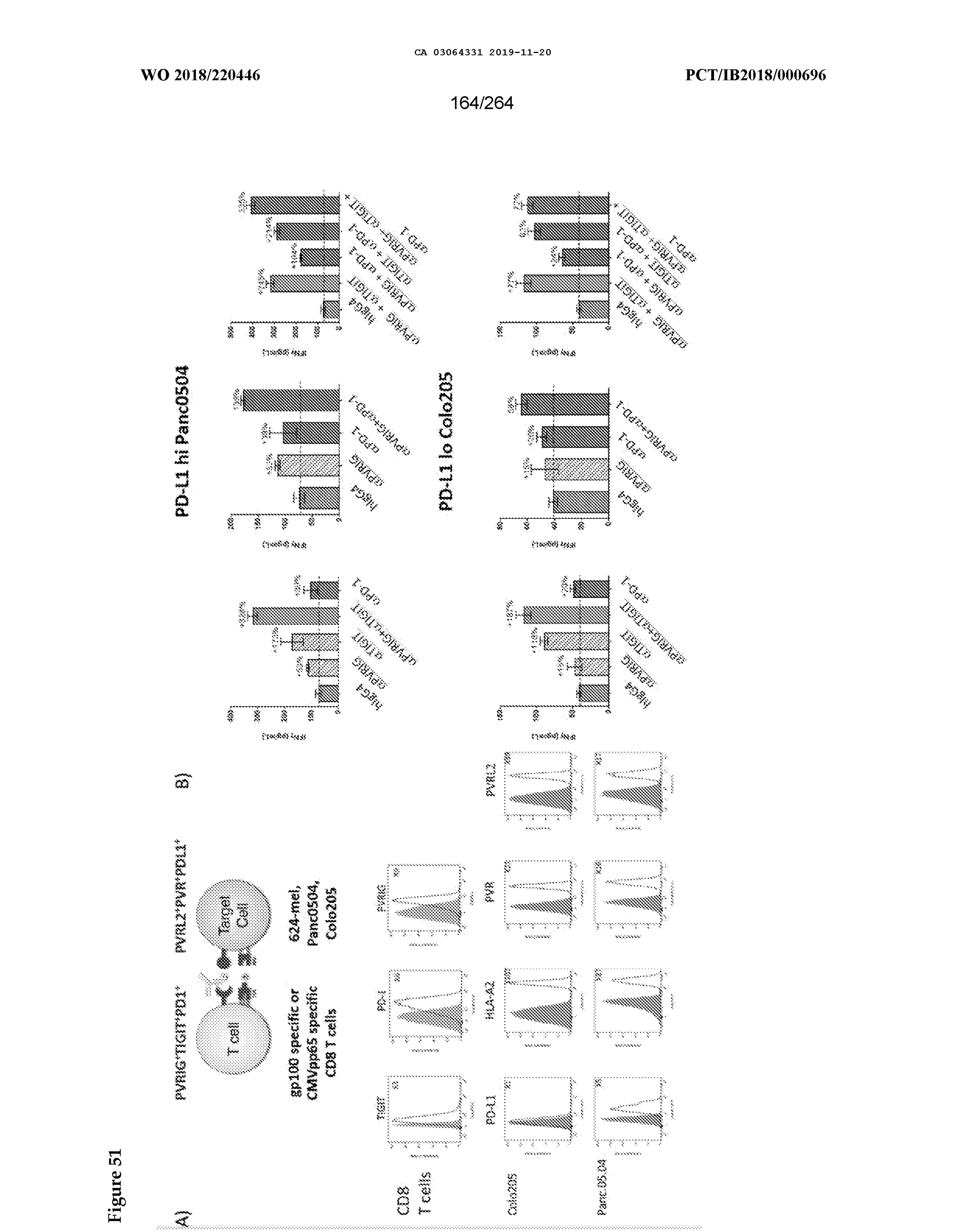

PVRL2 is Induced in the Tumor
A)
PVRL2 score
Lung
Cervical/ Endometrial
Normal
Malignant
Pathology
Squamous cell carcinoma
Adenocarcinoma
High grade serous carcinoma
Endometrioid carcinoma
Invasive ductal carcinoma
Triple negative ductal carcinoma
Primary tumor
Recurrent
Metastasis

Figure 50

Figure 51


A)
PVRL2+PVR+PDL1+
Target Cell
624-mel, Panc0504, Colo205
PVRL2+PVR+TIGIT+PD1+
T cell
gp100 specific or CMVpp65 specific CD8 T cells
CD8 T cells
Colo205
Panc 05.04
TIGIT
PD-1
PD-L1
HLA-A2
PVRIG
PVR
PVRL2
B)
PD-L1 lo Colo205
PD-L1 hi Panc0504
MFI (log10)
MFG4
cPVRIG
cTIGIT
cPVRIG+cTIGIT
cPD-1
cPVRIG+cPD-1
cTIGIT + cPD-1
cPVRIG + cPD-1
cPVRIG + cTIGIT + cPD-1

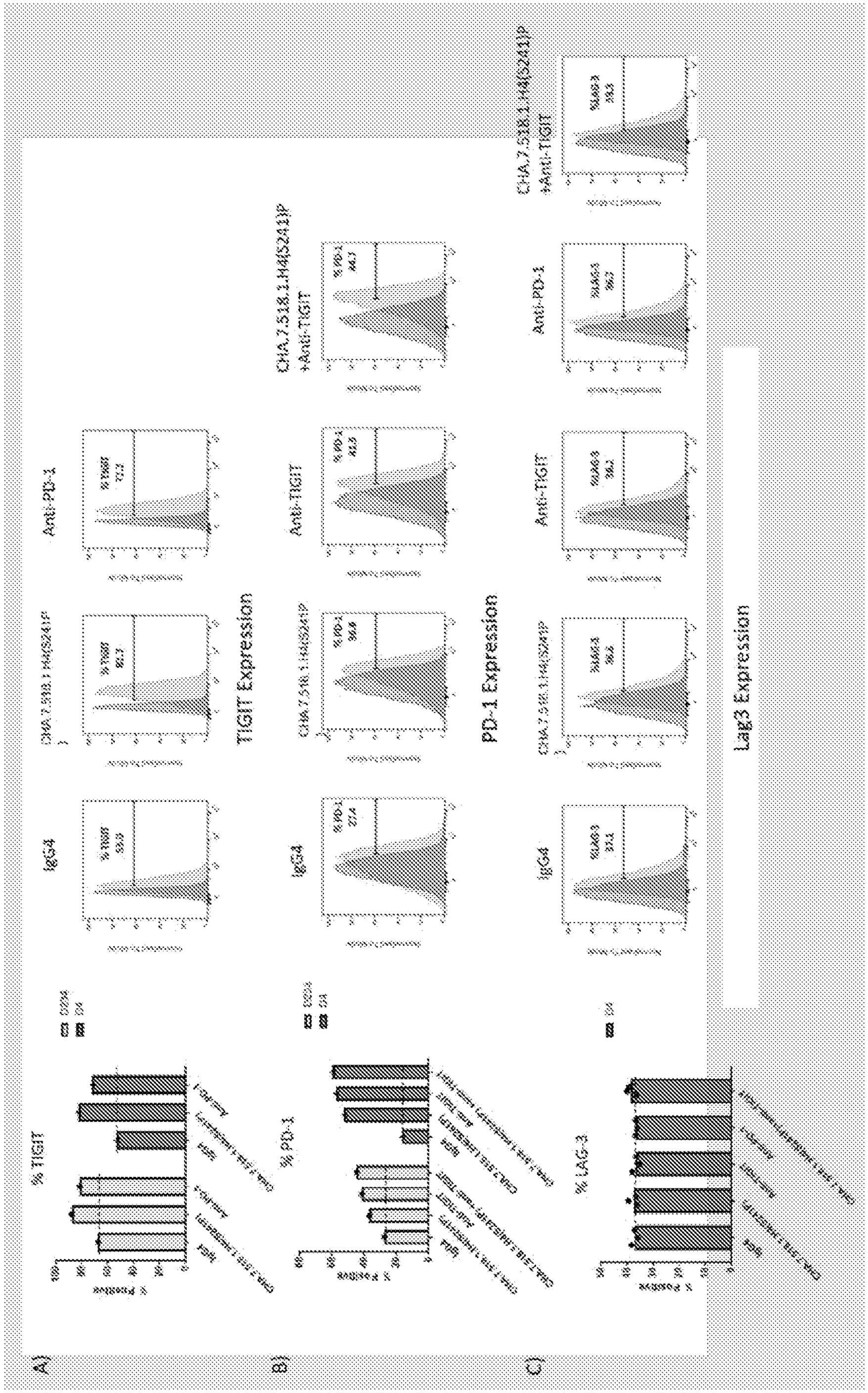

CHA.7.518.1.H4(S241P)
+Anti-TIGIT
Anti-PD-1
TIGIT Expression
Anti-TIGIT
PD-1 Expression
Anti-PD-1
Lag3 Expression
IgG4
PD-1
TIGIT
A)
% TIGIT
% Positive
CHA.7.518.1.H4(S241P) + Anti-TIGIT
CHA.7.518.1.H4(S241P) + Anti-PD-1
Anti-TIGIT
Anti-PD-1
B)
% PD-1
% Positive
CHA.7.518.1.H4(S241P) + Anti-TIGIT
CHA.7.518.1.H4(S241P) + Anti-PD-1
Anti-TIGIT
Anti-PD-1
C)
% LAG-3
% Positive
CHA.7.518.1.H4(S241P) + Anti-TIGIT
CHA.7.518.1.H4(S241P) + Anti-PD-1
Anti-TIGIT
Anti-PD-1

Figure 52

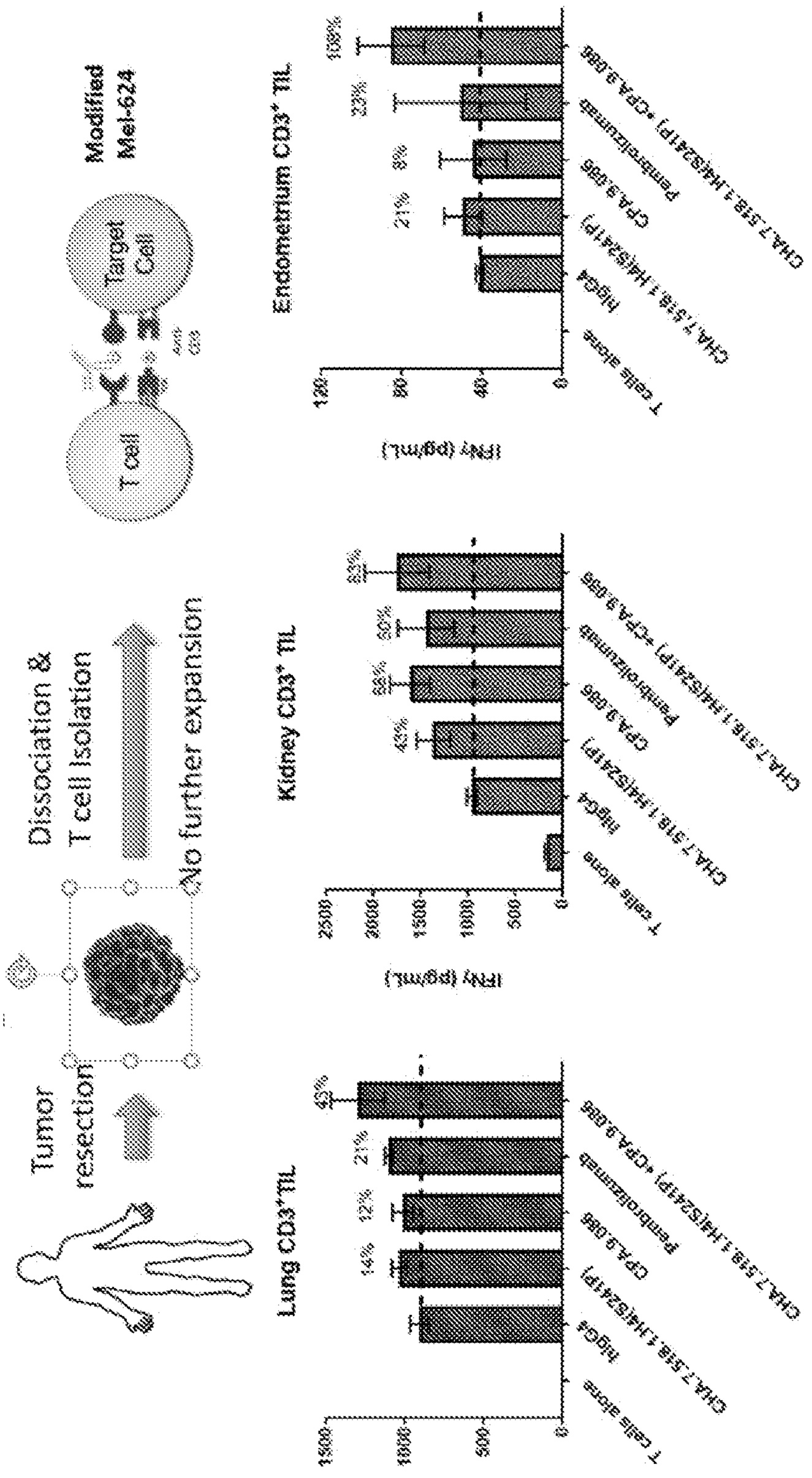

Modified Mel-624
Dissociation & T cell Isolation
No further expansion
Tumor resection
Target Cell
T cell
Endometrium CD3+ TIL
IFNγ (pg/mL)
Kidney CD3+ TIL
Lung CD3+TIL
T cells alone
NIgG4
CHA.7.518.1.H4(S)24.1P)
CPA.9.086
Pembrolizumab
CHA.7.518.1.H4(S)24.1P) +CPA.9.086

Figure 53

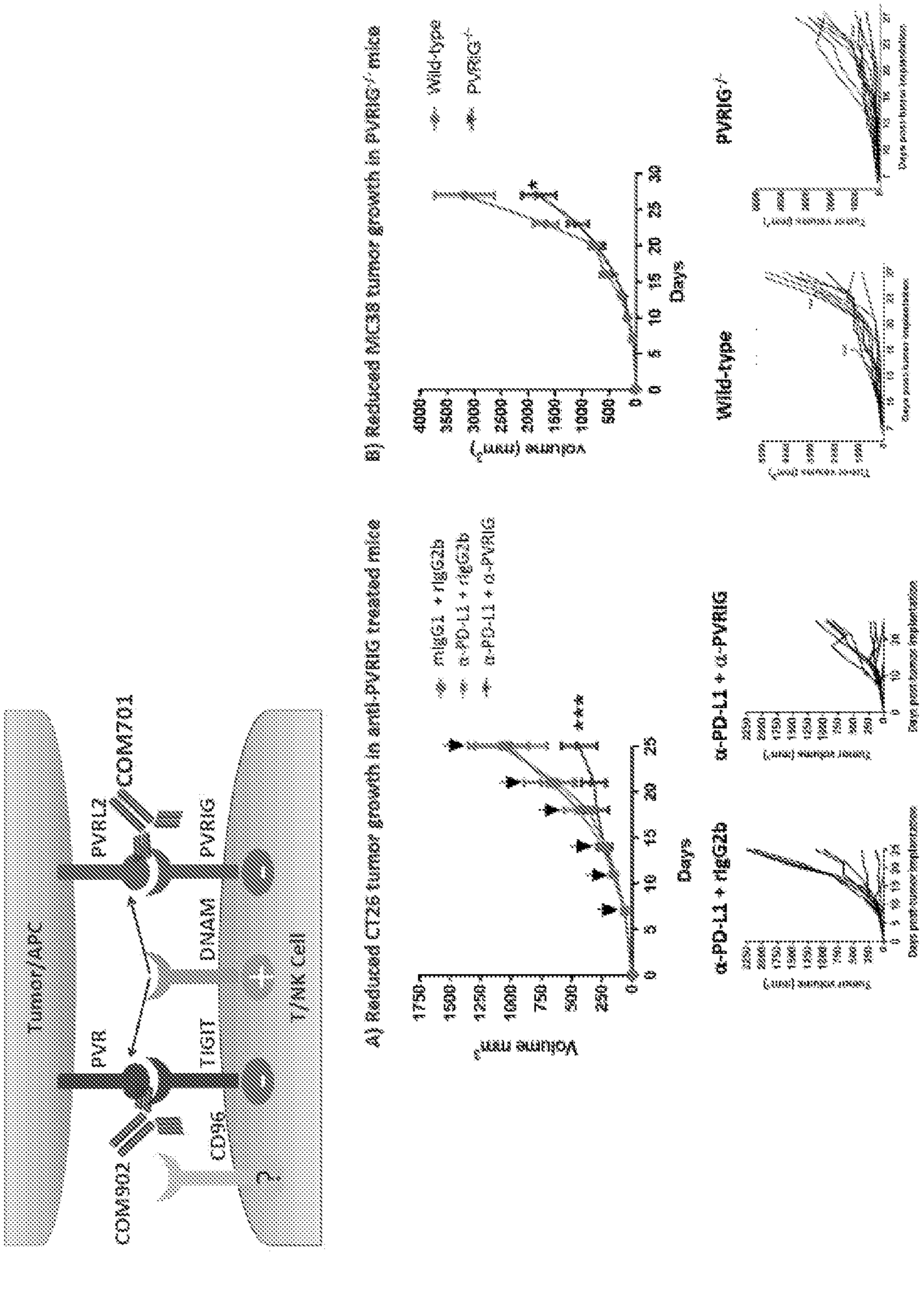

PVRL2
COM701
PVRIG
DNAM
TIGIT
CD96
PVR
COM902
Tumor/APC
T/NK Cell
?
Reduced MC38 tumor growth in PVRIG-/- mice
Wild-type
PVRIG-/-
Volume (mm3)
Days
Wild-type
PVRIG-/-
Reduced CT26 tumor growth in anti-PVRIG treated mice
mIgG1 + rIgG2b
α-PD-L1 + rIgG2b
α-PD-L1 + α-PVRIG
***
Days
α-PD-L1 + rIgG2b
α-PD-L1 + α-PVRIG
Volume mm3
Days post tumor implantation

Figure 54

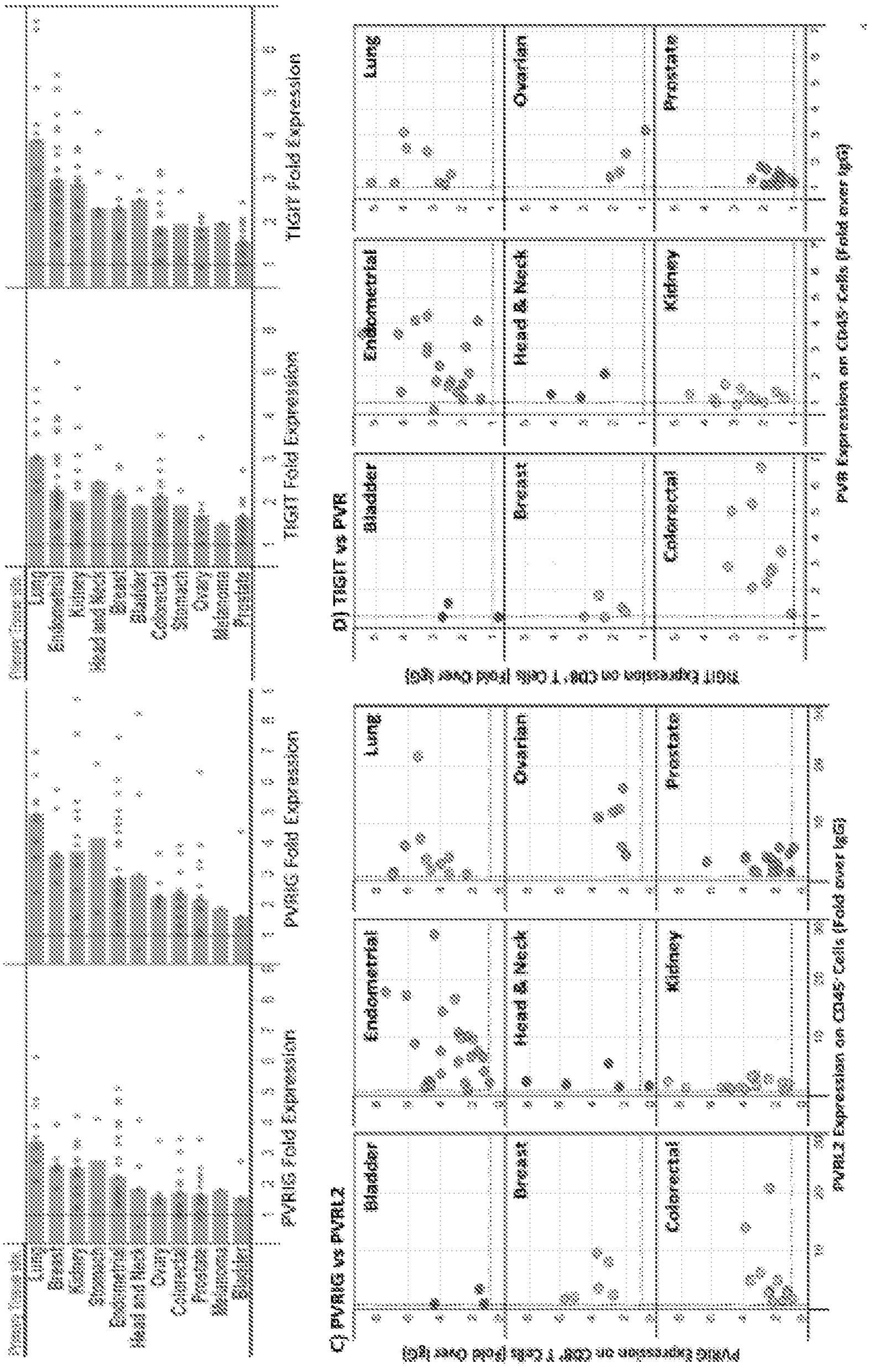

B) TIGIT
CD4+ T cells
CD8+ T cells
Tissue Specific
Lung
Endometrial
Kidney
Head and Neck
Breast
Bladder
Colorectal
Stomach
Ovary
Melanoma
Prostate
TIGIT Fold Expression
D) TIGIT vs PVR
Bladder
Endometrial
Breast
Head & Neck
Colorectal
Kidney
Lung
Ovarian
Prostate
PVR Expression on CD45- Cells (Fold over IgG)
A) PVRIG
PVRIG Fold Expression
C) PVRIG vs PVRL2
PVRL2 Expression on CD45- Cells (Fold over IgG)

Figure 55

Figure 56

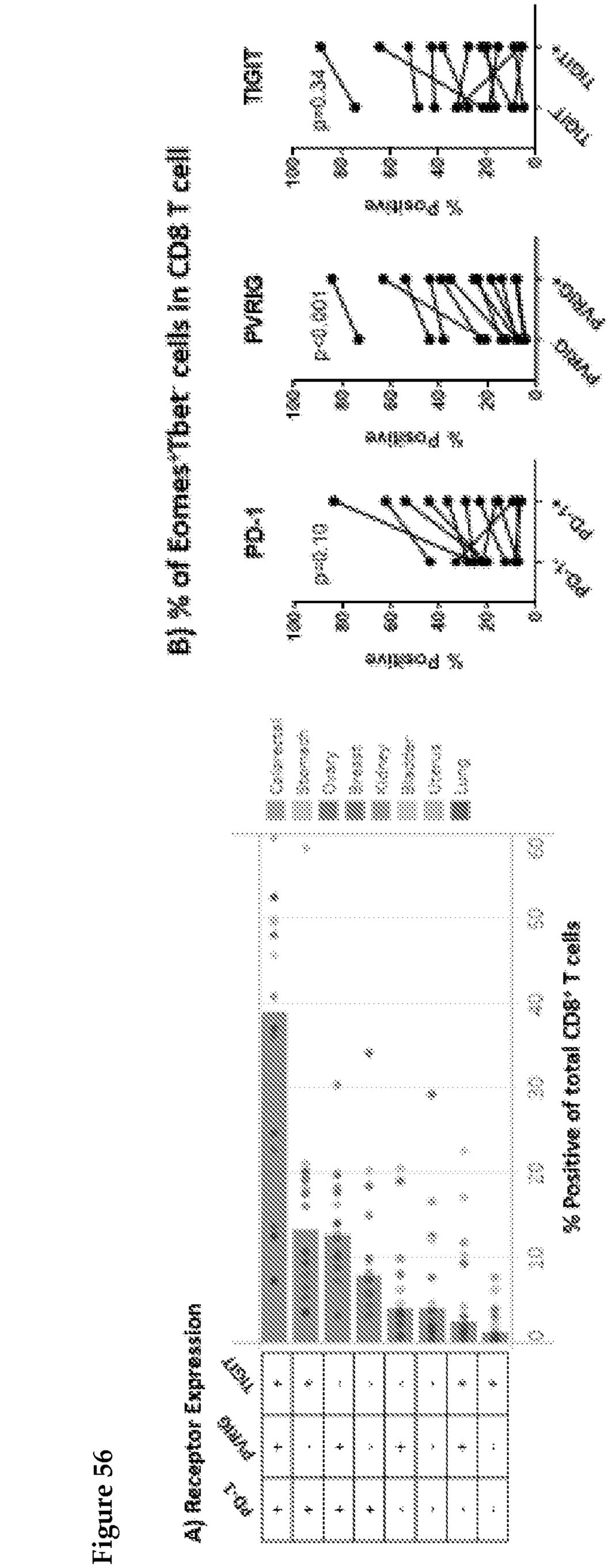
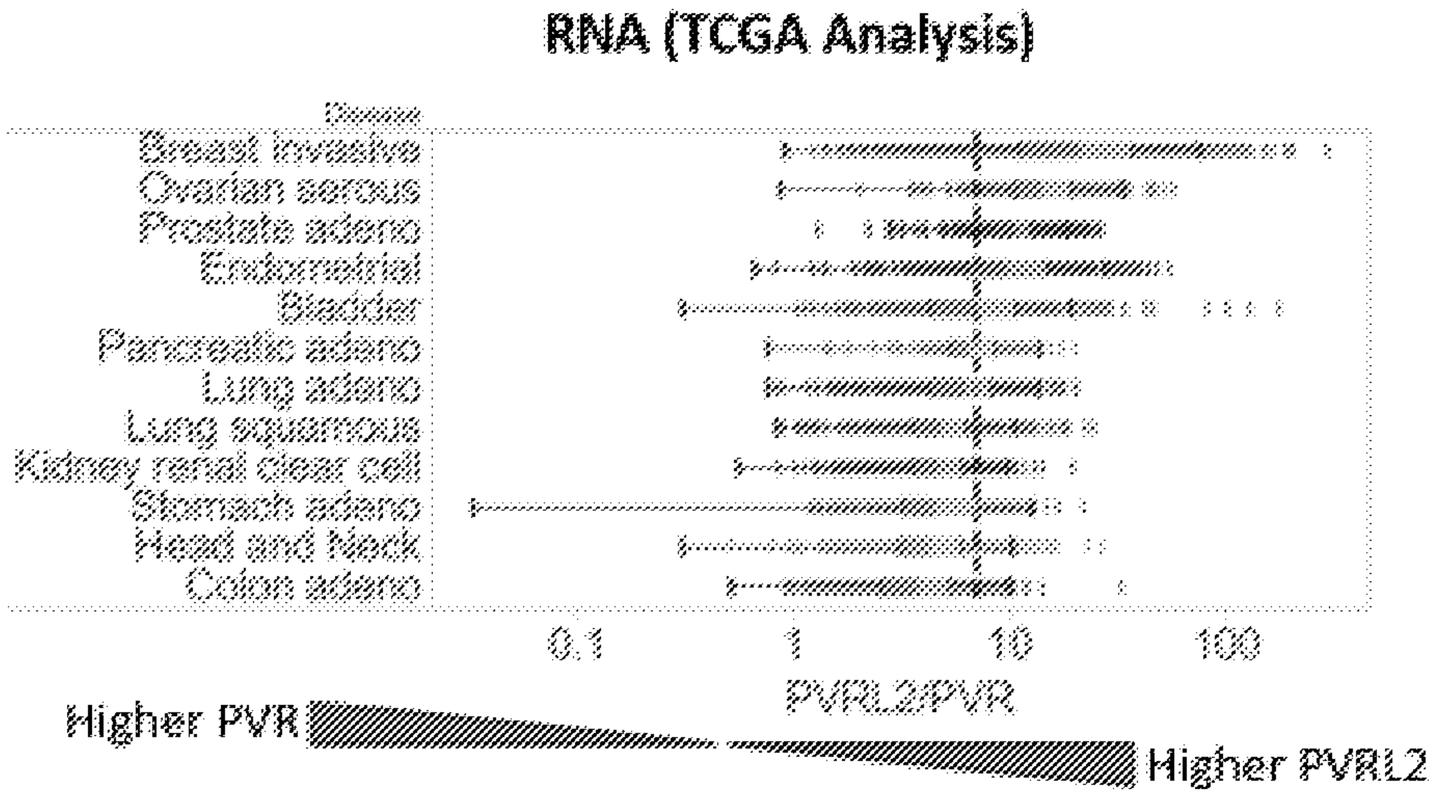
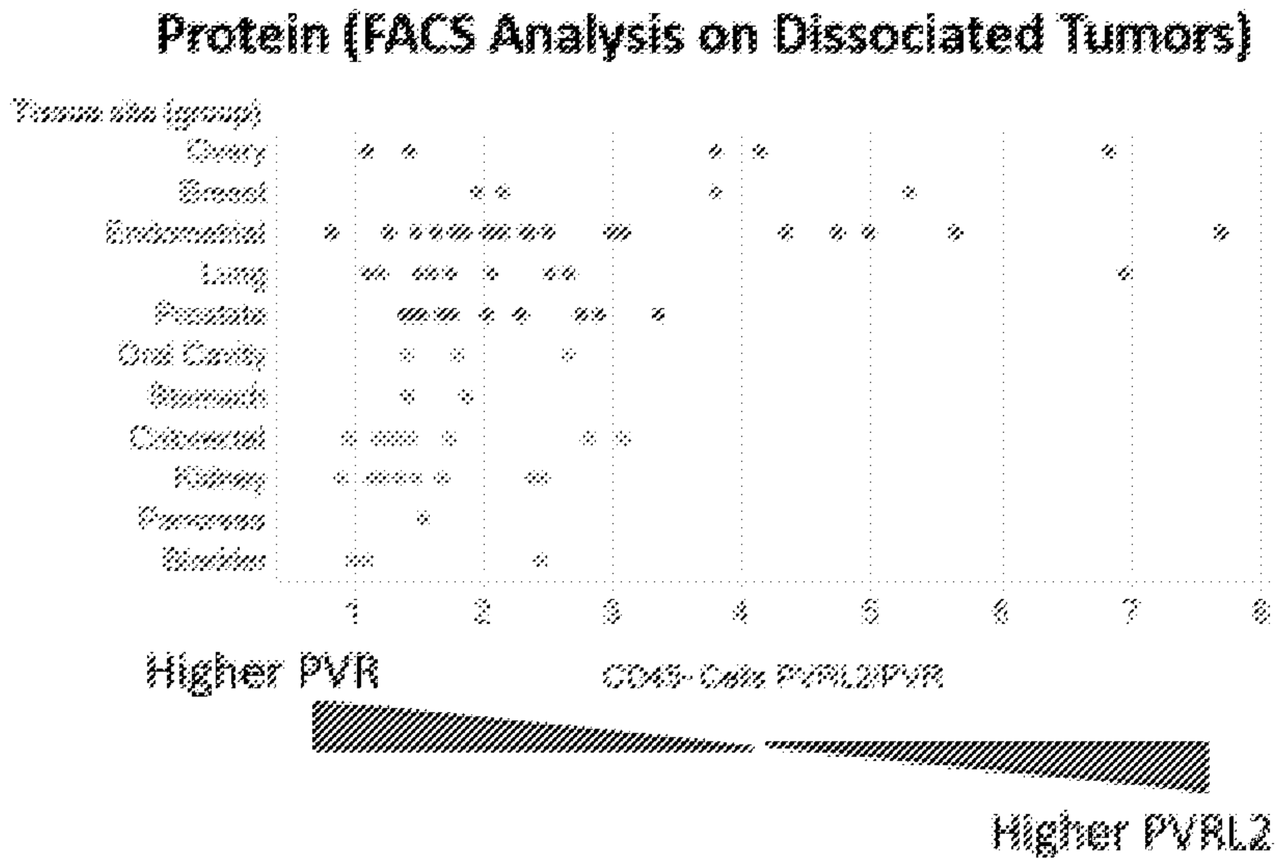

B) % of Eomes+Tbet+ cells in CD8+ T cell
TIGIT
p=0.34
TIGIT+
TIGIT-
% Positive
100
80
60
40
20
0
PD-1
p<0.19
PD-1+
PD-1-
PVRIG
p<0.001
PVRIG+
PVRIG-
A) Receptor Expression
PD-1
PVRIG
TIGIT
% Positive of total CD8+ T cells
Colorectal
Stomach
Ovary
Breast
Kidney
Bladder
Uterus
Lung
C) Receptor Expression
% Eomes+ Tbet+ of each PD1, PVRIG, TIGIT-expressing subset

Figure 57


RNA (TCGA Analysis)
Breast invasive
Ovarian serous
Prostate adeno
Endometrial
Bladder
Pancreatic adeno
Lung adeno
Lung squamous
Kidney renal clear cell
Stomach adeno
Head and Neck
Colon adeno
0.1
1
10
100
PVRL2/PVR
Higher PVR
Higher PVRL2


Protein (FACS Analysis on Dissociated Tumors)
Ovary
Breast
Endometrial
Lung
Prostate
Oral Cavity
Stomach
Colorectal
Kidney
Pancreas
Bladder
1
2
3
4
5
6
7
8
CD45- Cells PVRL2/PVR
Higher PVR
Higher PVRL2

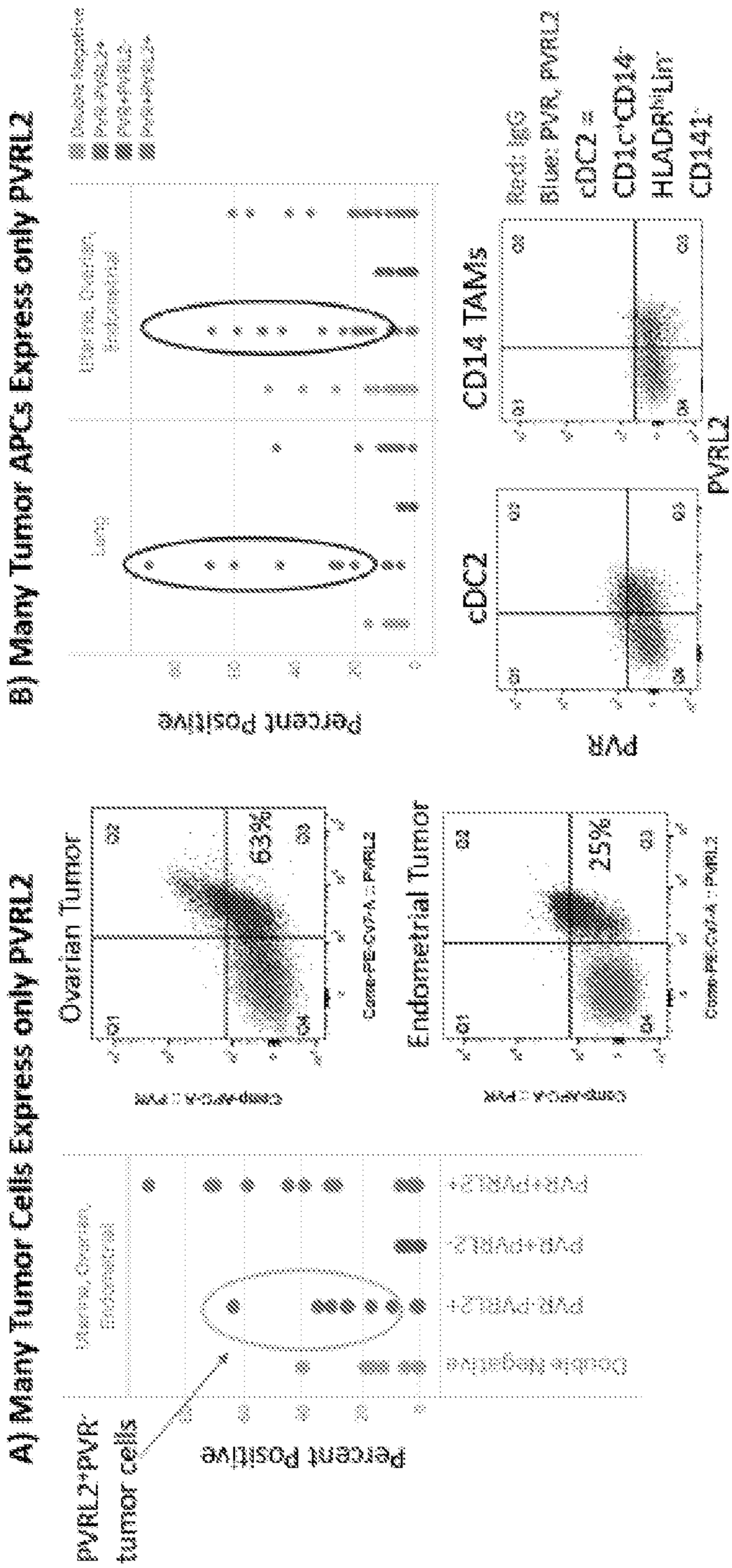

A) Many Tumor APCs Express only PVRL2
Percent Positive
PVRL2+ tumor cells
Double Negative
PVR+PVRL2+
PVR-PVRL2+
PVR+PVRL2-
Ovarian Tumor
Endometrial Tumor
63%
25%
cDC2
CD14 TAMs
B) Many Tumor APCs Express only PVRL2
Percent Positive
PVR
PVRL2
Double Negative
cDC2 =
CD1c+CD14-
HLADR^hiLin-
CD141-

Figure 58

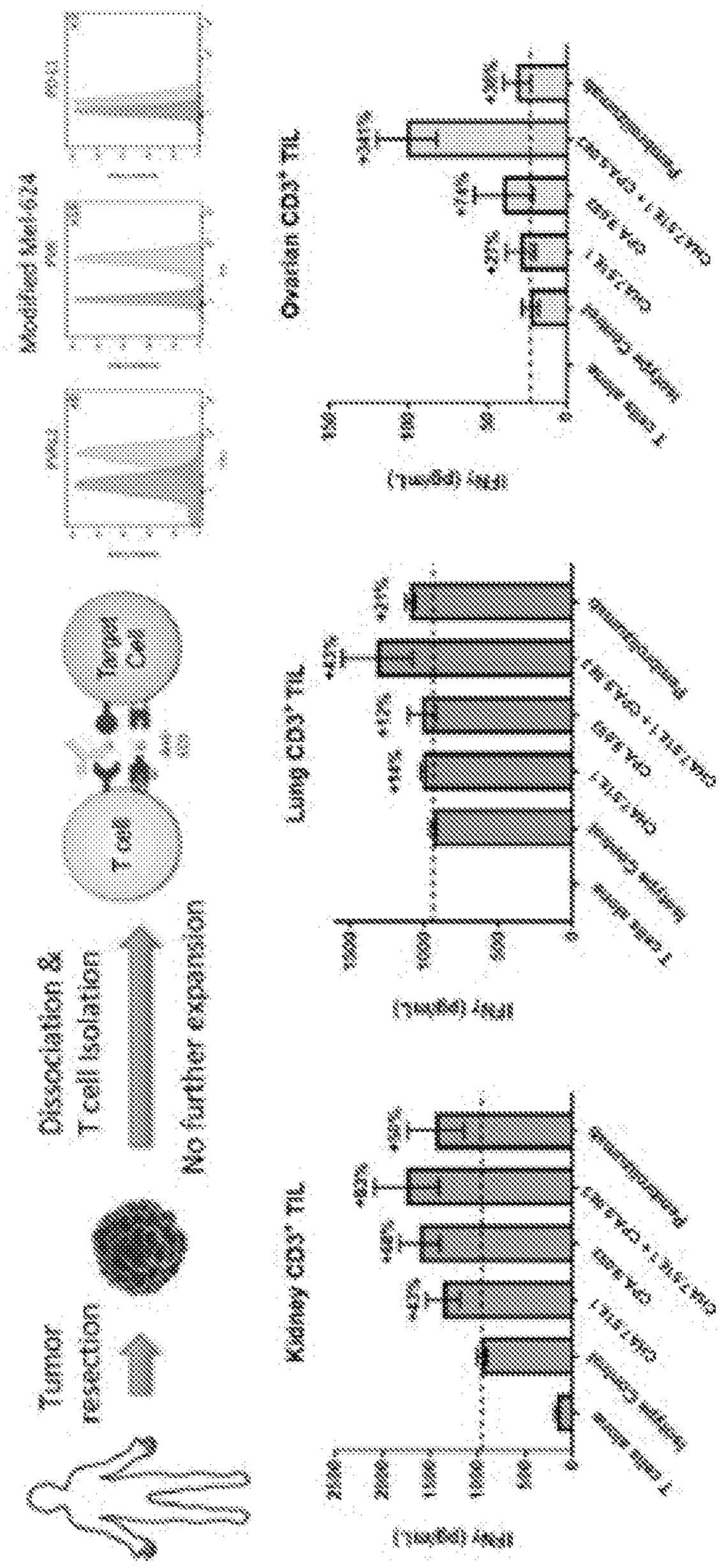
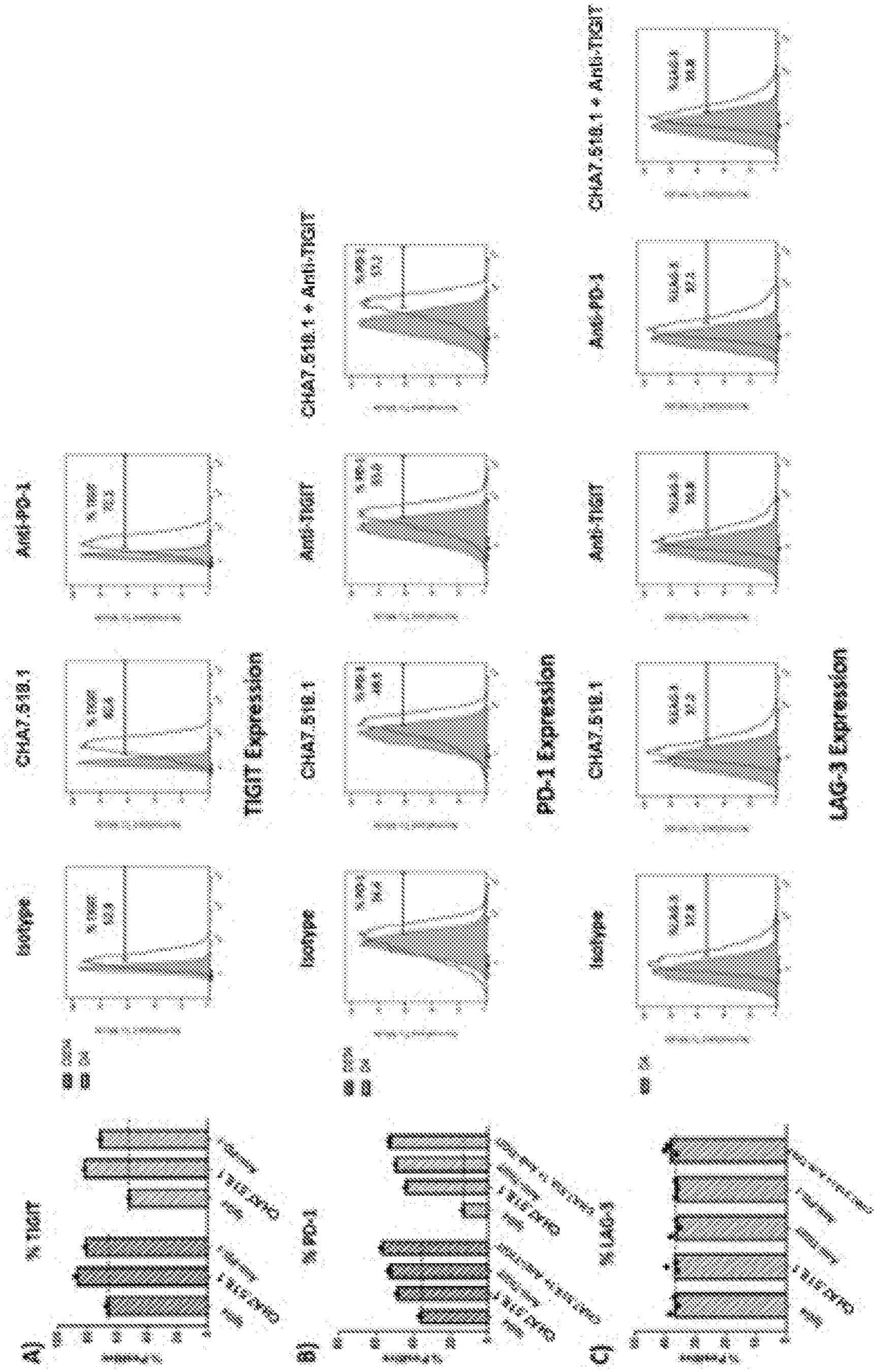

Tumor resection
Dissociation &
T cell isolation
No further expansion
T cells
Tumor
Lung CD3+ TIL
Kidney CD3+ TIL
Effector cells
Target cells

Figure 59


Anti-PD-1
CHA7.518.1
Anti-TIGIT
Isotype
CHA7.518.1 + Anti-TIGIT
CHA7.518.1 + Anti-PD-1
TIGIT Expression
PD-1 Expression
LAG-3 Expression
% MAX
Mode
22.2
22.6
22.8
22.9
23.1
23.2
23.3
23.4
23.5
23.6
23.7
23.8
23.9
24.0
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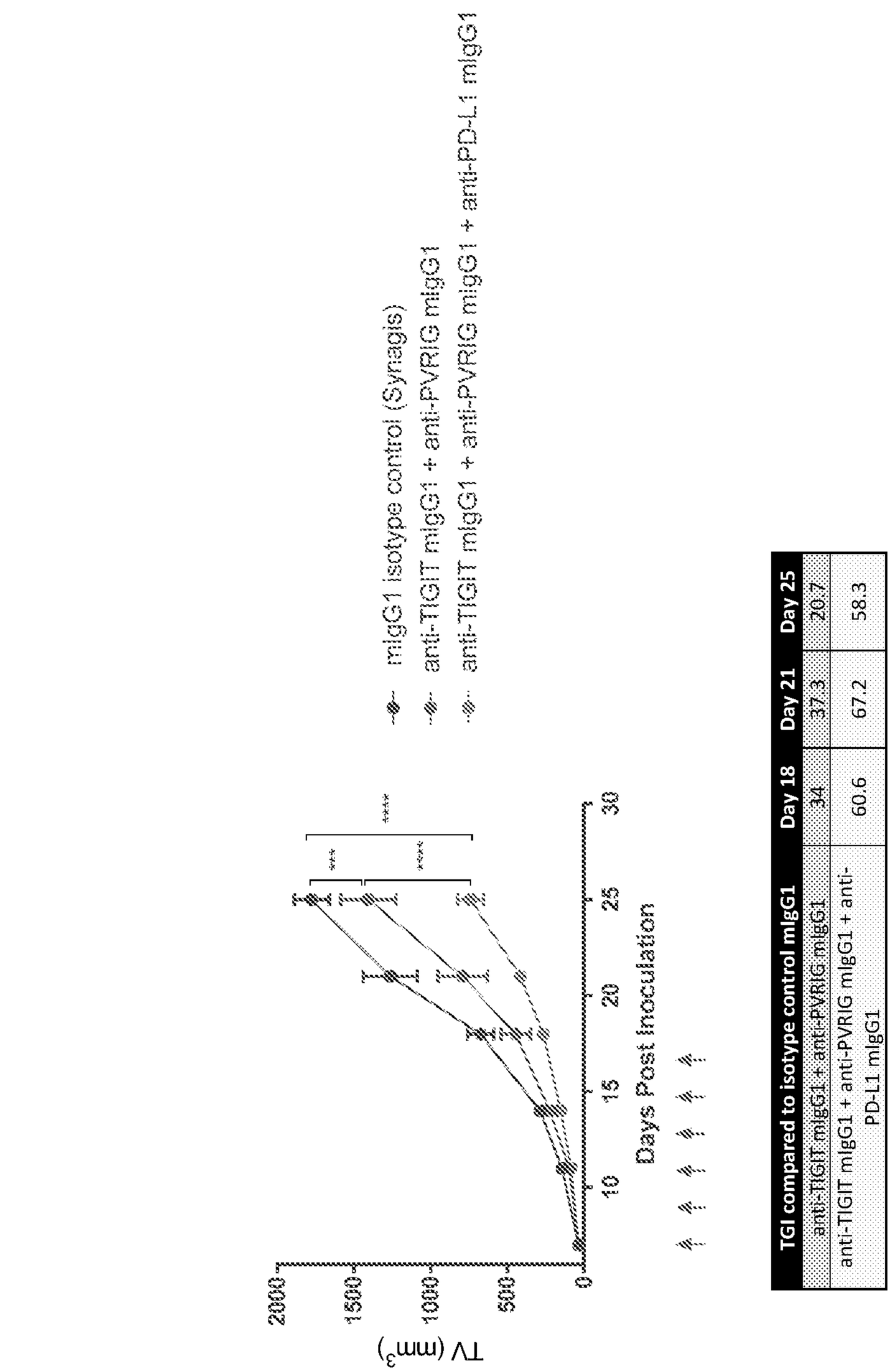
Isotype
CHA7.518.1
TIGIT Expression
PD-1 Expression
LAG-3 Expression

Figure 60



TGI compared to isotype control mIgG1	Day 18	Day 21	Day 25
anti-TIGIT mIgG1 + anti-PVRIG mIgG1	34	37.3	20.7
anti-TIGIT mIgG1 + anti-PVRIG mIgG1 + anti-PD-L1 mIgG1	60.6	67.2	58.3

Figure 61A

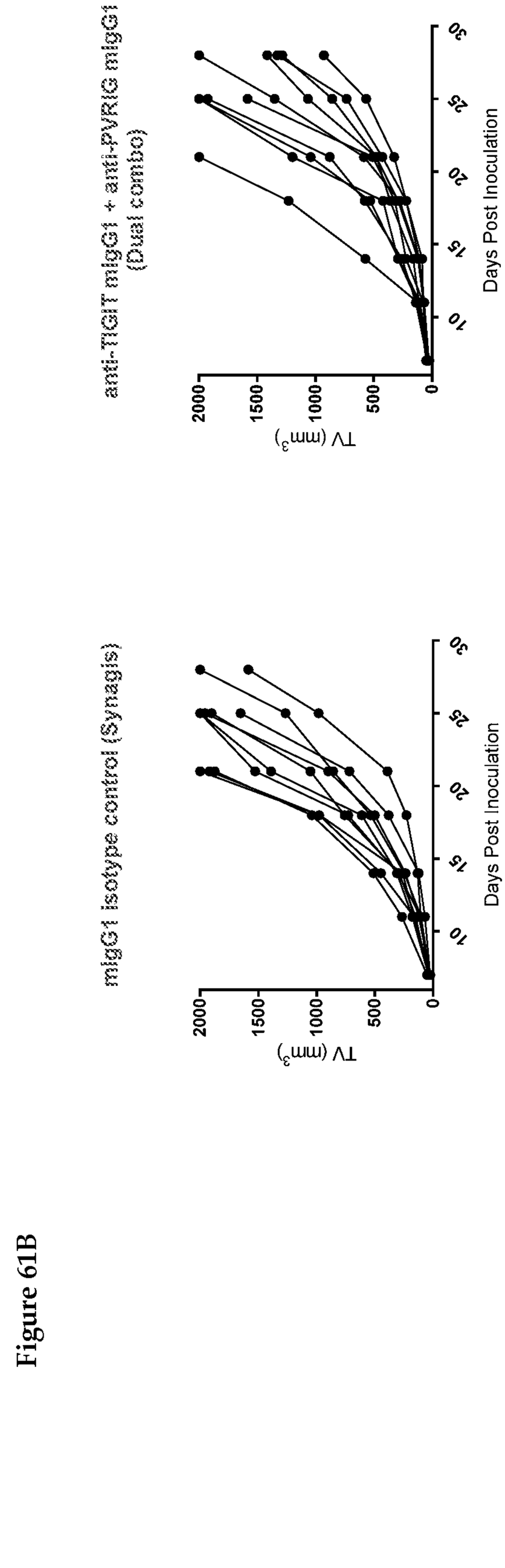

anti-TIGIT mIgG1 + anti-PVRIG mIgG1
(Dual combo)
mIgG1 isotype control (Synagis)
anti-TIGIT mIgG1 + anti-PVRIG mIgG1 + anti-PD-L1
(Triple Combo)
TV (mm3)
Days Post Inoculation
0
500
1000
1500
2000
10
15
20
25
30

Figure 61B

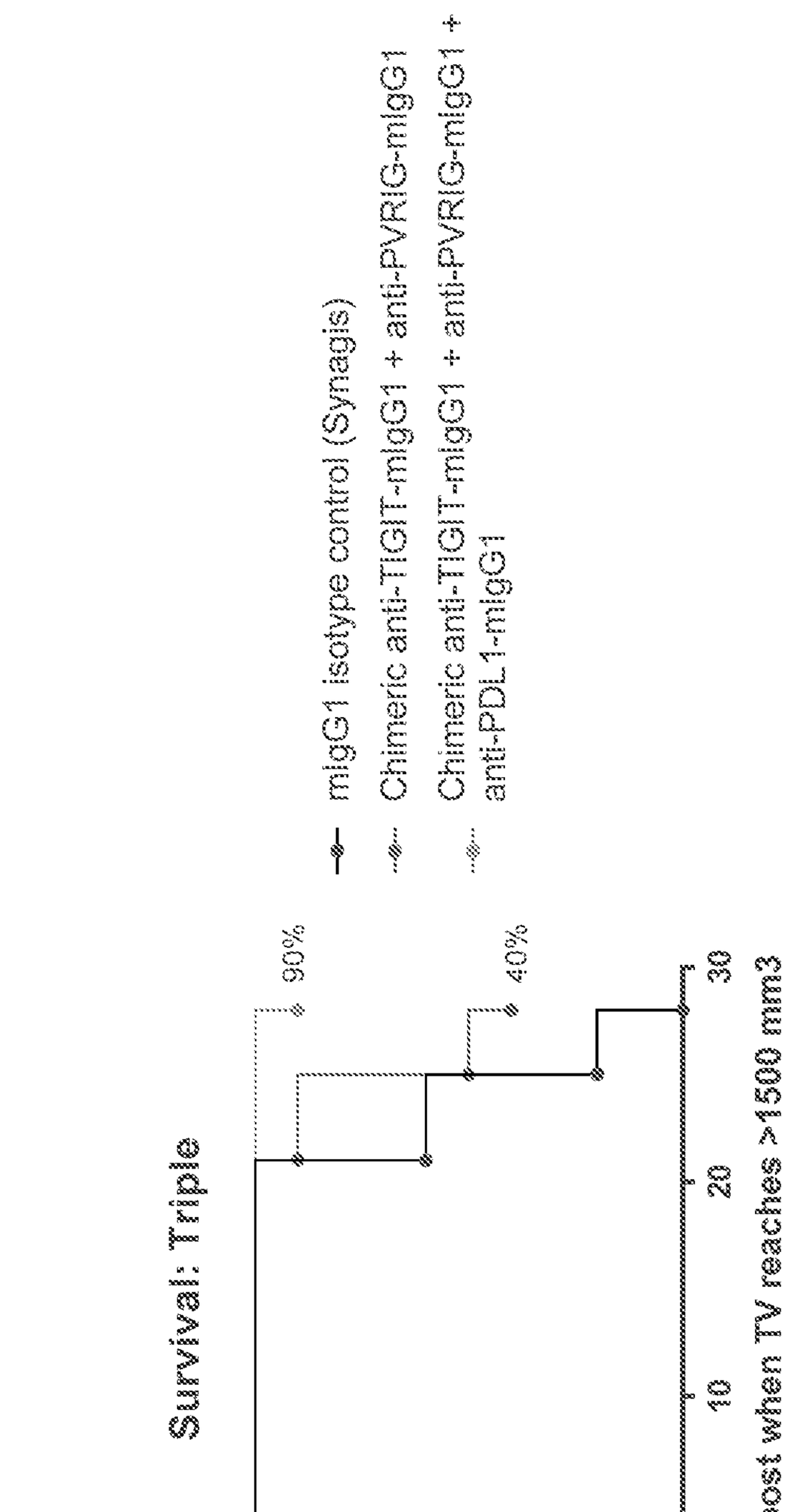

mIgG1 isotype control (Synagis)
Chimeric anti-TIGIT-mIgG1 + anti-PVR-mIgG1
Chimeric anti-TIGIT-mIgG1 + anti-PVR-mIgG1 + anti-PDL1-mIgG1
Survival: Triple
90%
40%
Days post when TV reaches >1500 mm3
0
10
20
30
Percent survival (%)
0
20
40
60
80
100

Figure 61C

Figure 62A

From W02017100541 (Medimmune, LLC; also US20170306025; Durvalumab)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:2 from W02017100541)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKYYV DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQGTLVTVSS	1117
vhCDR1 (SEQ ID NO:3 from W02017100541)	RYWMS	1118
vhCDR2 (SEQ ID NO:4 from W02017100541)	NIKQDGSEKYYVDSVKG	1119
vhCDR3 (SEQ ID NO:5 from W02017100541)	EGGWFGELAFD	1120
Light chain (SEQ ID NO:1 from W02017100541)	EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGTKVEIK	1121
vlCDR1 (SEQ ID NO:6 from W02017100541)	RASQRVSSSYLA	1122
vlCDR2 (SEQ ID NO:7 from W02017100541)	DASSRAT	1123
vlCDR3 (SEQ ID NO:8 from W02017100541)	QQYGSLPWT	1124

Figure 62B

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 62B

From US20170281764 (JN Biosciences)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:34 from US2017281764)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYADS VKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSAASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	1125
Light chain (SEQ ID NO:36 from US2017281764)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYLFTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC	1126

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 62C

From WO2015009856 (GENENTECH, INC. and F. HOFFMANN-LA ROCHE AG)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:23 from WO2015009856)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGST YYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVT VSA	1127
vhCDR1 (SEQ ID NO:17 from WO2015009856)	GFTFSDSWIH	1128
vhCDR2 (SEQ ID NO:18 from WO2015009856)	A WISPYGGSTYYADSVKG	1129
vhCDR3 (SEQ ID NO:19 from WO2015009856)	RHWPGGFDY	1130
Light chain (SEQ ID NO:24 from WO2015009856)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR	1131
vlCDR1 (SEQ ID NO:20 from WO2015009856)	RASQDVSTAVA	1132
vlCDR2 (SEQ ID NO:21 from WO2015009856)	SASFLYS	1133
vlCDR3 (SEQ ID NO:22 from WO2015009856)	QQYLYHPAT	1134

RECTIFIED SHEET (RULE 91) ISA/EP

CA 03064331 2019-11-20

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 62D

From WO2015009856 (GENENTECH, INC. and F. HOFFMANN-LA ROCHE AG)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO: 40 from WO2015009856)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWV A WISPYGG STYY ADSVKGRFTISADTSKNTA YLQMNSLRAEDTA VYYCARRHWPGGFDYWGQG TLVTVSSASTK (SEQ ID N0:40), or	1135
Light chain (SEQ ID NO: from WO2015009856)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTA VA WYQQKPGKAPKLLIYSASFL YSG VPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQYL YHPATFGQGTKVEIKR (SEQ ID N0:24).	1136

From WO2015009856 (GENENTECH, INC. and F. HOFFMANN-LA ROCHE AG)

What	sequence	SEQ ID NO
Heavy chain (SEQ ID NO: 41 from WO2015009856)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGG STYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTA VYYCARRHWPGGFDYWGQG TLVTVSS	1137
Light chain (SEQ ID NO: from WO2015009856)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR	1138

Figure 62E

From US20160222117 (GENENTECH, INC.)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:20 from US20160222117)	EVQLVESCGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGST YYADSVKGRFTISRDTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVT VSA	1139
Heavy chain (SEQ ID NO:23 from US20160222117)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGST YYADSVKGRFTISRDTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVT VSA	1140
Heavy chain (SEQ ID NO:24 from US20160222117)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSGSWIHWVRQAPGKGLEWVAWILPYGGSS YYADSVKGRFTISRDTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVT VSA	1141

From US20160222117 (GENENTECH, INC.)

What	sequence	SEQ ID NO
Light chain (SEQ ID NO:21 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKR	1142
Light chain (SEQ ID NO:26 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYNVPWTFGQGTKVEIKR	1143
Light chain (SEQ ID NO:27 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYAPPWTFGQGTKVEIKR	1144

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Figure 62F

From US20160222117 (GENENTECH, INC.)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:28 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYTVPWTFGQGTKVEIKR	1145
Light chain (SEQ ID NO:29 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQVINTFLAWYQQKPGKAPKLLIYSASTLASGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYTVPRTFGQGTKVEIKR	1146
Light chain (SEQ ID NO:30 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQGYGVPRTFGQGTKVEIKR	1147
Light chain (SEQ ID NO:31 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYLFTPPTFGQGTKVEIKR	1148
Light chain (SEQ ID NO:32 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYFITPTTFGQGTKVEIKR	1149
Light chain (SEQ ID NO:33 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYTPPTFGQGTKVEIKR	1150
Light chain (SEQ ID NO:34 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQFFYTPPTFGQGTKVEIKR	1151

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Figure 62G

From US20160222117 (GENENTECH, INC.)

What	sequence	SEQ ID NO:
Light chain (SEQ ID NO:35 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSLFTPPTFGQGTKVEIKR	1152
Light chain (SEQ ID NO:36 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSLYTPPTFGQGTKVEIKR	1153
Light chain (SEQ ID NO:37 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSWYHPPTFGQGTKVEIKR	1154
Light chain (SEQ ID NO:38 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYFYIPPTFGQGTKVEIKR	1155
Light chain (SEQ ID NO:39 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYWYTPYTFGQGTKVEIKR	1156
Light chain (SEQ ID NO:40 from US20160222117)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSYFIPPTFGQGTKVEIKR	1157

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Figure 62H

From WO2013079174 (Merck; Avelumab or A09-246- 2)

What	sequence	SEQ ID NO:
Heavy chain (SEQ ID NO:32 from WO2013079174)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYADT VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	1158
Light chain (SEQ ID NO: from WO2013079174)	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNR FSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTGTKVTVLGQPKANPTVTLFPPSSEE LQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQW KSHRSYSCQVTHEGSTVEKTVAPTECS	1159

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Figure 62I

From US8217149 (Hoffman La Roche; Atezolizumab)

What	sequence	SEQ ID NO:
Heavy chain (VH) (SEQ ID NO:20 from US8217149)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSA	1160
Light chain (VL) (SEQ ID NO:21 from US8217149)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKWYSASFLYSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYC QQYLYH PATFGQGTKVEIKR	1161

Atezolizumab (alternate sequence))

What	sequence	SEQ ID NO:
Heavy chain (from IMGT database or DrugBank database)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYYA DSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	1162
Light chain (from IMGT database or DrugBank database)	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC	1163

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Figure 63A

CPA.7.001

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCAREEVSSPYGMDVWGQGTTVTVSS	1164
vhCDR1	GGTFSSYA	1165
vhCDR2	IIPIFGTA	1166
vhCDR3	AREEVSSPYGMDV	1167
Full length HC	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYME LSSLRSEDTAVYYCAREEVSSPYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1168
Variable light (vl) domain	QAVVTQEPSLTVSPGGTVTLTCGTSTGAVTSGHYPYWFQQKPGQAPKTLIYDTGNKHSWTPARFSGSLLGGKAALTLSGAQPE DEADYYCLLSYSGASWVFGGGTKLTVLG	1169
vlCDR1	TGAVTSGHY	1170
vlCDR2	DTG	1171
vlCDR3	LLSYSGASWV	1172
Full length light chain	QAVVTQEPSLTVSPGGTVTLTCGTSTGAVTSGHYPYWFQQKPGQAPKTLIYDTGNKHSWTPARFSGSLLGGKAALTLSGAQPE DEADYYCLLSYSGASWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1173

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Figure 63B
CPA.7.003

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKVSGFSLSHFSMHWVRQVPGKGLEWLGGFDPEEGGTIPAQKFQGRLTMTEDTST ETAYMELSSLRSEDTAVYYCATGIWYSSGWPVDYWGPGTLVTVSS	1174
vhCDR1	GFSLSHFS	1175
vhCDR2	FDPEEGGT	1176
vhCDR3	ATGIWYSSGWPVDY	1177
Full length HC	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADKSTST AYMELSSLRSEDTAVYYCARGPWYYDSSGYSSYAYYMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1178
Variable light (vl) domain	DVVMTQSPLSLPVTPGGPASISCRSSQSLLDSSGYNYVDWYLQKPGQSPQLLISLGSDRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGIYYCMQALQTPITFGQGTRLEIKR	1179
vlCDR1	QSLLDSSGYNY	1180
vlCDR2	LGS	1181
vlCDR3	MQALQTPIT	1182
Full length light chain	DVVMTQSPLSLPVTPGGPASISCRSSQSLLDSSGYNYVDWYLQKPGQSPQLLISLGSDRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGIYYCMQALQTPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1183

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Figure 63C
CPA.7.004

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATVSRVRGVINYYYYMDV WGKGTTVTVSS	1184
vhCDR1	GYTLTELS	1185
vhCDR2	FDPEDGET	1186
vhCDR3	ATVSRVRGVINYYYYMDV	1187
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATVSRVRGVINYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1188
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKR	1189
vlCDR1	QSLLYRNGNNY	1190
vlCDR2	LGS	1191
vlCDR3	MQALQTPPT	1192
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1193

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Figure 63D
CPA.7.006

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVRRPGSSVRVSCKPSGGTFGTYAFTWVRQAPGQGLEWMGGITPISATINRAQNLQDRLTITADESTT TVHMDLTSLRSEDTAVYYCARGFEYSDGLLDDWGQGTLVTVSS	1194
vhCDR1	GGTFGTYA	1195
vhCDR2	ITPISATI	1196
vhCDR3	ARGFEYSDGLLDD	1197
Full length HC	QVQLVQSGAEVRRPGSSVRVSCKPSGGTFGTYAFTWVRQAPGQGLEWMGGITPISATINRAQNLQDRLTITADESTT TVHMDLTSLRSEDTAVYYCARGFEYSDGLLDDWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1198
Variable light (vl) domain	DIVMTQTPLSLPVIPGEPASISCRSSQSLFYSDDGNTYLDWYLQKPGQSPQLLIYRLSHRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQHMEFPLTFGGGTKVEIKR	1199
vlCDR1	QSLFYSDDGNTY	1200
vlCDR2	RLS	1201
vlCDR3	MQHMEFPLT	1202
Full length light chain	DIVMTQTPLSLPVIPGEPASISCRSSQSLFYSDDGNTYLDWYLQKPGQSPQLLIYRLSHRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQHMEFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1203

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Figure 63E
CPA.7.008

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQESGPGLVKPSGTLSLTCVVSSGSISSTNWWTWVRQPPGKGLEWIGEIYHSGSTSYNSSLKSRVTISEDKSKNQIS LRLSSVTAADTAVYYCARVGPAAIYYWGQGTLVTVSS	1204
vhCDR1	SGSISSTNW	1205
vhCDR2	IYHSGST	1206
vhCDR3	ARVGPAAIYY	1207
Full length HC	QVQLQESGPGLVKPSGTLSLTCVVSSGSISSTNWWTWVRQPPGKGLEWIGEIYHSGSTSYNSSLKSRVTISEDKSKNQIS LRLSSVTAADTAVYYCARVGPAAIYYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1208
Variable light (vl) domain	QAGLTQPPSVSKGLRQTATLTCTGNSNNVGYEGAAWLQQHQGHAPKLLLYRNNNRPSGISKRFSASRSGNTASLTITG LQPEDEADYYCSAWDSSLNAVVFGGGTQLTVLG	1209
vlCDR1	SNNVGYEG	1210
vlCDR2	RNN	1211
vlCDR3	SAWDSSLNAVV	1212
Full length light chain	QAGLTQPPSVSKGLRQTATLTCTGNSNNVGYEGAAWLQQHQGHAPKLLLYRNNNRPSGISKRFSASRSGNTASLTITG LQPEDEADYYCSAWDSSLNAVVFGGGTQLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1213

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Figure 63F
CPA.7.009

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATAKPGIAVAGQNYYYYYMDVWGKGTTVTVSS	1214
vhCDR1	GYTLTELS	1215
vhCDR2	FDPEDGET	1216
vhCDR3	ATAKPGIAVAGQNYYYYYMDV	1217
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATAKPGIAVAGQNYYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1218
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKR	1219
vlCDR1	QSLLYRNGNNY	1220
vlCDR2	LGS	1221
vlCDR3	MQALQTPPT	1222
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1223

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Figure 63G
CPA.7.010

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGLVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCASSPIGYSYGYWGGMDVWGQGTTVTVSS	1224
vhCDR1	GFTFSSYA	1225
vhCDR2	ISYDGSNK	1226
vhCDR3	ASSPIGYSYGYWGGMDV	1227
Full length HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCASSPIGYSYGYWGGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1228
Variable light (vl) domain	QAVLTQPASLSASPGASASLTCTLRSGIDVRTNKIFWYQVKPGSPPQHLLTFQSDSDKQQGSGVPSRFSGSKDASANA GILIISGLQSEDEADYYCLIWHTSGWVFGGGTQLTVLG	1229
vlCDR1	SGIDVRTNK	1230
vlCDR2	FQSDSDK	1231
vlCDR3	LIWHTSGWV	1232
Full length light chain	QAVLTQPASLSASPGASASLTCTLRSGIDVRTNKIFWYQVKPGSPPQHLLTFQSDSDKQQGSGVPSRFSGSKDASANA GILIISGLQSEDEADYYCLIWHTSGWVFGGGTQLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1233

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Figure 63H
CPA.7.011

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGPAAAGVGYYYYMDV WGKGTTVTVSS	1234
vhCDR1	GYTLTELS	1235
vhCDR2	FDPEDGET	1236
vhCDR3	ATGPAAAGVGYYYYMDV	1237
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGPAAAGVGYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1238
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKVEIKR	1239
vlCDR1	QSLLYRNGYNY	1240
vlCDR2	LGS	1241
vlCDR3	MQALQTPPT	1242
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1243

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63I
CPA7.012

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCARDVMVYCSSTSCYFYGMDVWGQGTTVTVSS	1244
vhCDR1	GFTFSSYA	1245
vhCDR2	ISYDGSNK	1246
vhCDR3	ARDVMVYCSSTSCYFYGMDV	1247
Full length HC	EVQLVETGGGLIQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCARDVMVYCSSTSCYFYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1248
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTVTCQASQDIRDYLNWYQKKPGKAPKLLIYDASNLEAGVPSRFSGSGSGTDFTFTISGLQ PEDVATYYCQQFENLPITFGQGTRLEIKR	1249
vlCDR1	QDIRDY	1250
vlCDR2	DAS	1251
vlCDR3	QQFENLPIT	1252
Full length light chain	DIQMTQSPSSLSASVGDRVTVTCQASQDIRDYLNWYQKKPGKAPKLLIYDASNLEAGVPSRFSGSGSGTDFTFTISGLQ PEDVATYYCQQFENLPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1253

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63J
CPA.7.013

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGGYSSGFNYYYYYMDV WGKGTTVTVSS	1254
vhCDR1	GYTLTELS	1255
vhCDR2	FDPEDGET	1256
vhCDR3	ATGGYSSGFNYYYYYMDV	1257
Full length HC	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGGYSSGFNYYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1258
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKR	1259
vlCDR1	QSLLYRNGNNY	1260
vlCDR2	LGS	1261
vlCDR3	MQALQTPPT	1262
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGNNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1263

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63K
CPA.7.014

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVTTYYYYGMDVWGQGTTVTVSS	1264
vhCDR1	GYTLTELS	1265
vhCDR2	FDPEDGET	1266
vhCDR3	ATGVTTYYYYGMDV	1267
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVTTYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1268
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGNNFLDWYLQKPGQSPRLLISLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGIYYCMQALQTPPTFGQGTKVEIKR	1269
vlCDR1	QSLLYSNGNNF	1270
vlCDR2	LGS	1271
vlCDR3	MQALQTPPT	1272
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGNNFLDWYLQKPGQSPRLLISLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGIYYCMQALQTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1273

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63L
CPA.7.015

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QITLKESGGGVVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCARDLFDFWWDGMDVWGQGTTVTVSS	1274
vhCDR1	GFTFSSYG	1275
vhCDR2	IRYDGSNK	1276
vhCDR3	ARDLFDFWWDGMDV	1277
Full length HC	QITLKESGGGVVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFIRYDGSNKYYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCARDLFDFWWDGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1278
Variable light (vl) domain	EIVLTQSPGTLSLSPGEKATLSCRVSQSVSSMYLAWYQQKPGQAPRLLIYGASYRATGIPDRFSGSGSGTDFNLTISRLEP EDFAVYYCQQYVSSPMYTFGLGTKLEIKR	1279
vlCDR1	QSVSSMY	1280
vlCDR2	GAS	1281
vlCDR3	QQYVSSPMYT	1282
Full length light chain	EIVLTQSPGTLSLSPGEKATLSCRVSQSVSSMYLAWYQQKPGQAPRLLIYGASYRATGIPDRFSGSGSGTDFNLTISRLEP EDFAVYYCQQYVSSPMYTFGLGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1283

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63M
CPA.7.017

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFNNYGISWVRQAPGKGLEWMGQIIPLFGTTKYAQKFQGRVTIAADEPTS TAYMELGSLRSEDTAIYYCARDRMAADGMAVFDYWGQGTLVTVSS	1284
vhCDR1	GGTFNNYG	1285
vhCDR2	IIPLFGTT	1286
vhCDR3	ARDRMAADGMAVFDY	1287
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFNNYGISWVRQAPGKGLEWMGQIIPLFGTTKYAQKFQGRVTIAADEPTS TAYMELGSLRSEDTAIYYCARDRMAADGMAVFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1288
Variable light (vl) domain	QSVLTQPPSVSGTPGQKVIISCSGSSSNIGRHFVFWYQQLPGTAPKLLIYKNDERPSGVPDRFSGSKSGTSASLAVSGLRS EDEADYYCSSWDAALNGVVFGGGTKLTVLG	1289
vlCDR1	SSNIGRHF	1290
vlCDR2	KND	1291
vlCDR3	SSWDAALNGVV	1292
Full length light chain	QSVLTQPPSVSGTPGQKVIISCSGSSSNIGRHFVFWYQQLPGTAPKLLIYKNDERPSGVPDRFSGSKSGTSASLAVSGLRS EDEADYYCSSWDAALNGVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPV KAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1293

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63N
CPA.7.018

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEVPMVRGARRYYYYMDVWGKGTTVTVSS	1294
vhCDR1	GYTLTELS	1295
vhCDR2	FDPEDGET	1296
vhCDR3	ATEVPMVRGARRYYYYMDV	1297
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEVPMVRGARRYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1298
Variable light (vl) domain	DVVMTQSPLFLAVTPGEPASISCRSSQTLLYINENNYLDWYVQKPGQSPQLLIYLGSTRASGVPDRFSGGGSGTDFTLTI SRVEAEDVGLYYCMQGLQTPPTFGQGTRLEIKR	1299
vlCDR1	QTLLYINENNY	1300
vlCDR2	LGS	1301
vlCDR3	MQGLQTPPT	1302
Full length light chain	DVVMTQSPLFLAVTPGEPASISCRSSQTLLYINENNYLDWYVQKPGQSPQLLIYLGSTRASGVPDRFSGGGSGTDFTLTI SRVEAEDVGLYYCMQGLQTPPTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1303

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 630
CPA.7.019

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQESGPGLVKSSETLSLTCSVSGGSISNSNYYWGWIRQPPGKGLEWIGGIYYSGSTYYNPSLESRVTISEDTSKNQIS LKLSSVTAADTAVYYCARGAWELSLGDWFDPWGPGTLVTVSS	1304
vhCDR1	GGSISNSNYY	1305
vhCDR2	IYYSGST	1306
vhCDR3	ARGAWELSLGDWFDP	1307
Full length HC	QVQLQESGPGLVKSSETLSLTCSVSGGSISNSNYYWGWIRQPPGKGLEWIGGIYYSGSTYYNPSLESRVTISEDTSKNQIS LKLSSVTAADTAVYYCARGAWELSLGDWFDPWGPGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1308
Variable light (vl) domain	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDIQWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSRSGTSASLAITGL QAEDEADYYCQSYDSSLSVYVVFGGGTQLTVLG	1309
vlCDR1	SSNIGAGYD	1310
vlCDR2	GNN	1311
vlCDR3	QSYDSSLSVYVV	1312
Full length light chain	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDIQWYQQLPGTAPKLLIYGNNNRPSGVPDRFSGSRSGTSASLAITGL QAEDEADYYCQSYDSSLSVYVVFGGGTQLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1313

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63P
CPA.7.021

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVESGGGVVKPGGSLRLSCAASGFTFGTSSMNWVRQAPGKGLEWVAVISFDGTEIHYADSVKGRFTISRDNSKST VFLQMNSLRPDDTALYYCAKGSGNIYFYSGMDVWGQGTTVTVSS	1314
vhCDR1	GFTFGTSS	1315
vhCDR2	ISFDGTEI	1316
vhCDR3	AKGSGNIYFYSGMDV	1317
Full length HC	EVQLVESGGGVVKPGGSLRLSCAASGFTFGTSSMNWVRQAPGKGLEWVAVISFDGTEIHYADSVKGRFTISRDNSKST VFLQMNSLRPDDTALYYCAKGSGNIYFYSGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1318
Variable light (vl) domain	DIQMTQSPSTLSASVGDRVTITCRAGQSISGWLAWFQQKPGKAPNLLIYETSTLESGVPSRFSGSGSGTEYTLTISSLQP DDFATYYCQQYYSYPLTFGQGTKVEIKR	1319
vlCDR1	QSISGW	1320
vlCDR2	ETS	1321
vlCDR3	QQYYSYPLT	1322
Full length light chain	DIQMTQSPSTLSASVGDRVTITCRAGQSISGWLAWFQQKPGKAPNLLIYETSTLESGVPSRFSGSGSGTEYTLTISSLQP DDFATYYCQQYYSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1323

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63Q
CAP.7.022

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVPAAIGVYYYYYYMDVWGKGTTVTVSS	1324
vhCDR1	GYTLTELS	1325
vhCDR2	FDPEDGET	1326
vhCDR3	ATGVPAAIGVYYYYYYMDV	1327
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVPAAIGVYYYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1328
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLISLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQSPVTFGGGTKVEIKR	1329
vlCDR1	QSLLYSNGYNY	1330
vlCDR2	LGS	1331
vlCDR3	MQALQSPVT	1332
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQLLISLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQSPVTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1333

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63R
CPA.7.023

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATDSRDGPAARGGYYYYMDVWGQGTTVTVSS	1334
vhCDR1	GYTLTELS	1335
vhCDR2	FDPEDGET	1336
vhCDR3	ATDSRDGPAARGGYYYYMDV	1337
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATDSRDGPAARGGYYYYMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1338
Variable light (vl) domain	DVVMTQSPLSLPVTLGQPASISCRSSQSLLYINGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKVEIKR	1339
vlCDR1	QSLLYINGYNY	1340
vlCDR2	LGS	1341
vlCDR3	MQALQTPPT	1342
Full length light chain	DVVMTQSPLSLPVTLGQPASISCRSSQSLLYINGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1343

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63S
CPA.7.024

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTST AYMELSSLRSEDTAVYYCARDAYYYDSSGYYNPDAFDIWGQGTMVTVSS	1344
vhCDR1	GGTFSSYA	1345
vhCDR2	IIPIFGTA	1346
vhCDR3	ARDAYYYDSSGYYNPDAFDI	1347
Full length HC	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTST AYMELSSLRSEDTAVYYCARDAYYYDSSGYYNPDAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1348
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSSRASGVPDRFSGSVSGTDFTLKI SRVEAEDVGVYYCMQGLQTPRTFGRGTKLEIKR	1349
vlCDR1	QSLLHSNGYNY	1350
vlCDR2	LGS	1351
vlCDR3	MQGLQTPRT	1352
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSSRASGVPDRFSGSVSGTDFTLKI SRVEAEDVGVYYCMQGLQTPRTFGRGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1353

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63T

CPA.7.033

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1354
vhCDR1	GGTFSSSA	1355
vhCDR2	IIPIYGIT	1356
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1357
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1358
Variable light (vl) domain	ETTLTQSPAFMSATPGDEVNISCKASQDIDDDVSWYQQKPGGAPIFLIQEASTLVPGIPPRFSGSGFGTDFTLTIKNMES EDAAYYFCLQHDNLPLTFGGGTKVDIKR	1359
vlCDR1	QDIDDD	1360
vlCDR2	EAS	1361
vlCDR3	LQHDNLPLT	1362
Full length light chain	ETTLTQSPAFMSATPGDEVNISCKASQDIDDDVSWYQQKPGGAPIFLIQEASTLVPGIPPRFSGSGFGTDFTLTIKNMES EDAAYYFCLQHDNLPLTFGGGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1363

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63U

CPA.7.034

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEDPGPVAGPYYYYGMDVWGQGTTVTVSS	1364
vhCDR1	GYTLTELS	1365
vhCDR2	FDPEDGET	1366
vhCDR3	ATEDPGPVAGPYYYYGMDV	1367
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEDPGPVAGPYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1368
Variable light (vl) domain	DVVMTQSPLVLPVTPGEPASISCRSSQSLLYINGYHYLDWYVQRPGQSPQLLIFLGSTRASGVPDRFSGSGSGTDFTLEIS KVEAEDVGIYFCMQALQTPPTFGGGTKVEIKR	1369
vlCDR1	QSLLYINGYHY	1370
vlCDR2	LGS	1371
vlCDR3	MQALQTPPT	1372
Full length light chain	DVVMTQSPLVLPVTPGEPASISCRSSQSLLYINGYHYLDWYVQRPGQSPQLLIFLGSTRASGVPDRFSGSGSGTDFTLEIS KVEAEDVGIYFCMQALQTPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1373

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63V

CPA.7.036

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1374
vhCDR1	GGTFSSSA	1375
vhCDR2	IIPIYGIT	1376
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1377
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1378
Variable light (vl) domain	DIVMTQTPLSLPVTPGEPASISCRPSQSLLDSDDGNTYLDWYLQKPGQSPQLLIHTLSYRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQRLQFPLTFGGGTKVEIKR	1379
vlCDR1	QSLLDSDDGNTY	1380
vlCDR2	TLS	1381
vlCDR3	MQRLQFPLT	1382
Full length light chain	DIVMTQTPLSLPVTPGEPASISCRPSQSLLDSDDGNTYLDWYLQKPGQSPQLLIHTLSYRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQRLQFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1383

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Figure 63W

CPA.7.040

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVPAAIGVYYYYYYMDVWGKGTTVTVSS	1384
vhCDR1	GYTLTELS	1385
vhCDR2	FDPEDGET	1386
vhCDR3	ATGVPAAIGVYYYYYYMDV	1387
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATGVPAAIGVYYYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1388
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYWGSYRASGVPDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQAVQNPPTFGQGTKVDIKR	1389
vlCDR1	QSLLYRNGYNY	1390
vlCDR2	WGS	1391
vlCDR3	MQAVQNPPT	1392
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYWGSYRASGVPDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQAVQNPPTFGQGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1393

Figure 63X

CPA.7.046

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1394
vhCDR1	GGTFSSSA	1395
vhCDR2	IIPIYGIT	1396
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1397
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1398
Variable light (vl) domain	DVVMTQSPAFLSVTPGERVTLSCKASQTMNNYLAWYQQKPGQAPRLLIYDASTRATDTPPRFSGSGSGTEFTLTISSV QSEDFALYYCQQYGDWLPITFGQGTRLEIKR	1399
vlCDR1	QTMNNY	1400
vlCDR2	DAS	1401
vlCDR3	QQYGDWLPIT	1402
Full length light chain	DVVMTQSPAFLSVTPGERVTLSCKASQTMNNYLAWYQQKPGQAPRLLIYDASTRATDTPPRFSGSGSGTEFTLTISSV QSEDFALYYCQQYGDWLPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1403

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Figure 63Y

CPA.7.047

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATAFPEATISYYYYMDVWGKGTTVTVSS	1404
vhCDR1	GYTLTELS	1405
vhCDR2	FDPEDGET	1406
vhCDR3	ATAFPEATISYYYYMDV	1407
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATAFPEATISYYYYMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1408
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYWGSYRASGVPDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQAVQNPPTFGQGTKVEIKR	1409
vlCDR1	QSLLYRNGYNY	1410
vlCDR2	WGS	1411
vlCDR3	MQAVQNPPT	1412
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGYNYLDWYLQKPGQSPQLLIYWGSYRASGVPDRFSGSGSGTDFTLK ISRVEAEDVGVYYCMQAVQNPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1413

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63Z

CPA.7.049

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1414
vhCDR1	GGTFSSSA	1415
vhCDR2	IIPIYGIT	1416
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1417
Full length HC	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1418
Variable light (vl) domain	DIVMTQTPLSLPVTPGEPASMSCRSSRSLLDSDDGNTHLDWYLQKPGQSPQLLIQSLSYRASGVPDRFSGSGSGTDFTL EISRVEAEDVGIYYCMQRKEFPLTFGGGTKVEIKR	1419
vlCDR1	RSLLDSDDGNTH	1420
vlCDR2	SLS	1421
vlCDR3	MQRKEFPLT	1422
Full length light chain	DIVMTQTPLSLPVTPGEPASMSCRSSRSLLDSDDGNTHLDWYLQKPGQSPQLLIQSLSYRASGVPDRFSGSGSGTDFTL EISRVEAEDVGIYYCMQRKEFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1423

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63AA

CPA.7.050

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADKSTST AYMELSSLRSEDTAVYYCARGPWYYDSSGYSSYAYYMDVWGQGTTVTVSS	1424
vhCDR1	GGTFSSYA	1425
vhCDR2	IIPIFGTA	1426
vhCDR3	ARGPWYYDSSGYSSYAYYMDV	1427
Full length HC	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADKSTST AYMELSSLRSEDTAVYYCARGPWYYDSSGYSSYAYYMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1428
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALHTPGVTFGGGTKVEIKR	1429
vlCDR1	QSLLHSDGYNY	1430
vlCDR2	LGS	1431
vlCDR3	MQALHTPGVT	1432
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALHTPGVTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1433

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63BB
CPA.7.028

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QLQLQESGPGLVKPSETLSLTCTVTGGSISSSSYYWAWIRQPPGKGLEWIGGIYYSGSTYYNVSLESRVTISQDTSKNQFS LKLTSVTAADTAVYYCARGAWELRLGDWFDPWGQGTLVTVSS	1434
vhCDR1	GGSISSSSYY	1435
vhCDR2	IYYSGST	1436
vhCDR3	ARGAWELRLGDWFDP	1437
Full length HC	QLQLQESGPGLVKPSETLSLTCTVTGGSISSSSYYWAWIRQPPGKGLEWIGGIYYSGSTYYNVSLESRVTISQDTSKNQFS LKLTSVTAADTAVYYCARGAWELRLGDWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1438
Variable light (vl) domain	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDIQWYQQLPGTAPKLLIYGYSNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLSVYVVFGGGTQLTVLGQPKAA	1439
vlCDR1	SSNIGAGYD	1440
vlCDR2	GYS	1441
vlCDR3	QSYDSSLSVYVV	1442
Full length light chain	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDIQWYQQLPGTAPKLLIYGYSNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLSVYVVFGGGTQLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1443

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63CC
CPA.7.030

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQESGGGVVQPGGSLRLSCAASRFTFEDYAMHWVRQPPGKGLEWVSGISWKSGGINYADSVKGRFTISRDNAQ NSLYLQMNSLRAEDTALYYCVKDPTLVATDRAFNIWGQGTMVTVSS	1444
vhCDR1	RFTFEDYA	1445
vhCDR2	ISWKSGGI	1446
vhCDR3	VKDPTLVATDRAFNI	1447
Full length HC	QVQLQESGGGVVQPGGSLRLSCAASRFTFEDYAMHWVRQPPGKGLEWVSGISWKSGGINYADSVKGRFTISRDNAQ NSLYLQMNSLRAEDTALYYCVKDPTLVATDRAFNIWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1448
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQYLQTPDTFGQGTKLEIKRAAPS	1449
vlCDR1	QSLLHSNGYNY	1450
vlCDR2	LGS	1451
vlCDR3	MQYLQTPDT	1452
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQYLQTPDTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1453

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63DD
CPA.7.041

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1454
vhCDR1	GGTFSSSA	1455
vhCDR2	IIPIYGIT	1456
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1457
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1458
Variable light (vl) domain	EIVLTQSPDFQSVTPKEKVTITCRASQNIDSSLHWYQQKPGQSPKLLINYASQSFSGVPSRFSGSGSGTDFTLTIDSLEPE DAATYFCHQSSSLPLTFGGGTKVEIRRTVAAPS	1459
vlCDR1	QNIDSS	1460
vlCDR2	YAS	1461
vlCDR3	HQSSSLPLT	1462
Full length light chain	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDIQWYQQLPGTAPKLLIYGYSNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLSVYVVFGGGTQLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	1463

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Figure 63EE
CPA.7.016

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGSSVKVSCKTSGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTSTA YMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1464
vhCDR1	GGTFSSSA	1465
vhCDR2	IIPIYGIT	1466
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1467
Full length HC	EVQLVQSGAEVKKPGSSVKVSCKTSGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTSTA YMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1468
Variable light (vl) domain	EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLQSE DFAVYYCQQYDDWPQTFGQGTRLEIKRTVAAPS	1469
vlCDR1	QSVSSY	1470
vlCDR2	DAS	1471
vlCDR3	QQYDDWPQT	1472
Full length light chain	EIVLTQSPGTLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLQSE DFAVYYCQQYDDWPQTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1473

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Figure 63FF
CPA.7.020

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDES TSTAYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1474
vhCDR1	GGTFSSSA	1475
vhCDR2	IIPIYGIT	1476
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1477
Full length HC	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDES TSTAYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	1478
Variable light (vl) domain	EIVMTQSPATLSLSTGERATLFCRTSQNVYGEVAWYQQKPGQAPRLLIYDTFERAAGIPAKFSGSGSGTDFTLTISR VEPEDFAVYYCQQRRDWPITFGQGTRLEIKRTVAAPS	1479
vlCDR1	QNVYGE	1480
vlCDR2	DTF	1481
vlCDR3	QQRRDWPIT	1482
Full length light chain	EIVMTQSPATLSLSTGERATLFCRTSQNVYGEVAWYQQKPGQAPRLLIYDTFERAAGIPAKFSGSGSGTDFTLTISR VEPEDFAVYYCQQRRDWPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1483

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Figure 63GG
CPA.7.038

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1484
vhCDR1	GGTFSSSA	1485
vhCDR2	IIPIYGIT	1486
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1487
Full length HC	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1488
Variable light (vl) domain	DIQMTQSPSSLSASVGDRVTITCQASRDISDSLSWYQQKPGKAPKLLIFDASNLKTGVSSRFSGSGSGTDFTFTISSLQPE DIATYYCHQYDNLPLTFGGGTKVEIKRTVAAPS	1489
vlCDR1	RDISDS	1490
vlCDR2	DAS	1491
vlCDR3	HQYDNLPLT	1492
Full length light chain	DIQMTQSPSSLSASVGDRVTITCQASRDISDSLSWYQQKPGKAPKLLIFDASNLKTGVSSRFSGSGSGTDFTFTISSLQPE DIATYYCHQYDNLPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1493

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Figure 63HH
CPA.7.044

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSS	1494
vhCDR1	GGTFSSSA	1495
vhCDR2	IIPIYGIT	1496
vhCDR3	ARDDTARRVRGVPYYYYYAMDV	1497
Full length HC	QMQLVQSGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGFEWMGGIIPIYGITDYAQKFQGRVTITTDESTST AYMELSSLTSEDTAVYYCARDDTARRVRGVPYYYYYAMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1498
Variable light (vl) domain	EIVMTQSPATLSLSPGERATLSCRASESVTTFLAWYQQKPGQAPRLLITDASNRATGIPGRFSGSGSGTDFTLTISSLEPE DFAVYYCHQHTNWPLTFGGGTKLEIKRTVAAPS	1499
vlCDR1	ESVTTF	1500
vlCDR2	DAS	1501
vlCDR3	HQHTNWPLT	1502
Full length light chain	EIVMTQSPATLSLSPGERATLSCRASESVTTFLAWYQQKPGQAPRLLITDASNRATGIPGRFSGSGSGTDFTLTISSLEPE DFAVYYCHQHTNWPLTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1503

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Figure 63II
CPA.7.045

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEVGYCSGGSCYISYYYGMDVWGQGTTVTVSS	1504
vhCDR1	GYTLTELS	1505
vhCDR2	FDPEDGET	1506
vhCDR3	ATEVGYCSGGSCYISYYYGMDV	1507
Full length HC	EVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEWMGGFDPEDGETIYAQKFQGRVTMTEDTS TDTAYMELSSLRSEDTAVYYCATEVGYCSGGSCYISYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	1508
Variable light (vl) domain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGHNFLDWYVQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKLEIKRTVAAPS	1509
vlCDR1	QSLLYRNGHNF	1510
vlCDR2	LGS	1511
vlCDR3	MQALQTPPT	1512
Full length light chain	DVVMTQSPLSLPVTPGEPASISCRSSQSLLYRNGHNFLDWYVQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKI SRVEAEDVGVYYCMQALQTPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	1513

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 63JJ

CHA.7.502

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	DVQLVESGGDLVQPGGSRKLSCTASGFTFSNFGMHWVRQAPEKGLEWVAYISSGS STIYYADTVKGRFTISRDNPENTLFLQMTSLRSEDTAMYYCTRLDYYTNSYSMDHWG QGTSVTVSS	1514
vhCDR1	GFTFSNFG	1515
vhCDR2	ISSGSSTI	1516
vhCDR3	TRLDYYTNSYSMDH	1517
Variable light (vl) domain	QIVLTQSPALMSASPGEKVTLTCSASSSLPYIYWYQQKPGSSPKPWIYLTSNLASGVP ARFSGSRSGTSYSLTISSVEAEDAATYYCQQWSSNPFTFGSGTKLEIK	1518
vlCDR1	SSLPY	1519
vlCDR2	LTS	1520
vlCDR3	QQWSSNPFT	1521

Figure 63KK

CHA.7.503

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGAELAKPGASVKMSCKASGYTFTSNWMHWVKQRPGQGLEWIGYINP SNGYTECNQKFRDKATLSADKSSSTAYMQLNSLTSADSAVYYCALMISAWLPYWG QGTLVTVSA	1522
vhCDR1	GYTFTSNW	1523
vhCDR2	INPSNGYT	1524
vhCDR3	ALMISAWLPY	1525
Variable light (vl) domain	DIVLTQSPASLAISLGQRATISCRASQSVSASSYSYVHWYQQKPGQPPKLLIKYASSLE SGVPARFSGSGSGTDFTLNIHPVEEEDTATYYCLHTWEIPYTFGGGTKLEIK	1526
vlCDR1	QSVSASSYSY	1527
vlCDR2	YAS	1528
vlCDR3	LHTWEIPYT	1529

Figure 63LL

CHA.7.506

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGAELTRPGASVNLSCKASGYTFTSYWMQWVKQRPGQGLEWIGAIYPG DGDTRFNQKFKGKATLTADESSSTAYMQLSSLASEDSAVYYCATYYRYDDYWGQGT TLTVSS	1530
vhCDR1	GYTFTSYW	1531
vhCDR2	IYPGDGDT	1532
vhCDR3	ATYYRYDDY	1533
Variable light (vl) domain	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASG VPTRFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPYTFGGGTKLEIK	1534
vlCDR1	SSVSY	1535
vlCDR2	DTS	1536
vlCDR3	QQWSSNPYT	1537

Figure 63MM

CHA.7.508

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPDLVKPGASMKISCKASGYTFIDYNIHWVKQSQGKSLDWIGYIYPYNG GTGYNQKFKNKATLTVDSSSSTAYMEVRSLTFEDSAVYFCAREADYYGNRGQFDYW GQGTLVTVSA	1538
vhCDR1	GYTFIDYN	1539
vhCDR2	IYPYNGGT	1540
vhCDR3	AREADYYGNRGQFDY	1541
Variable light (vl) domain	DIQMTQSPASLSVSVGETVTITCRASENIFSNLAWYQQKQGKSPQLLVYGEANLAD GVPSRFSGSGSGTQYSLKINSLQSEDFGNYYCQHFWGTPYTFGGGTTLEIK	1542
vlCDR1	ENIFSN	1543
vlCDR2	GEA	1544
vlCDR3	QHFWGTPYT	1545

Figure 63NN

CHA.7.510

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVTLKESGPGILQPSQTLSLTCSFSGFSLNTSGTGVGWIRQPSGKGLEWLTHIWWN DNKFYNTFLKSRLTISKETSNNQVFLKIASVDTADAATYYCARMAYGNLWFVNWGQ GTLVAVST	1546
vhCDR1	GFSLNTSGTG	1547
vhCDR2	IWWNDNK	1548
vhCDR3	ARMAYGNLWFVN	1549
Variable light (vl) domain	DIVLTQSPASLAVSLGQRASISCRASRSVTISGYSYMYWYQQKPGQPPRLLFYLASNL ASGVPARFSGSGSGTDFTLNIHPVEEEDAAIYYCQHSRELPYTFGGGTKLEIK	1550
vlCDR1	RSVTISGYSY	1551
vlCDR2	LAS	1552
vlCDR3	QHSRELPYT	1553

Figure 6300

CHA.7.512

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QIQLVQSGPELKKPRETVKISCKASGYTFTDYSMHWVKQAPGKGLKWMGWINTETGEPTYADDFKGRFAFSLEASASSAYLQINILKDEDTATYFCARSRGGYYEDYYALDYWGQGTSVTVSS	1554
vhCDR1	GYTFTDYS	1555
vhCDR2	INTETGEP	1556
vhCDR3	ARSRGGYYEDYYALDY	1557
Variable light (vl) domain	DIQMTQSPASLSASVGESVTITCRASGNIHYYLAWYQQKQGKSPQLLVYNAKNLADGVPSRFSGSGSGTQFSLKINSLQPEDFGSYYCQHFWISPPTFGGGTKLEIK	1558
vlCDR1	GNIHYY	1559
vlCDR2	NAK	1560
vlCDR3	QHFWISPPT	1561

Figure 63PP

CHA.7.514

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLRQSGADLVKPGASVKLSCTASGFNIKDTYIDWVKQRPEQGLDWIGRIDPANGNTKYDPKFQGKATIITDTSSNTAYLQLSNLTSEDTAVYYCARYGSYPYFDYWGRGTTLAVSS	1562
vhCDR1	GFNIKDTY	1563
vhCDR2	IDPANGNT	1564
vhCDR3	ARYGSYPYFDY	1565
Variable light (vl) domain	SIVMTQTPKFLLISAGDRVTITCKASQSVRNDVAWYQQKPGQSPKLLMYYASNRYTGVPDRFTGSGYGTDFTFTISTVQAEDLAVYFCQQDYSSPPTFGGGTKLEIK	1566
vlCDR1	QSVRND	1567
vlCDR2	YAS	1568
vlCDR3	QQDYSSPPT	1569

Figure 63QQ

CHA.7.516

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGPELVRPGVSVKISCKVSGYTFTDYVMHWVKQSHAKSLEWIGIISPYSG NTNYNQNFKGKATMTVDKSSSTAYMALARLTSEDSAIYYCAREGDLPMFAYWGQG TLVTVSA	1570
vhCDR1	GYTFTDYV	1571
vhCDR2	ISPYSGNT	1572
vhCDR3	AREGDLPMFAY	1573
Variable light (vl) domain	QIVLTQSPTIMSASPGEKVTMTCSASSSVSYIYWYQQNPGSSPRLLIYDTSILASGVPF RFSGSGSGTSYSLTISRMEAEDAATYYCQQWTSYPLTFGSGTKLELK	1574
vlCDR1	SSVSY	1575
vlCDR2	DTS	1576
vlCDR3	QQWTSYPLT	1577

Figure 63RR

CHA.7.518

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGASVKISCKASGYTFTDYNINWVKQSHGKSLEWIGYIYPYIGGS GYNQKFKSKATLSADNPSSTAYMELRSLTSEDSAVYYCAREDKTARNAMDYWGQG TPVTVSS	1578
vhCDR1	GYTFTDYN	1579
vhCDR2	IYPYIGGS	1580
vhCDR3	AREDKTARNAMDY	1581
Variable light (vl) domain	DIQMTQSPASLSVSVGETVTIICRVSENIYSNLAWYQQKQGKSPQLLVYEATNLAEG VPSRFSGSGSGTQYSLKINSLQSEDFGSYYCQHFWGTPYTFGGGTKLEIK	1582
vlCDR1	ENIYSN	1583
vlCDR2	EAT	1584
vlCDR3	QHFWGTPYT	1585

Figure 635S

CHA.7.520_1

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWIRQFPGNKLEWMGYISYSG STSYNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYYCARHYRYPPYAMDYWGQG TSVTVSS	1586
vhCDR1	GYSITSDYA	1587
vhCDR2	ISYSGST	1588
vhCDR3	ARHYRYPPYAMDY	1589
Variable light (vl) domain	DIVMTQSPSSLAMSVGQKVTMSCKSSQSLLNSSNQKNYLAWYQQKPGQSPKLLVY FASTRESGVPDRFIGSGSGTDFTLTITSVQAEDLADYFCQQHYSTPFTFGSGTKLEIK	1590
vlCDR1	QSLLNSSNQKNY	1591
vlCDR2	FAS	1592
vlCDR3	QQHYSTPFT	1593

Figure 63TT

CHA.7.520_2

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLKQSGPGLVQPSQSLSITCTVSGFSLTSFGVHWVRQSPGKGLEWLGVIWSGGTTVYDAAFISRLSISKDNSKSQVFFKMNSLQTNDTAIYYCARKRGNFYVMDYWGQGTSVTVSS	1594
vhCDR1	GFSLTSFG	1595
vhCDR2	IWSGGTT	1596
vhCDR3	ARKRGNFYVMDY	1597
Variable light (vl) domain	DIVMTQSPSSLAMSVGQKVTMSCKSSQSLLNSSNQKNYLAWYQQKPGQSPKLLVYFASTRESGVPDRFIGSGSGTDFTLTITSVQAEDLADYFCQQHYSTPFTFGSGTKLEIK	1598
vlCDR1	QSLLNSSNQKNY	1599
vlCDR2	FAS	1600
vlCDR3	QQHYSTPFT	1601

Figure 63UU

CHA.7.522

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQPGSELVRPGTSVKLSCKASGYTFTSYWVHWVRQRHGQGLEWIGNVYPG SGSTNYDEKFKSKGTLTVDTSSSTAYMHLSSLTSEDSAVYYCTRGVLRFPLDYWGQG TTLTVSS	1602
vhCDR1	GYTFTSYW	1603
vhCDR2	VYPGSGST	1604
vhCDR3	TRGVLRFPLDY	1605
Variable light (vl) domain	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPHLLIYRMS NLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTFGAGTKLELK	1606
vlCDR1	KSLLHSNGNTY	1607
vlCDR2	RMS	1608
vlCDR3	MQHLEYPLT	1609

Figure 63VV

CHA.7.524

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGPEVVRPGVSVKISCKGSGYKFPDYVMHWVKQSHAKSLEWIGIISIYSG NTNYNQKFKGKATMTVDKSSSTAYMELARLTSEDSAIYYCAREGDLPMFAYWGQG TLVTVSA	1610
vhCDR1	GYKFPDYV	1611
vhCDR2	ISIYSGNT	1612
vhCDR3	AREGDLPMFAY	1613
Variable light (vl) domain	QIVLTQSPAIMSASPGEKVTMTCNASSSVSYMYWYQQKPISSPRLLIYDTSNLASGV PVRFSGSGSGTSYSLTIGRMEAEDAATYYCQQWSSYPLTFGAGTKVEVK	1614
vlCDR1	SSVSY	1615
vlCDR2	DTS	1616
vlCDR3	QQWSSYPLT	1617

Figure 63WW

CHA.7.526

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLKESGPGLVAPSQSLSITCTVSGFSLTAYNINWVRQPPGKGLEWLGMIWGDG NTDYNSPLKSRLTISKDNSKSQVFLKMDSLQTDDTARYYCARDLKVRRDSPYTMDY WGQGTSVTVSS	1618
vhCDR1	GFSLTAYN	1619
vhCDR2	IWGDGNT	1620
vhCDR3	ARDLKVRRDSPYTMDY	1621
Variable light (vl) domain	NIMMTQSPSSLAVSAGEKVTMSCKSSQSVLYSSNQKNYLAWYQQKPGQSPKLLIY WASNRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCHQYLSSYTFGGGTKLEIK	1622
vlCDR1	QSVLYSSNQKNY	1623
vlCDR2	WAS	1624
vlCDR3	HQYLSSYT	1625

Figure 63XX

CHA.7.527

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	DVQLQESGPGLVKPSQSLSLTCTVTGYSLTSDYAWNWIRQFPGNKLEWMGYITYSGGTTYNPSLKSRISITRDTSKNQFFLQLTSVTTEDTATYYCARRGSGTTVVGDWYFDVWGAGTTVTVSS	1626
vhCDR1	GYSLTSDYA	1627
vhCDR2	ITYSGGT	1628
vhCDR3	ARRGSGTTVVGDWYFDV	1629
Variable light (vl) domain	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSFNQKYYLAWYQQKPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTPTISSVTAEDLAVYYCQQFYTYPYTFGGGTKLEMK	1630
vlCDR1	QSLLYSFNQKYY	1631
vlCDR2	WAS	1632
vlCDR3	QQFYTYPYT	1633

Figure 63YY

CHA.7.528

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQVQQSGPELVKPGASVKISCKASGYTFTKSNMHWVKQSHGKSLEWIGYIYPYNG GTGYNQNFKSKATLTVDISSSTAYMELRSLTLEDSAVYLCAREADYYGNRGQFDYW GQGTLVTVSA	1634
vhCDR1	GYTFTKSN	1635
vhCDR2	IYPYNGGT	1636
vhCDR3	AREADYYGNRGQFDY	1637
Variable light (vl) domain	DIQMTQSPASLSVSVGETVTITCRASDNIFSNLAWYHQKQGKSPHLLVYGATNLAD GVPSRFSGSGSGTQYSLKINSLQSEDFGDYYCQHFWGTPYTFGGGTKLEIK	1638
vlCDR1	DNIFSN	1639
vlCDR2	GAT	1640
vlCDR3	QHFWGTPYT	1641

Figure 63ZZ

CHA.7.530

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGAELMRPGTSVKVSCKASGYAFTNHLIEWIKQRPGQGLEWIGVINPGS DSTDYNEKFKDKATLTADKSSSTAYMQLSSLTSDDSAVYFCARSLYYNSWFVYWGQ GTLVTVSA	1642
vhCDR1	GYAFTNHL	1643
vhCDR2	INPGSDST	1644
vhCDR3	ARSLYYNSWFVY	1645
Variable light (vl) domain	DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKRGKSPQLLVYNAKTLVEG VPSRFSGSGSGTQFSLKINSLQPEDFGSYYCQHHYGTPYTFGGGTKLEIK	1646
vlCDR1	ENIYSY	1647
vlCDR2	NAK	1648
vlCDR3	QHHYGTPYT	1649

Figure 63AAA

CHA.7.534

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGAELVKPGASVRLSCTASGFSIRDTYIHWVKQRPEQGLDWIGKIDPANG KSEYDPKFQGRATMTTDTSSNTAYLQLSSLTSEDTAVYYCTRYGYYPYFDVWGAGTT VTVFS	1650
vhCDR1	GFSIRDTY	1651
vhCDR2	IDPANGKS	1652
vhCDR3	TRYGYYPYFDV	1653
Variable light (vl) domain	SIVMTQTPKFLLVSAGDRVAITCKASQSVRHDVVWYQQKPGQSPKLLIYYASSRYTG VPDRFTGSGYGTDFTFTISTVQAEDLALYFCLQDFSSPWTFGGGTKLEIK	1654
vlCDR1	QSVRHD	1655
vlCDR2	YAS	1656
vlCDR3	LQDFSSPWT	1657

Figure 63BBB

CHA.7.535

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGASVKISCKTSGYTFTKNTMHWVRQSHGKSLEWIGGINPNSGGASFNQKFMGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARDGYDGDWFFDVWGAGTTVTVSS	1658
vhCDR1	GYTFTKNT	1659
vhCDR2	INPNSGGA	1660
vhCDR3	ARDGYDGDWFFDV	1661
Variable light (vl) domain	DIQMNQSPFSLSASLGDTVTITCHASQNIYVWLSWYQQKPGNIPKLLIYKASDLHTGVPSRFSGSGSGTDFTLNISSLQPEDIATYYCQQGQSYPRTFGGGTKLEIK	1662
vlCDR1	QNIYVW	1663
vlCDR2	KAS	1664
vlCDR3	QQGQSYPRT	1665

Figure 63CCC

CHA.7.537

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLKESGPGLVAPSQSLSITCTVSGFSLIGHGVNWIRQPPGKGLEWLGVIWGDGNTDYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTARYFCAVNSAMDYWGQGTAVTVSS	1666
vhCDR1	GFSLIGHG	1667
vhCDR2	IWGDGNT	1668
vhCDR3	AVNSAMDY	1669
Variable light (vl) domain	NIVMTQSPKSMSMSVGERVTLNCTASENVASFVSWYQQKPEQSPKLLIYGTSNRYTGVPDRFTGSGSATDFTLTISSVQAEDLGDYHCGQSYNYPFTFGSGTKLEIE	1670
vlCDR1	ENVASF	1671
vlCDR2	GTS	1672
vlCDR3	GQSYNYPFT	1673

Figure 63DDD

CHA.7.538_1

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGAELVRPGASVKVSCKTSGYAFTNYLIEWVKQRPGQGLEWIGVINPGSGGIYYNDKFKVKTTLTADKSSSTAYMQLSSLTSDDSAVYFCARSETHDTWFAYWGQGTLVTVSA	1674
vhCDR1	GYAFTNYL	1675
vhCDR2	INPGSGGI	1676
vhCDR3	ARSETHDTWFAY	1677
Variable light (vl) domain	DIVMTQSQKFISTSVGDRVSITCKASQSVRIAVAWFQQKPGQSPKALIYLASTRHTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWNYPYTFGGGTKLEIKR	1678
vlCDR1	QSVRIA	1679
vlCDR2	LAS	1680
vlCDR3	LQHWNYPYT	1681

Figure 63EEE

CHA.7.538_2

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQSGAELVRPGTSVKMSCKAAGYTFTNYWIGWVKQRPGHGLEWIGDIYPG GGYTNYNEKFKGKATLTADTSSSTAYMQLSSLTSEDSAIYYCASPYYGSSYGFAFWG QGTLVTVSA	1682
vhCDR1	GYTFTNYW	1683
vhCDR2	IYPGGGYT	1684
vhCDR3	ASPYYGSSYGFAF	1685
Variable light (vl) domain	DIVMTQSQKFISTSVGDRVSITCKASQSVRIAVAWFQQKPGQSPKALIYLASTRHTG VPDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWNYPYTFGGGTKLEIKR	1686
vlCDR1	QSVRIA	1687
vlCDR2	LAS	1688
vlCDR3	LQHWNYPYT	1689

Figure 63FFF

CHA.7.543

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLKESGPGLVAPSQSLSITCTVSGFSLSGYGIKWVRQPPGKGLEWLGTIWGDGST DYNSALKSRLSISKDNSKSQVFLKMTSLQTDDTARYYCASDSLGITFGYWGQGTLV TVSA	1690
vhCDR1	GFSLSGYG	1691
vhCDR2	IWGDGST	1692
vhCDR3	ASDSLGITFGY	1693
Variable light (vl) domain	DIQMTQTTSSLSASLGDRVTISCRASQDISNYLNWYQQKPDGTVKLLIYYTSRLHSGV PSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPLTFGAGTKLELK	1694
vlCDR1	QDISNY	1695
vlCDR2	YTS	1696
vlCDR3	QQGNTLPLT	1697

Figure 63GGG

CHA.7.544

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLKESGPGLVAPSQSLSITCTVSGFSLTSYAITWVRQPPGKGLEWLGVIWPGGGT NYNSALKSRLSISKDNSKSHLFLKMNSLQTDDTARYYCVRSYDGYLDWYFDVWGTG TTVTVSS	1698
vhCDR1	GFSLTSYA	1699
vhCDR2	IWPGGGT	1700
vhCDR3	VRSYDGYLDWYFDV	1701
Variable light (vl) domain	NIVMTQSPKSMSMSVGERVTLSCKASENVGTYVSWYQQKPDQSPKLLIYGASNRYT GVPDRFTGSGSATDFTLIISSVQAEDLSDYHCGQSYSYPYTFGGGTKLEII	1702
vlCDR1	ENVGTY	1703
vlCDR2	GAS	1704
vlCDR3	GQSYSYPYT	1705

Figure 63HHH

CHA.7.545

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QIQLVQSGPDLKKPGETVKISCKASGYTFTTYGMSWVKQAPGRGLKWMGWINTYSGVSTFPDDFKGRFAFSLETSASTAYLQINNLKNEDSATYFCARLGMGSTTGAGYFDVWGTGTTVTVSS	1706
vhCDR1	GYTFTTYG	1707
vhCDR2	INTYSGVS	1708
vhCDR3	ARLGMGSTTGAGYFDV	1709
Variable light (vl) domain	DIVLTQSPAIMSASPGEKVTMTCSASSSVSSWYLHWYQQKSGASPKLWIYGTSNLASGVPARFSGSGSGTSYSLTISSVEAEDAATYYCQQYRSDPYTFGSGTKLEIK	1710
vlCDR1	SSVSSWY	1711
vlCDR2	GTS	1712
vlCDR3	QQYRSDPYT	1713

Figure 63III

CHA.7.546

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QIQLVQSGPELKKPGETVKISCKASGYTFTTYGMSWVKQAPGKGLKWMGWINTYSGVSTYADDFEGRFAFSLETSVSTAYLQINNLKNEDTATYFCARLGRGSTTGAGYLDVWGTGTTVTVSS	1714
vhCDR1	GYTFTTYG	1715
vhCDR2	INTYSGVS	1716
vhCDR3	ARLGRGSTTGAGYLDV	1717
Variable light (vl) domain	DIVLTQSPAIMSASPGEKVSMTCSASSSVSSWYLHWYQQKSGASPKLWIYGTSNLASGVPARFSGSGSGTSYSLTISSVEAEDAATYYCQQYHSDPYTFGSGTKLEIK	1718
vlCDR1	SSVSSWY	1719
vlCDR2	GTS	1720
vlCDR3	QQYHSDPYT	1721

Figure 63JJJ

CHA.7.547

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QIQLVQSGPDLKKPGETVKISCKASGYTFTTYGMSWVKQAPGRGLKWMGWINTYS GVSTFPDDFKGRFAFSLETSASTAYLQINNLKNEDSATYFCARLGMGSTTGAGYFDV WGTGTTVTVSS	1722
vhCDR1	GYTFTTYG	1723
vhCDR2	INTYSGVS	1724
vhCDR3	ARLGMGSTTGAGYFDV	1725
Variable light (vl) domain	ENVLTQSPAIMSASLGEKVTLSCRASSSVNYMYWYQQKSDASPKLWIYYTSNLAPG VPARFSGSGSGNSYSLTISSVEGEDAATYYCQQFTSSPWTFGGGTKLEIK	1726
vlCDR1	SSVNY	1727
vlCDR2	YTS	1728
vlCDR3	QQFTSSPWT	1729

Figure 63KKK

CHA.7.548

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	EVQLQQSGPELVKPGASVKISCKASGYTFTDYSMNWVKQSHGKSLEWIGDITPNNG SPNYNQKFKDKATLTVDKSSSTVYMELRSLTSEDSAVYYCASLFFDYWGHGTTLTVSS	1730
vhCDR1	GYTFTDYS	1731
vhCDR2	ITPNNGSP	1732
vhCDR3	ASLFFDY	1733
Variable light (vl) domain	DIVMTQSPSSLSVSAGEKVTMSCKSSQSLLNSGNQKNYLAWYQQKPGQPPKLLIYG ASTRDSGVPDRFTGSGSGTDFTLTITSVQAEDLAVYYCQNDHTYPYTFGGGTKLEIK	1734
vlCDR1	QSLLNSGNQKNY	1735
vlCDR2	GAS	1736
vlCDR3	QNDHTYPYT	1737

Figure 63LLL

CHA.7.549

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQQPGTELVKPGASVKLSCKASGFTFTTHWMHWVRQRPGQGLEWIGNIYPS NGGSNYNEKFKTKATLTVDRSSSTAYMHLSSLTSEDSAVYYCARRVNWDGYYFDYW GQGTTLTVSS	1738
vhCDR1	GFTFTTHW	1739
vhCDR2	IYPSNGGS	1740
vhCDR3	ARRVNWDGYYFDY	1741
Variable light (vl) domain	DIVMTQSQKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKLLIYSASYRY SGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYNSYPLTFGGGTKLEIK	1742
vlCDR1	QNVGTN	1743
vlCDR2	SAS	1744
vlCDR3	QQYNSYPLT	1745

Figure 63MMM

CHA.7.550

What	sequence	SEQ ID NO:
Variable heavy (vh) domain	QVQLQESGTELVKPGASVKLSCKASGYTFTSYWIHWVKQRPGQGLEWIGNINPSNGGTNYNEKFKSKAALTVDKSSSTAYMQLSSLTSEDSAVYYCARRGLPYFFDYWGQGTTLTVSS	1746
vhCDR1	GYTFTSYW	1747
vhCDR2	INPSNGGT	1748
vhCDR3	ARRGLPYFFDY	1749
Variable light (vl) domain	DIVMTQSQKFMSTSVGDRVSVTCKGSQNVGYNVAWYQQKPGQSPKALVYSASDRHSGVPDRFAGSGSGTDFTLTISNVQSEDLAEYFCQQYNSYPLTFGAGTKLELK	1750
vlCDR1	QNVGYN	1751
vlCDR2	SAS	1752
vlCDR3	QQYNSYPLT	1753

Figure 63NNN
Humanized sequences of CHA.7.518 antibody VH

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework (AbM CDR definition)

IGHV1-46*01 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
(SEQ ID NO: 1754)

Joining region IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS (SEQ ID NO: 1755)

```
seq              10        20        30        40        50        60        70        80        90
AbM              10        20        30        40        50  a     60        70        80  abc   90
          b b b    p     p b b b   b b    b  bi i    i ibb  b         i  b   b b b x   b b b  b    bibibb
518       EVQLQQSGPELVKPGASVKISCKAS GYTFTDYNIN WVKQSHGKSLEWIG YIYPYIGGSG YNQKFKSKATLSADNPSSTAYMELRSLTSEDSAVYYCAR
          *   *   * **      *                  * ** **   *               *   **** *** *** *   *   *   *
1-46*01   QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h518H1    QVQLVQSGAEVKKPGASVKVSCKAS GYTFTDYNIN WVRQAPGQGLEWMG YIYPYIGGSG YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h518H2    QVQLVQSGAEVKKPGASVKVSCKAS GYTFTDYNIN WVRQAPGQGLEWIG YIYPYIGGSG YAQKFQGRVTMTADTSTSTVYMELSSLRSEDTAVYYCAR
h518H3    QVQLVQSGAEVKKPGASVKISCKAS GYTFTDYNIN WVRQAPGQGLEWIG YIYPYIGGSG YAQKFQGRATLTADTSTSTAYMELSSLRSEDTAVYYCAR
h518H4    QVQLVQSGAEVKKPGASVKISCKAS GYTFTDYNIN WVRQAPGQGLEWIG YIYPYIGGSG YAQKFQGRATLTADNSTSTAYMELSSLRSEDTAVYYCAR
                    V                            #                                 N
```

```
seq     100       110       120
AbM               110
                 i   b b b
518     EDKTARNAMDY WGQGTPVTVSS (SEQ ID NO: 1756)
                    *            ("1-46*01" sequence is disclosed as SEQ ID NO: 1757)
h518H1  EDKTARNAMDY WGQGTLVTVSS (SEQ ID NO: 1758)
h518H2  EDKTARNAMDY WGQGTLVTVSS (SEQ ID NO: 1759)
h518H3  EDKTARNAMDY WGQGTLVTVSS (SEQ ID NO: 1760)
h518H4  EDKTARNAMDY WGQGTLVTVSS (SEQ ID NO: 1761)
              #
```

deamidation substitutions: Q/S/A

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WO 2018/220446 PCT/IB2018/000696 CA 3064331 2019-11-20 252/264

Figure 63000
Humanized sequences of CHA.7.518 antibody VL

Potential humanized sequence based on IMGT IGKV1-39*01 acceptor framework

IGKV1-39*01
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP (SEQ ID NO: 1762)

Joining region IMGT J00242|IGKJ2*01|YTFGQGTKLEIK (SEQ ID NO: 1763)

```
seq                10        20        30        40        50        60        70        80
AbM                10        20        30        40        50        60        70        80
             b b b    p p     p b b  b   b   bi bi i    ii ibbi      i   b   b       b b b  b    ib bib
518        DIQMTQSPASLSVSVGETVTIIC RVSENIYSNLA WYQQKQGKSPQLLVY EATNLAE GVPSRFSGSGSGTQYSLKINSLQSEDFGSYYC
                 *   *   **   *                  *  *  *  *                      ***  *  *   *   **
IGKV1-39   DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h518L1     DIQMTQSPSSLSASVGDRVTITC RVSENIYSNLA WYQQKPGKAPKLLIY EATNLAE GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h518L2     DIQMTQSPSSLSASVGDRVTITC RVSENIYSNLA WYQQKPGKAPKLLIY EATNLAE GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC
h518L3     DIQMTQSPSSLSASVGDRVTITC RVSENIYSNLA WYQQKPGKAPKLLVY EATNLAE GVPSRFSGSGSGTDYTLTISSLQPEDFGTYYC
                       V                  #   #            S           #


seq        90        100
AbM        90        100
           ibi  iib  i   b b b
518        QHFWGTPYT FGGGTKLEIK (SEQ ID NO: 1764)
                     *
IGKV1-39   QQSYSTPP (SEQ ID NO: 1765)
h518L1     QHFWGTPYT FGQGTKLEIK (SEQ ID NO: 1766)
h518L2     QHFWGTPYT FGQGTKLEIK (SEQ ID NO: 1767)
h518L3     QHFWGTPYT FGQGTKLEIK (SEQ ID NO: 1768)
              @
```

deamidation substitutions: Q/S/A/D
@ tryptophan oxidation substitutions: Y/F/H

Figure 63PPP
Humanized sequences of CHA.7.538_1 antibody VH

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework
IGHV1-46*01
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR (SEQ ID NO: 1769)
Joining region IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS (SEQ ID NO: 1770)

```
seq              10        20        30        40        50        60        70        80        90
AbM              10        20        30        40        50  a     60        70        80  abc   90
          b b b     p     p b b b   b b    b  bi i     i ibb  b          i  b   b b b x    b b b  b     bibibb
538_1   QVQLQQSGAELVRPGASVKVSCKTS GYAFTNYLIE WVKQRPGQGLEWIG VINPGSGGIY YNDKFKVKTTLTADKSSSTAYMQLSSLTSDDSAVYFCAR
          *    ***          *                 * *       *                **  ****  * * * *  *  *    * * *   *
1-46*01 QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h5381H1 QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNYLIE WVRQAPGQGLEWMG VINPGSGGIY YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h5381H2 QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNYLIE WVRQAPGQGLEWIG VINPGSGGIY YAQKFQGRVTMTADTSTSTVYMELSSLRSEDTAVYYCAR
h5381H3 QVQLVQSGAEVKKPGASVKVSCKTS GYAFTNYLIE WVRQAPGQGLEWIG VINPGSGGIY YAQKFQGRVTLTADTSTSTAYMELSSLRSEDTAVYYCAR
h5381H4 QVQLVQSGAEVKKPGASVKVSCKTS GYAFTNYLIE WVRQAPGQGLEWIG VINPGSGGIY YAQKFQGRVTLTADKSTSTAYMELSSLRSEDTAVYYCAR
                  V                 #                   #         N         T                   F
```

```
seq     100       110
AbM               110
                 i   b b b
538_1   SETHDTWFAY WGQGTLVTVSA (SEQ ID NO: 1771)
                           * ("1-46*01" sequence is disclosed as SEQ ID NO: 1772)
h5381H1 SETHDTWFAY WGQGTLVTVSS (SEQ ID NO: 1773)
h5381H2 SETHDTWFAY WGQGTLVTVSS (SEQ ID NO: 1774)
h5381H3 SETHDTWFAY WGQGTLVTVSS (SEQ ID NO: 1775)
h5381H4 SETHDTWFAY WGQGTLVTVSS (SEQ ID NO: 1776)
           @
```

deamidation substitutions: Q/S/A
@ tryptophan oxidation substitutions: Y/F/H

Figure 63QQQ
humanized sequences of CHA.7.538_1 antibody VL

Potential humanized sequence based on IMGT IGKV1-39*01 acceptor framework
IGKV1-39*01
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP (SEQ ID NO: 1777)

Joining region IMGT J00242|IGKJ2*01|YTFGQGTKLEIK (SEQ ID NO: 1778)

IGKV1-17*02
DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYCLQHNSYPP (SEQ ID NO: 1779)

```
seq                10        20        30        40        50        60        70        80
AbM                10        20        30        40        50        60        70        80
           b b b    p p     p b b  b    b   bi bi i    ii ibbi      i   b   b        b b b  b    ib bib
538       DIVMTQSQKFISTSVGDRVSITC KASQSVRIAVA WFQQKPGQSPKALIY LASTRHT GVPDRFTGSGSGTDFTLTISNVQSEDLADYFC
            *    **** *      *                  *     **  *                 *  *                 ** *  * * *
IGKV1-39  DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h538L1    DIQMTQSPSSLSASVGDRVTITC KASQSVRIAVA WYQQKPGKAPKLLIY LASTRHT GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h538L2    DIQMTQSPSSLSASVGDRVTITC KASQSVRIAVA WFQQKPGKAPKALIY LASTRHT GVPSRFSGSGSGTDFTLTISSVQPEDFATYYC
                    I T                                 S                                        L   F

seq       90        100
AbM       90        100
          ibi  iib  i   b b b
538       LQHWNYPYT FGGGTKLEIK (SEQ ID NO: 1780)
                    *
IGKV1-39  QQSYSTPP (SEQ ID NO: 1781)
h538L1    LQHWNYPYT FGQGTKLEIK (SEQ ID NO: 1782)
h538L2    LQHWNYPYT FGQGTKLEIK (SEQ ID NO: 1783)
             @#
```

deamidation substitutions: Q/S/A/D
@ tryptophan oxidation substitutions: Y/F/H

Figure 63RRR
humanized sequences of CHA.7.538_2 antibody VH

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework
IGHV1-46*01
QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR (SEQ ID NO: 1784)
Joining region
IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS (SEQ ID NO: 1785)

```
seq              10        20        30        40        50        60        70        80        90
AbM              10        20        30        40        50  a     60        70        80  abc   90
          b b b     p     p b b b   b b    b  bi i     i ibb  b          i  b   b b b x    b b b  b     bibibb
538_2   QVQLQQSGAELVRPGTSVKMSCKAA GYTFTNYWIG WVKQRPGHGLEWIG DIYPGGGYTN YNEKFKGKATLTADTSSSTAYMQLSSLTSEDSAIYYCAS
          *     *** *   *    *              * *  *   *              **  * ** * *   *  *  *    *   * *   *
1-46*01 QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h5382H1 QVQLVQSGAEVKKPGASVKVSCKAS GYTFTNYWIG WVRQAPGQGLEWMG DIYPGGGYTN YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h5382H2 QVQLVQSGAEVKKPGASVKVSCKAS GYTFTNYWIG WVRQAPGQGLEWIG DIYPGGGYTN YAQKFQGRVTMTADTSTSTVYMELSSLRSEDTAVYYCAS
h5382H3 QVQLVQSGAEVKKPGASVKMSCKAS GYTFTNYWIG WVRQAPGQGLEWIG DIYPGGGYTN YAQKFQGRATLTADTSTSTAYMELSSLRSEDTAVYYCAS
                  V                 # @                 #  N                                          I
```

```
seq     100       110
AbM               110
                i   b b b
538_2   PYYGSSYGFAF WGQGTLVTVSA (SEQ ID NO: 1786)
                            * ("1-46*01" sequence is disclosed as SEQ ID NO: 1787)
h5382H1 PYYGSSYGFAF WGQGTLVTVSS (SEQ ID NO: 1788)
h5382H2 PYYGSSYGFAF WGQGTLVTVSS (SEQ ID NO: 1789)
h5382H3 PYYGSSYGFAF WGQGTLVTVSS (SEQ ID NO: 1790)
```

deamidation substitutions: Q/S/A
@ tryptophan oxidation substitutions: Y/F/H

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Figure 63SSS

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework (AbM CDR definition)
IGHV1-46*01 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR (SEQ ID NO: 1791)

Joining region IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS (SEQ ID NO: 1792)

```
seq              10        20        30        40        50        60        70        80        90
AbM              10        20        30        40        50  a     60        70        80  abc   90
          b b b     p     p b b b   b b    b  bi i     i ibb  b          i  b   b b b x    b b b  b     bibibb
524       QVQLQQSGPEVVRPGVSVKISCKGS GYKFPDYVMH WVKQSHAKSLEWIG IISIYSGNTN YNQKFKGKATMTVDKSSSTAYMELARLTSEDSAIYYCAR
             *   *  **  *   *   *              * *****   *              *   * **   * * *  *    ** *   * *
1-46*01   QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h524H1    QVQLVQSGAEVKKPGASVKVSCKAS GYKFPDYVMH WVRQAPGQGLEWMG IISIYSGNTN YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h524H2    QVQLVQSGAEVKKPGASVKVSCKAS GYKFPDYVMH WVRQAPGQGLEWIG IISIYSGNTN YAQKFQGRVTMTVDTSTSTVYMELSSLRSEDTAVYYCAR
h524H3    QVQLVQSGAEVKKPGASVKISCKGS GYKFPDYVMH WVRQAPGQGLEWIG IISIYSGNTN YAQKFQGRATMTVDTSTSTAYMELSSLRSEDTAVYYCAR
h524H4    QVQLVQSGAEVKKPGASVKISCKGS GYKFPDYVMH WVRQAPGQGLEWIG IISIYSGNTN YAQKFQGRATMTVDKSTSTAYMELSSLRSEDTAVYYCAR
                     V                                                  # #  N                                I
```

```
seq     100       110
AbM               110
                  i   b b b
524       EGDLPMFAY WGQGTLVTVSA (SEQ ID NO: 1793)
                              * ("1-46*01" sequence disclosed as SEQ ID NO: 1794)
h524H1    EGDLPMFAY WGQGTLVTVSS (SEQ ID NO: 1795)
h524H2    EGDLPMFAY WGQGTLVTVSS (SEQ ID NO: 1796)
h524H3    EGDLPMFAY WGQGTLVTVSS (SEQ ID NO: 1797)
h524H4    EGDLPMFAY WGQGTLVTVSS (SEQ ID NO: 1798)
               @
```

deamidation substitutions: Q/S/A
@ methionine oxidation substitutions: L/F/A

Figure 63TTT

Potential humanized sequence based on IMGT IGKV3-11*01 acceptor framework (AbM CDR definition)
IGKV3-11*01 EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPP
(SEQ ID NO: 1799)

Joining region IMGT J00242|IGKJ2*01|YTFGQGTKLEIK (SEQ ID NO: 1800)

```
seq                 10        20        30        40        50        60        70        80
AbM                 10        20        30        40        50        60        70        80
             b b b    p p     b b b  b   b   bi bi i    ii ibbi      i   b   b        b b b  b    ib bib
524          QIVLTQSPAIMSASPGEKVTMTC NASSSVS-YMY WYQQKPISSPRLLIY DTSNLAS GVPVRFSGSGSGTSYSLTIGRMEAEDAATYYC
             *       ** *    ** **                    ***                 * *          ***   *** * * * *
IGKV3-11     EIVLTQSPATLSLSPGERATLSC RASQSVSSYLA WYQQKPGQAPRLLIY DASNRAT GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC
h524L1       EIVLTQSPATLSLSPGERATLSC NASSSVS-YMY WYQQKPGQAPRLLIY DTSNLAS GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC
h524L2       EIVLTQSPATLSLSPGERATLSC NASSSVS-YMY WYQQKPGQAPRLLIY DTSNLAS GIPARFSGSGSGTDYTLTISSLEPEDFAVYYC
h524L3       EIVLTQSPATLSLSPGERVTMSC NASSSVS-YMY WYQQKPGQAPRLLIY DTSNLAS GVPARFSGSGSGTDYTLTISSMEPEDFAVYYC
                        M A           #                   S         #                                 A
```

```
seq          90        100
AbM          90        100
             ibi  iib  i   b b b
524          QQWSSYPLT FGAGTKVEVK (SEQ ID NO: 1801)
                       *   * *
IGKV3-11     QQRSNWPP             (SEQ ID NO: 1802)
h524L1       QQWSSYPLT FGQGTKLEIK (SEQ ID NO: 1803)
h524L2       QQWSSYPLT FGQGTKLEIK (SEQ ID NO: 1804)
h524L3       QQWSSYPLT FGQGTKVEIK (SEQ ID NO: 1805)
               @             V
```

deamidation substitutions: Q/S/A/D
@ tryptophan oxidation substitutions: Y/F/H

WO 2018/220446
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Figure 63UUU

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework (AbM CDR definition)
IGHV1-46*01 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR (SEQ ID NO: 1806)

Joining region IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS (SEQ ID NO: 1807)

```
seq              10        20        30        40        50        60        70        80        90
AbM              10        20        30        40        50  a     60        70        80  abc   90
          b b b     p     p b b b   b b    b  bi i     i ibb  b          i  b   b b b x    b b b  b     bibibb
530       QVQLQQSGAELMRPGTSVKVSCKAS GYAFTNHLIE WIKQRPGQGLEWIG VINPGSDSTD YNEKFKDKATLTADKSSSTAYMQLSSLTSDDSAVYFCAR
             *     ***  *                      ** *       *              **  **** * * * *  *  *    * * *   *
1-46*01   QVQLVQSGAEVKKPGASVKVSCKAS GYTFTSYYMH WVRQAPGQGLEWMG IINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h530H1    QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNHLIE WVRQAPGQGLEWMG VINPGSDSTD YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
h530H2    QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNHLIE WVRQAPGQGLEWIG VINPGSDSTD YAQKFQGRVTMTADTSTSTVYMELSSLRSEDTAVYYCAR
h530H3    QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNHLIE WIRQAPGQGLEWIG VINPGSDSTD YAQKFQGRATLTADTSTSTAYMELSSLRSEDTAVYYCAR
h530H4    QVQLVQSGAEVKKPGASVKVSCKAS GYAFTNHLIE WIRQAPGQGLEWIG VINPGSDSTD YAQKFQGRATLTADKSTSTAYMELSSLRSEDTAVYYCAR
                     M                   #                   #         N                                   F
```

```
seq     100       110
AbM               110
                 i   b b b
530     SLYYNSWFVY WGQGTLVTVSA (SEQ ID NO: 1808)
                           * ("1-46*01" sequence disclosed as SEQ ID NO: 1809)
h530H1  SLYYNSWFVY WGQGTLVTVSS (SEQ ID NO: 1810)
h530H2  SLYYNSWFVY WGQGTLVTVSS (SEQ ID NO: 1811)
h530H3  SLYYNSWFVY WGQGTLVTVSS (SEQ ID NO: 1812)
h530H4  SLYYNSWFVY WGQGTLVTVSS (SEQ ID NO: 1813)
            # @
```

deamidation substitutions: Q/S/A
@ tryptophan oxidation substitutions: Y/F/H

Figure 63VVV

Potential humanized sequence based on IMGT IGKV1-39*01 acceptor framework (AbM CDR definition)
IGKV1-39*01 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPP (SEQ ID NO: 1814) Joining region IMGT J00242|IGKJ2*01|YTFGQGTKLEIK (SEQ ID NO: 1815)

```
seq              10        20        30        40        50        60        70        80
AbM              10        20        30        40        50        60        70        80
          b b b    p p     p b b  b   b   bi bi i    ii ibbi      i   b   b        b b b  b    ib bib
530       DIQMTQSPASLSASVGETVTITC RASENIYSYLA WYQQKRGKSPQLLVY NAKTLVE GVPSRFSGSGSGTQFSLKINSLQPEDFGSYYC
                 *       **                      *  * * *                       * * * *       **
IGKV1-39  DIQMTQSPSSLSASVGDRVTITC RASQSISSYLN WYQQKPGKAPKLLIY AASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h530L1    DIQMTQSPSSLSASVGDRVTITC RASENIYSYLA WYQQKPGKAPKLLIY NAKTLVE GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
h530L2    DIQMTQSPSSLSASVGDRVTITC RASENIYSYLA WYQQKPGKAPKLLVY NAKTLVE GVPSRFSGSGSGTDFTLTISSLQPEDFQTYYC
                                   #                 S       #
```

```
seq          90        100
AbM          90        100
             ibi  iib  i   b b b
530          QHHYGTPYT FGGGTKLEIK (SEQ ID NO: 1816)
                        *
IGKV1-39     QQSYSTPP             (SEQ ID NO: 1817)
h530L1       QHHYGTPYT FGQGTKLEIK (SEQ ID NO: 1818)
h530L2       QHHYGTPYT FGQGTKLEIK (SEQ ID NO: 1819)
```

deamidation substitutions: Q/S/A/D

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Figure 63WWW

What	Sequences
humanized CHA.7.518 VH h518HH1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNINWVRQAPGQGLEWMGYIYPYIGGSGYAQKFQ GRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSS **(SEQ ID NO: 1820)**
humanized CHA.7.518 VH h518HH2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNINWVRQAPGQGLEWIGYIYPYIGGSGYAQKFQG RVTMTADTSTSTVYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSS **(SEQ ID NO: 1821)**
humanized CHA.7.518 VH h518HH3	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYNINWVRQAPGQGLEWIGYIYPYIGGSGYAQKFQG RATLTADTSTSTAYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSS **(SEQ ID NO: 1822)**
humanized CHA.7.518 VH h518HH4	QVQLVQSGAEVKKPGASVKISCKASGYTFTDYNINWVRQAPGQGLEWIGYIYPYIGGSGYAQKFQGR ATLTADNSTSTAYMELSSLRSEDTAVYYCAREDKTARNAMDYWGQGTLVTVSS **(SEQ ID NO: 1823)**
humanized CHA.7.518 VL h518HL1	DIQMTQSPSSLSASVGDRVTITCRVSENIYSNLAWYQQKPGKAPKLLIYEATNLAEGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQHFWGTPYTFGQGTKLEIK **(SEQ ID NO: 1824)**
humanized CHA.7.518 VL h518HL2	DIQMTQSPSSLSASVGDRVTITCRVSENIYSNLAWYQQKPGKAPKLLIYEATNLAEGVPSRFSGSGSGT DYTLTISSLQPEDFATYYCQHFWGTPYTFGQGTKLEIK **(SEQ ID NO: 1825)**
humanized CHA.7.518 VL h518HL3	DIQMTQSPSSLSASVGDRVTITCRVSENIYSNLAWYQQKPGKAPKLLVYEATNLAEGVPSRFSGSGSG TDYTLTISSLQPEDFGTYYCQHFWGTPYTFGQGTKLEIK **(SEQ ID NO: 1826)**

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Figure 63XXX

What	Sequences
humanized CHA.7.538_1 VH h5381HH1	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPGQGLEWMGVINPGSGGIYYAQKFQ GRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSS **(SEQ ID NO: 1827)**
humanized CHA.7.538_1 VH h5381HH2	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNYLIEWVRQAPGQGLEWIGVINPGSGGIYYAQKFQG RVTMTADTSTSTVYMELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSS **(SEQ ID NO: 1828)**
humanized CHA.7.538_1 VH h5381HH3	QVQLVQSGAEVKKPGASVKVSCKTSGYAFTNYLIEWVRQAPGQGLEWIGVINPGSGGIYYAQKFQG RVTLTADTSTSTAYMELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSS **(SEQ ID NO: 1829)**
humanized CHA.7.538_1 VH h5381HH4	QVQLVQSGAEVKKPGASVKVSCKTSGYAFTNYLIEWVRQAPGQGLEWIGVINPGSGGIYYAQKFQG RVTLTADKSTSTAYMELSSLRSEDTAVYYCARSETHDTWFAYWGQGTLVTVSS **(SEQ ID NO: 1830)**
humanized CHA.7.538_1/538_2 VL h538HL1	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWYQQKPGKAPKLLIYLASTRHTGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCLQHWNYPYTFGQGTKLEIK **(SEQ ID NO: 1831)**
humanized CHA.7.538_1/538_2 VL h538HL2	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWFQQKPGKAPKALIYLASTRHTGVPSRFSGSGSGT DFTLTISSVQPEDFATYYCLQHWNYPYTFGQGTKLEIK **(SEQ ID NO: 1832)**

Figure 63YYY

What	Sequences
humanized CHA.7.538_2 VH h5382HH1	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWIGWVRQAPGQGLEWMGDIYPGGGYTNYAQKF QGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARPYYGSSYGFAFWGQGTLVTVSS (SEQ ID NO: 1833)
humanized CHA.7.538_2 VH h5382HH2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWIGWVRQAPGQGLEWIGDIYPGGGYTNYAQKFQ GRVTMTADTSTSTVYMELSSLRSEDTAVYYCASPYYGSSYGFAFWGQGTLVTVSS (SEQ ID NO: 1834)
humanized CHA.7.538_2 VH h5382HH3	QVQLVQSGAEVKKPGASVKMSCKASGYTFTNYWIGWVRQAPGQGLEWIGDIYPGGGYTNYAQKFQ GRATLTADTSTSTAYMELSSLRSEDTAVYYCASPYYGSSYGFAFWGQGTLVTVSS (SEQ ID NO: 1835)
humanized CHA.7.538_1/538_2 VL h538HL1	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWYQQKPGKAPKLLIYLASTRHTGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCLQHWNYPYTFGQGTKLEIK (SEQ ID NO: 1836)
humanized CHA.7.538_1/538_2 VL h538HL2	DIQMTQSPSSLSASVGDRVTITCKASQSVRIAVAWFQQKPGKAPKALIYLASTRHTGVPSRFSGSGSGT DFTLTISSVQPEDFATYYCLQHWNYPYTFGQGTKLEIK (SEQ ID NO: 1837)

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Figure 63ZZZ

What	Sequences
humanized CHA.7.524 VH h524H1	QVQLVQSGAEVKKPGASVKVSCKASGYKFPDYVMHWVRQAPGQGLEWMGIISIYSGNTNYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYCAREGDLPMFAYWGQGTLVTVSS (SEQ ID NO: 1838)
humanized CHA.7.524 VH h524H2	QVQLVQSGAEVKKPGASVKVSCKASGYKFPDYVMHWVRQAPGQGLEWIGIISIYSGNTNYAQKFQGRVT MTVDTSTSTVYMELSSLRSEDTAVYYCAREGDLPMFAYWGQGTLVTVSS (SEQ ID NO: 1839)
humanized CHA.7.524 VH h524H3	QVQLVQSGAEVKKPGASVKISCKGSGYKFPDYVMHWVRQAPGQGLEWIGIISIYSGNTNYAQKFQGRAT MTVDTSTSTAYMELSSLRSEDTAVYYCAREGDLPMFAYWGQGTLVTVSS (SEQ ID NO: 1840)
humanized CHA.7.524 VH h524H4	QVQLVQSGAEVKKPGASVKISCKGSGYKFPDYVMHWVRQAPGQGLEWIGIISIYSGNTNYAQKFQGRAT MTVDKSTSTAYMELSSLRSEDTAVYYCAREGDLPMFAYWGQGTLVTVSS (SEQ ID NO: 1841)
humanized CHA.7.524 VL h524L1	EIVLTQSPATLSLSPGERATLSCNASSSVSYMYWYQQKPGQAPRLLIYDTSNLASGIPARFSGSGSGTDFTLT ISSLEPEDFAVYYCQQWSSYPLTFGQGTKLEIK (SEQ ID NO: 1842)
humanized CHA.7.524 VL h524L2	EIVLTQSPATLSLSPGERATLSCNASSSVSYMYWYQQKPGQAPRLLIYDTSNLASGIPARFSGSGSGTDYTL TISSLEPEDFAVYYCQQWSSYPLTFGQGTKLEIK (SEQ ID NO: 1843)
humanized CHA.7.524 VL h524L3	EIVLTQSPATLSLSPGERVTMSCNASSSVSYMYWYQQKPGQAPRLLIYDTSNLASGVPARFSGSGSGTDYT LTISSMEPEDFAVYYCQQWSSYPLTFGQGTKVEIK (SEQ ID NO: 1844)

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Figure 63AAAA

What	Sequences
humanized CHA.7.530 VH h530H1	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNHLIEWVRQAPGQGLEWMGVINPGSDSTDYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTAVYYCARSLYYNSWFVYWGQGTLVTVSS (SEQ ID NO: 1845)
humanized CHA.7.530 VH h530H2	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNHLIEWVRQAPGQGLEW**I**GVINPGSDSTDYAQKFQGRVT MT**A**DTSTSTVYMELSSLRSEDTAVYYCARSLYYNSWFVYWGQGTLVTVSS (SEQ ID NO: 1846)
humanized CHA.7.530 VH 530H3	hQVQLVQSGAEVKKPGASVKVSCKASGYAFTNHLIEW**I**RQAPGQGLEW**I**GVINPGSDSTDYAQKFQGR**A**T **L**T**A**DTSTST**A**YMELSSLRSEDTAVYYCARSLYYNSWFVYWGQGTLVTVSS (SEQ ID NO: 1847)
humanized CHA.7.530 VH h530H4	QVQLVQSGAEVKKPGASVKVSCKASGYAFTNHLIEWIRQAPGQGLEWIGVINPGSDSTDYAQKFQGRATL TAD**K**STSTAYMELSSLRSEDTAVYYCARSLYYNSWFVYWGQGTLVTVSS (SEQ ID NO: 1848)
humanized CHA.7.530 VL h530L1	DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIYNAKTLVEGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQHHYGTPYTFGQGTKLEIK (SEQ ID NO: 1849)
humanized CHA.7.530 VL h530L2	DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLL**V**YNAKTLVEGVPSRFSGSGSGTDF TLTISSLQPEDF**G**TYYCQHHYGTPYTFGQGTKLEIK (SEQ ID NO: 1850)

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