# GUIDANCE AND NAVIGATION CONTROL PROTEINS AND METHOD OF MAKING AND USING THEREOF

## CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 62/648880 filed March 27, 2018, and U.S. Provisional Patent Application No. 62/648888 filed March 27, 2018, the entire disclosures of which are expressly incorporated by reference herein.

## TECHNICAL FIELD

The present application generally relates to the technical field of Guidance and Navigation Control (GNC) proteins with multi-specific binding activities against surface molecules on both immune cells and tumor cells, and more particularly relates to making and using GNC proteins.

## BACKGROUND

Cancer cells develop various strategies to evade the immune system. One of the underlaying mechanisms for the immune escape is the reduced recognition of cancer cells by the immune system. Defective presentation of cancer specific antigens or lack of thereof results in immune tolerance and cancer progression. In the presence of effective immune recognition tumors use other mechanisms to avoid elimination by the immune system. Immunocompetent tumors create suppressive microenvironment to downregulate the immune response. Multiple players are involved in shaping the suppressive tumor microenvironment, including tumor cells, regulatory T cells, myeloid-derived suppressor cells, stromal cells, and other cell types. The suppression of immune response can be executed in a cell contact-independent manner via secretion of immunosuppressive cytokines or elimination of essential survival factors from the local environment. The cell contact-dependent suppression relies on molecules expressed on the cell surface, e.g. Programmed Death Ligand 1 (PD-L1), T-lymphocyte-associated protein 4 (CTLA-4), and others [Dunn, et al., 2004, Immunity, 21(2): 137-48; Adachi & Tamada, 2015, Cancer Sci., 106(8): 945-50].

As the mechanisms by which tumors evade recognition by the immune system continue to be better understood, new treatment modalities that target these mechanisms have recently emerged. On March 25, 2011, the U. S. Food and Drug Administration (FDA) approved Ipilimumab injection (Yervoy, Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. Yervoy binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expressed on activated T cells and blocks the interaction of CTLA-4 with CD80/86 on antigen-presenting cells thereby blocking the negative or inhibitory signal delivered into the T cell through CTLA-4 resulting in re-activation of the antigen-specific T cell leading to, in many patients, eradication of the tumor. A few years later in 2014 the FDA approved Keytruda (Pembrolizumab, Merck) and Opdivo (Nivolumab, Bristol-Myers Squibb) for treatment of advanced melanoma. These monoclonal antibodies bind to PD-1 which is expressed on activated and/or exhausted T cells and block the interaction of PD-1 with PD-L1 expressed on tumors thereby eliminating the inhibitory signal through PD-1 into the T cell resulting in re-activation of the antigen-specific T cell leading to again, in many patients, eradication of the tumor. Since then additional clinical trials have been performed comparing the single monoclonal antibody Yervoy to the combination of the monoclonal antibodies Yervoy and Opdivo in the treatment of advanced melanoma which showed improvement in overall survival and progression-free survival in the patients treated with the combination of antibodies. (Hodi et al., 2016, Lancet Oncol. 17(11):1558-1568, Hellman et al., 2018, Cancer Cell 33(5): 853-861). However, as many clinical trials have shown a great benefit of treating cancer patients with monoclonal

antibodies that are specific for one or more immune checkpoint molecules data has emerged that only those patients with a high mutational burden that generates a novel T cell epitope(s) which is recognized by antigen-specific T cells show a clinical response (Snyder et al., 2014, NEJM 371:2189-2199). Those patients that have a low tumor mutational load mostly do not show an objective clinical response (Snyder et al., 2014, NEJM 371:2189-2199, Hellman et al., 2018, Cancer Cell 33(5): 853-861).

In recent years other groups have developed an alternate approach that does not require the presence of neoepitope presentation by antigen-presenting cells to activate T cells. One example is the development of a bi-specific antibody where the binding domain of an antibody which is specific for a tumor associated antigen, e.g., CD19, is linked to and antibody binding domain specific for CD3 on T cells thus creating a bi-specific T cell engager or BiTe molecule. In 2014, the FDA approved a bi-specific antibody called Blinatumumab for the treatment of Precursor B-Cell Acute Lymphoblastic Leukemia. Blinatumumab links the scFv specific for CD19 expressed on leukemic cells with the scFv specific for CD3 expressed on T cells (Bejnjamin and Stein 2016, Ther Adv Hematol 7(3):142-146). However, despite an initial response rate of >50% in patients with relapsed or refractory ALL many patients are resistant to Blinatumumab therapy or relapse after successful treatment with Blinatumumab. Evidence is emerging that the resistant to Blinatumumab or who relapse after Blinatumumab treatment is attributable to the expression of immune checkpoint inhibitory molecules expressed on tumor cells, such as PD-L1 that drives an inhibitory signal through PD-1 expressed on activated T cells (Feucht et al., 2016, Oncotarget 7(47):76902-76919). In a case study of a patient who was resistant to therapy with Blinatumumab, a second round of Blinatumumab therapy was performed but with the addition of a monoclonal antibody, pembrolizumab (Keytruda, Merck), which specifically binds to PD-1 and blocks the interaction of T cell-expressed PD-1 with tumor cell expressed PD-L1, resulted in a dramatic response and reduction of tumor cells in the bone marrow from 45% to less than 5% in this one patient (Feucht et al., 2016, Oncotarget 7(47):76902-76919). These results show that combining a bi-specific BiTe molecule with one or more monoclonal antibodies can significantly increase clinical activity compared to either agent alone. Despite the promising outcome, the cost leading to the combined therapy must be high due to multiple clinical trials and the difficulty in recruiting representative populations.

Adoptive cell therapy with chimeric antigen receptor T cells (CAR-T) is another promising immunotherapy for treating cancer. The clinical success of CAR-T therapy has revealed durable complete remissions and prolonged survival of patients with CD19-positive treatment-refractory B cell malignancies (Gill & June. 2015. Immunol Rev, 263: 68–89). However, the cost and complexity associated with the manufacture of a personalized and genetically modified CAR-T immunotherapy has restricted their production and use to specialized centers for treating relatively small numbers of patients. Cytokine release syndrome (CRS), also known as cytokine storms, is the most notable adverse effect after the infusion of engineered CAR-T cells (Bonifant et al., 201, Mol Ther Oncolytics. 3: 16011). In many cases, the onset and severity of CRS seems to be specialized personal events. Current options of mitigating CRS are mainly focused on rapid response and management care because the option of controlling CRS prior to T cell infusion is limited.

While the efficacy of CAR-T therapy specific for a CD19-positive B cell malignancy is now established, the efficacy of CAR-T therapy against solid tumors has not been unequivocally demonstrated to date. Currently, many clinical trials are in progress to explore a variety of solid tumor-associated antigens (TAA) for CAR-T therapy. Inefficient T cell trafficking into the tumors, an immunosuppressive

tumor micro-environment, suboptimal antigen recognition specificity, and lack of control over treatment-related adverse events are currently considered as the main obstacles in solid tumor CAR-T therapy (Li et al., 2018, J Hematol Oncol. 11(1):22-40). The option of managing the therapeutic effect, as well as any adverse effect before and after the CAR-T cell infusion, is limited.

## SUMMARY

The present application provides guidance and navigation control (GNC) proteins with multi-specific antigen binding activities to the surface molecules of a T cell and a tumour cell. In one embodiment, the guidance and navigation control (GNC) protein comprises a binding domain for a T cell activating receptor, a binding domain for a tumor associated antigen, a bind domain for an immune checkpoint receptor, and a binding domain for a T cell co-stimulating receptor.

In one embodiment, the binding domain for the tumor associated antigen is not adjacent to the binding domain for the T cell co-stimulating receptor. In one embodiment, the binding domain for the T cell activating receptor is adjacent to the binding domain for the tumor associated antigen (TAA). The T cell activating receptor may include without limitation CD3. The T cell co-stimulating receptor may include without limitation 4-1BB, CD28, OX40, GITR, CD40L, ICOS, Light, CD27, CD30, or a combination thereof. The immune checkpoint receptor may include without limitation PD-L1, PD-1, TIGIT, TIM-3, LAG-3, CTLA4, BTLA, VISTA, PDL2, CD160, LOX-1, siglec-15, CD47, or a combination thereof.

The tumor associated antigen (TAA) may include without limitation ROR1, CD19, EGFRVIII, BCMA, CD20, CD33, CD123, CD22, CD30, CEA, HER2, EGFR, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, or a combination thereof. In one embodiment, the tumor associated antigen may be ROR1. In one embodiment, the tumor associated antigen may be CD19. In one embodiment, the tumor associated antigen may be EGFRVIII.

In on embodiment, the tumor associated antigen may be a receptor on a lung cancer cell, a liver cancer cell, a breast cancer cell, a colorectal cancer cell, an anal cancer cell, a pancreatic cancer cell, a gallbladder cancer cell, a bile duct cancer cell, a head and neck cancer cell, a nasopharyngeal cancer cell, a skin cancer cell, a melanoma cell, an ovarian cancer cell, a prostate cancer cell, a urethral cancer cell, a lung cancer cell, a non-small lung cell cancer cell, a small cell lung cancer cell, a brain tumour cell, a glioma cell, a neuroblastoma cell, an esophageal cancer cell, a gastric cancer cell, a liver cancer cell, a kidney cancer cell, a bladder cancer cell, a cervical cancer cell, an endometrial cancer cell, a thyroid cancer cell, an eye cancer cell, a sarcoma cell, a bone cancer cell, a leukemia cell, a myeloma cell, a lymphoma cell, or a combination thereof. In one embodiment, the tumor associated antigen may be a receptor on a B cell.

In one embodiment, the guidance and navigation control (GNC) protein may be an antibody or an antibody monomer or a fragment thereof. In one embodiment, the GNC protein may be a tri-specific antibody. In one embodiment, the GNC protein may be a tetra-specific antibody. In one embodiment, the GNC protein includes Fc domain or a fragment thereof. Any Fc domain from an antibody may be used. Example Fc domains may include Fc domains from IgG, IgA, IgD, IgM, IgE, or a fragment or a combination thereof. Fc domain may be natural or engineered. In one embodiment, the Fc domain may contain an antigen binding site.

In one embodiment, the guidance and navigation control (GNC) protein is an antibody. In one embodiment, the tumor associated antigen comprises ROR1, CD19, or EGRFVIII. In on embodiment, the T cell activating receptor comprises CD3 and the binding domain for CD3 may be linked to the binding domain for the tumor associated (TAA) antigen through a linker to form a CD3-TAA pair. In one

embodiment, the IgG Fc domain may intermediate the CD3-TAA pair and the binding domain for the immune checkpoint receptor. In one embodiment, the immune checkpoint receptor may be PD-L1.

In one embodiment, the linker may be a covalent bond. In one embodiment, the linker may be a peptide linker. In one embodiment, the peptide linker has length not exceeding 100 amino acids. In one embodiment, the peptide linker has a length not exceeding 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids. In one embodiment, the peptide linker has a length not exceeding 10 amino acids. In one embodiment, the peptide linker has a length from about 2 amino acids to about 10 amino acids. In one embodiment, the peptide linker includes 2, 5, or 10 amino acids.

In on embodiment, the guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for CD3, the binding domain for EGFRVIII, IgG Fc domain, the bind domain for PD-L1, and the binding domain for 41-BB. In one embodiment, the GNC protein may include an amino acid sequence having a percentage homology to SEQ ID NO. 80 and 82. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%. In one embodiment, the GNC protein is a tetra- specific antibody.

In one embodiment, the guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for 4-1BB, the binding domain for PD-L1, IgG Fc domain, the bind domain for ROR1, and the binding domain for CD3. In one embodiment, the GNC protein includes an amino acid sequence having a percentage homology to SEQ ID NO. 88 and 90. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%. In one embodiment, the GNC protein is a tetra- specific antibody.

The guidance and navigation control (GNC) protein has a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal, the binding domain for CD3, the binding domain for CD19, IgG Fc domain, the bind domain for PD-L1, and the binding domain for 4-1BB. In one embodiment, the GNC protein includes an amino acid sequence having a percentage homology to SEQ ID NO. 104 and 106. The percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%. In one embodiment, the GNC protein is a tetra- specific antibody.

In one embodiment, the GNC protein comprises an amino acid having a percentage homology to SEQ ID NO. 50, 52, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110, and the percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In another aspect, the application provides nucleic acid sequences encoding the GNC protein or its fragments disclosed thereof. In one embodiment, the nucleic acid has a percentage homology to SEQ ID NO. 49, 51, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, and 109, and the percentage homology is not less than 70%, 80%, 90%, 95%, 98% or 99%.

In one embodiment, the guidance and navigation control (GNC) protein, comprising a cytotoxic cell binding moiety and a cancer-targeting moiety. Any cytotoxic cells may be a potential binding target by the disclosed GNC proteins. Examples of the cytotoxic cell include, without limitation, T-cell, NK cell, macrophage cell, and dendritic cell.

In one embodiment, the GNC protein includes a T-cell binding moiety. The T-cell binding moiety has a binding specificity to a T-cell receptor. Examples T-cell receptor include without limitation CD3, CD28, PDL1, PD1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40L, VISTA, ICOS, BTLA, Light, CD30, NKp30, CD28H, CD27, CD226, CD96, CD112R, A2AR, CD160, CD244, CECAM1, CD200R, TNFRSF25 (DR3), or a combination thereof.

In one embodiment, the GNC protein includes a NK cell binding moiety. The NK cell binding moiety has a binding specificity to a NK cell receptor. Examples NK cell receptor include, without limitation, receptors for activation of NK cell such as CD16, NKG2D, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DS1, NKG2C, NKG2E, NKG2H; agonist receptors such as NKp30a, NKp30b, NKp46, NKp80, DNAM-1, CD96, CD160, 4-1BB, GITR, CD27, OX-40, CRTAM; and antagonist receptors such as KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR3DL3, NKG2A, NKp30c, TIGIT, SIGLEC7, SIGLEC9, LILR, LAIR-1, KLRG1, PD-1, CTLA-4,CD161.

In one embodiment, the GNC protein includes a macrophage binding moiety. The macrophage binding moiety has a binding specificity to a macrophage receptor. Examples macrophage receptor include, without limitation, agonist receptor on macrophage such as TLR2, TLR4, CD16, CD64, CD40, CD80, CD86, TREM-1, TREM-2, ILT-1, ILT-6a, ILT-7, ILT-8, EMR2, Dectin-1, CD69; antagonist receptors such as CD32b, SIRPα, LAIR-1, VISTA, TIM-3, CD200R, CD300a, CD300f, SIGLEC1, SIGLEC3, SIGLEC5,SIGLEC7, SIGLEC9, ILT-2, ILT-3, ILT-4, ILT-5, LILRB3, LILRB4, DCIR; and other surface receptors such as CSF-1R, LOX-1, CCR2, FRβ, CD163, CR3, DC-SIGN, CD206, SR-A, CD36, MARCO.

In one embodiment, the GNC protein includes a dendritic cell binding moiety. The dendritic cell binding moiety has a binding specificity to a dendritic cell receptor. Examples dendritic cell receptor include, without limitation, agonist receptors on dendritic cell such as TLR, CD16, CD64, CD40, CD80, CD86, HVEM,CD70; antagonist receptors such as VISTA, TIM-3, LAG-3, BTLA; and other surface receptors such as CSF-1R, LOX-1, CCR7, DC-SIGN, GM-CSF-R, IL-4R, IL-10R, CD36, CD206, DCIR, RIG-1, CLEC9A, CXCR4.

The cancer targeting moiety has a binding specificity to a cancer cell receptor. Example cancer cell receptor include without limitation BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, or a combination thereof.

In one embodiment, GNC proteins comprise at least one T-cell binding moiety and at least one cancer cell binding moiety, wherein the T-cell binding moiety has a binding specificity to a T-cell receptor comprising CD3, CD28, PDL1, PD1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40, VISTA, ICOS, BTLA, Light, CD30, CD27, or a combination thereof, and wherein the cancer cell binding moiety has a binding specificity to a cancer cell receptor.

In one embodiment, the GNC protein is capable of activating a T-cell by binding the T-cell binding moiety to a T-cell receptor on the T-cell. In one embodiment, the GNC protein comprises a bi-specific antibody or antibody monomer, a tri-specific antibody or antibody monomer, a tetra-specific antibody or antibody monomer, an antigen-binding fragment thereof, or a combination thereof.

In one embodiment, the GNC protein may have a first moiety and a second moiety. In one embodiment, the first moiety may include a T-cell binding moiety, a NK cell binding moiety, a macrophage binding moiety, or a dendritic cell binding moiety. The second moiety comprises the cancer-targeting moiety.

The application further provides a cytotoxic cell incorporating the GNC protein disclosed herein. In one embodiment, the cytotoxic includes the GNC protein and a cytotoxic cell. The cytotoxic cell may T cell, NK cell, macrophage, dendritic cell, or a combination thereof. In one embodiment, the T cell may be autologous T cells, allo T cells, or universal donor T cells. In one embodiment, the cytotoxic cell includes a T cell having a T cell activating receptor and a T cell co-stimulating receptor, and the GNC protein bound to the T cell through interaction with the T cell activating receptor, the T cell co-stimulating receptor, or a combination there.

The application further provides a cancer cell incorporating the GNC protein disclosed herein. In one embodiment, the cancer cell, comprising a cancer cell having a tumor associated antigen, and the GNC protein of Claim 1 bound to cancer cell through the interaction with the tumor associated antigen.

The application further provides a biological complex incorporating the GNC protein disclosed herein. In one embodiment, the biological complex includes a T cell having a T cell activating receptor and a T cell co-stimulating receptor, a cancer cell having a tumor associated antigen, and the GNC protein of Claim 1, wherein the GNC protein is bound to the T cell through the interaction with the T cell activating receptor, the T cell co-stimulating receptor, or a combination thereof and wherein the GNC protein is bound to the cancer cell through the interaction with the tumor associated antigen.

In a further aspect, the application provides a pharmaceutical composition useful for treating a cancer condition. In one embodiment, the pharmaceutical composition includes the GNC protein or cytotoxic cell disclosed herein, and a pharmaceutically acceptable carrier.

In a further aspect, the application provides methods for making and using the disclosed GNC proteins.

In a further aspect, the application provides methods for treating a subject having a cancer. In one embodiment, the method includes the step of administering to the subject an effective amount of the pharmaceutical composition disclosed herein.

The objectives and advantages of the present application will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

## BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features of this disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only several embodiments arranged in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings, in which:

FIGURE 1 shows a general scheme of GNC proteins characterized by their composition of multiple antigen binding domains (AgBd) and linkers;

FIGURE 2 shows examples of GNC antibodies as an embodiment of the GNC protein disclosed herein: 2A, a tetra-specific GNC antibody with an EGFRvIII AgBD (SI-39E18); 2B, a tetra-specific GNC antibody with an ROR1 AgBD (SI-35E20); and 2C, a tetra-specific GNC antibody with an CD19 AgBD (SI-38E17);

FIGURE 3 illustrates how a tetra-specific GNC antibody may bind to both a T cell and a tumor cell through multiple AgBDs;

FIGURE 4 shows examples of tetra-specific GNC antibody binding to human ROR1 transfected CHO cells;

FIGURE 5 shows examples of tetra-specific GNC antibody binding to human 4-1BB transfected CHO cells;

FIGURE 6 shows examples of tetra-specific GNC antibody binding to human PD-L1 transfected CHO cells;

FIGURE 7 shows the example tetra-specific GNC antibodies with the binding domain 323H7, which is specific for the Ig domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with PBMC as effectors;

FIGURE 8 shows the example tetra -specific GNC antibodies with the binding domain 323H7, which is specific for the Ig domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with CD8+, CD45RO+ memory T cells as effectors;

FIGURE 9 shows the example tetra-specific GNC antibodies with the binding domain 323H7, which is specific for the Ig domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with CD8+, CD45RA+ naive T cells as effectors;

FIGURE 10 shows the example tetra-specific GNC antibodies with the binding domain 338H4, which is specific for the Frizzled domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with PBMC as effectors;

FIGURE 11 shows the example tetra-specific GNC antibodies with the binding domain 338H4, which is specific for the Frizzled domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with CD8+, CD45RO+ memory T cells as effectors;

FIGURE 12 shows the example tetra-specific GNC antibodies with the binding domain 338H4, which is specific for the Frizzled domain of ROR1 meditated RTCC of the B-ALL cell line Kasumi2 with CD8+, CD45RA+ naive T cells as effectors;

FIGURE 13 displays redirected panT cell activity against bladder cancer cell line UM-UC-3- EGFRvIII in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies;

FIGURE 14 shows the results of measuring CD8 T cell proliferation in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies;

FIGURE 15 shows the results of tracking IFNγ secretion in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies;

FIGURE 16 shows the results of demonstrating redirected naïve T cell cytotoxicity against bladder cancer cell line UM-UC-3- EGFRvIII;

FIGURRE 17 shows the results of measuring the response of PBMC to treatment with EGFRvIII targeting tetra-specific GNC antibodies, proliferation of CD8 T cells;

FIGURE 18 shows the results of redirected panT cell activity against bladder cancer cell line UM-UC-3- EGFRvIII in the presence of monocytes in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies;

FIGURE 19 shows the functional impact of PD-L1 and 4-1BB domains on activity of tetra-specific GNC antibodies and redirected PBMC cytotoxicity against bladder cancer cell line UM-UC-3-EGFRvIII;

FIGURE 20 shows the results of redirected panT cell activity against Kasumi-2 target cell line in response to treatment with ROR1 targeting tetra-specific GNC antibodies;

FIGURE 21 shows the results of redirected PBMC activity against Kasimu-2 tumor cell line in response to treatment with CD19 targeting tetra-specific GNC antibodies;

FIGURE 22 shows CD8 T cells proliferation in response to treatment with CD19 targeting tetra-specific GNC antibodies; and

FIGURE 23 displays IFNγ production by PBMC in response to treatment with CD19 targeting tetra-specific GNC antibodies.

## DETAILED DESCRIPTION

In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

The present application relates to methods of making and using GNC proteins. In one embodiment, the guidance navigation control (GNC) proteins may include multiple antigen-specific binding domains (AgBDs) and may have the ability of directing T cells (or other effector cells) to cancer cells (or other target cells) through the binding of multiple surface molecules on a T cell and a tumor cell (FIGURE 1). In one embodiment, GNC proteins may be composed of Moiety 1 for binding at least one surface molecule on a T cell and Moiety 2 for binding at least one surface antigen on a cancer cell (TABLE 1A).

In a T cell therapy, the cytotoxic T cells are regulated by T cell proliferation signaling, as well as co-stimulation signaling via either agonist receptors or antagonist receptors on their surface. To regulate these signaling, as well as the interplay between a T cell and a cancer, multiple AgBDs may be included for Moiety 1 and Moiety 2, respectively and independently. GNC proteins may have at least one linker to link Moiety 1 and Moiety 2. The linker may vary in length. In one embodiment, the linker may be a covalent bond. In one embodiment, the linker may be a peptide having from about 1 to about 100 amino acid residues.

In some embodiments, any linker molecule can be used to link two or more AgBDs together either *in vitro* or *in vivo* by using complementary linkers of DNA/RNA or protein-protein interactions, including but not limited to, that of biotin-avidin, leucine-zipper, and any two-hybrid positive protein.

In some embodiments, the linkers may be an antibody backbone structure or antibody fragments, so that GNC protein and GNC antibody may have the same meaning, as show in FIGURE 2, an example tetra-specific GNC antibody structure. In one embodiment, the GNC protein may be a bi-specific, tri-specific, tetra-specific, penta-specific, hexa-specific, hepta-specific, or octa-specific proteins. In one embodiment, the GNC protein may be a monoclonal antibody. In one embodiment, the GNC protein may be a bi-specific, tri-specific, tetra-specific, penta-specific, hexa-specific, hepta-specific, or octa-specific antibody monomers. In one embodiment, the GNC protein may be a bi-specific, tri-specific, tetra-specific, penta-specific, hexa-specific, hepta-specific, or octa-specific antibodies.

GNC proteins or antibodies may be capable of directing the binding of a T cell to a cancer cell *in vivo* or *ex vivo*, mediated by multiple AgBDs (FIGURE 3). The T cells may be derived from the same patient or different individuals, and the cancer cell may exist *in vivo, in vitro,* or *ex vivo*. The examples provided in the present application enable GNC proteins as a prime agent in a T cell therapy, i.e. GNC-T therapy, for activating and controlling cytotoxic T cells *ex vivo*, prior to adoptive transfer.

In addition to T cells, other cytotoxic cells may be utilized by the GNC proteins for cancer killing or preventing purposes. TABLE 1B shows the example compositions of functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with NK cell binding domains. TABLE 1C shows the

example compositions of functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with macrophage binding domains. TABLE 1D shows the example compositions of functional moieties (Moiety 1 and Moiety 2) and antigen binding domain in GNC proteins with dendritic cell binding domains.

Multiple AgBDs can be divided into Moiety 1 and Moiety 2 due to their interface with a cytotoxic cell such as a T cell and a cancer cell, respectively (TABLE 1A). However, the rearrangement of multiple AgBDs may be random and in unequal numbers (TABLE 2). A GNC protein with two AgBDs may simultaneously bind to a surface molecule, such as CD3 on a T cell, and a tumor antigen, such as ROR1 on a tumor cell, for re-directing or guiding the T cell to the tumor cell. The addition of the third AgBD, e.g. specifically bind to 41BB, may help enhance anti-CD3-induced T cell activation because 41BB is a co-stimulation factor and the binding stimulates its agonist activity to activated T cells. The addition of the fourth AgBD to a GNC protein, e.g. specifically bind to PD-L1 on a tumor cell, may block the inhibitory pathway of PD-L1 on tumor cells that is mediated through its binding to PD-1 on the T cells. With these basic principles, GNC proteins may be designed and constructed to acquire multiple AgBDs specifically for binding unequal numbers of T cell antagonists and agonists, not only to re-direct activated T cells to tumor cells but also to control their activity *in vivo* (TABLE 2). Therefore, the design of GNC proteins may be any multi-specific proteins. TABLE 3 provides some example GNC proteins and antibodies with the specificity of antibody binding domains.

In one embodiment, the GNC proteins may include multi-specific antigen binding moieties characterized by two functional groups: Moiety 1 comprises multiple antigen binding domains (AgBD) whose specificities are implicated in T-cell activation, agonist co-stimulation, and/or inhibitory antagonist activity, and Moiety 2 comprises at least one cancer cell binding specificity. GNC proteins may simultaneously bind to a surface molecule, such as CD3 of a T cell, and a tumor antigen, such as ROR1 of a tumor cell, thereby re-directing or guiding the T cell to the tumor cell. An addition of the third binding domain in a GNC protein may help enhance the CD3-induced T cell activation through its direct binding of 41BB, which is a co-stimulation factor exerting agonist activity. Furthermore, an addition of the fourth binding domain in a GNC protein may bind to PD-L1 on the tumor cell to block the inhibitory pathway of PD-L1 on tumor cells that is mediated through its binding to PD-1 on the T cells. In some embodiments, GNC proteins acquire multiple binding capacities to re-direct activated T cells to tumor cells, and multiple binding may help modulate T cell activation through modulating either agonist or antagonist activity or both. Some binding capacities may be similar to that of either the chimeric antigen receptor on a CAR-T cell or a bi-specific antibody, such as the BiTe antibody. Not wanting to be bound by theory, through the interactions of various domains with cytotoxic cell receptors and tumor associated antigen, the GNC proteins may provide significant advantage as a therapeutic agent than traditional cell-based therapeutics (such as CAR-T and antibody therapy) including, without limitation, improved binding efficacy, optimized cellular signaling and cytotoxicity, as well as reduced side effects such as reduced severity of cytokine storm syndrome.

In one embodiment, the application provides an example GNC protein having 4 different binding domains. The GNC protein may a “tetra-specific antibody” with its linkers and backbone comprises antibody fragments. Of the 4 different antigen binding domains, one specifically binds to CD3 on T cells, the second binding domain is specific against a tumor associated antigen, including but not limited to other tumor antigens, such as ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM,

glypican-3, gpA33, GD2, TROP2, BCMA, CD19, CD20, CD33, CD123, CD22, CD30, and the third and fourth binding domains are specific against two distinct immune checkpoint modulators, namely, PD-L1, PD-1, OX40, 4-1BB, GITR, TIGIT, TIM-3, LAG-3, CTLA4, CD40, VISTA, ICOS, BTLA, Light, HVEM, CD73, CD39, etc. Because of their definition in function and variety in composition, GNC proteins is classified as a new class of immune-modulators for treating cancer. TABLE 4 shows the list of the example tetra-specific GNC antibodies.

In one embodiment, GNC-mediated immunotherapy may include types of antibody therapy and cell therapy. Herein, the advantages may include, but not limited to, the inclusion of an IgG Fc domain may confer the characteristic of a longer half-life in serum compared to a bi-specific BiTe molecule; second, the inclusion of two binding domains specific for immune checkpoint modulators may inhibit the suppressive pathways and engage the co-stimulatory pathways at the same time; third, that cross-linking CD3 on T cells with tumor associated antigens re-directs and guides T cells to kill the tumor cells without the need of removing T cells from the patient and genetically modifying them to be specific for the tumor cells before re-introducing them back into the patient, also known as chimeric antigen receptor T cells (CAR-T) therapy; and fourth, that GNC protein-mediated antibody therapy or T cell therapy does not involve genetic modification of T cells, the latter of which may carry the risk of transforming modified T cells to clonal expansion, i.e. T cell leukemia.

With one or more addition of the binding capacity, the advantage of GNC protein-mediated immunotherapy over conventional immunotherapies include, but not limited to, first, that inclusion of an IgG Fc domain may confer the characteristic of a longer half-life in serum compared to a bi-specific BiTe molecule; second, that inclusion of two binding domains specific for immune checkpoint modulators may inhibit the suppressive pathways and engage the co-stimulatory pathways at the same time; third, that cross-linking CD3 on T cells with tumor associated antigens re-directs and guides T cells to kill the tumor cells without the need of removing T cells from the patient and genetically modifying them to be specific for the tumor cells before re-introducing them back into the patient, also known as chimeric antigen receptor T cells (CAR-T) therapy; and fourth, that GNC protein-mediated antibody therapy or T cell therapy does not involve genetic modification of T cells, the latter of which may carry the risk of transforming modified T cells to clonal expansion, i.e. T cell leukemia.

The present disclosure may be understood more readily by reference to the following detailed description of specific embodiments and examples included herein. Although the present disclosure has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the disclosure.

EXAMPLES

While the following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially the same or similar results.

**Example 1: FACS analysis of binding of tetra-specific GNC antibody to human ROR1 transfected CHO cells**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for binding to Chinese hamster ovary cells (CHO) cells stably expressing a full-length human ROR1. Antibodies were prepared at 2X final concentration and titrated 1:5 across 3 wells of a 96 well plate in 50 ul of PBS/2% FBS and then 5,000 ROR1-CHO cells in 50 ul PBS/2%FBS were added. This mixture was incubated for 30 minutes on ice,

washed once with 200 ul PBS/2%FBS, and then the secondary antibody PE Goat anti-Human IgG Fc at 1:1000 dilution of stock was added, and this mixture was incubated for 30 minutes on ice. Cells were washed 2 x 200 ul PBS/2%FBS, resuspended in 50 ul PBS/2%FBS and analyzed on a BD LSRFORTESSA and the binding profile is shown in FIGURE 4. The tetra-specific antibodies SI-35E18, 19, and 20, with the 323H7 binding domain specific for the Ig domain of ROR1, showed higher binding than the tetra-specific GNC antibodies SI-3521, 22, and 23, with the 338H4 binding domain specific for the frizzled domain of ROR1, and the tetra-specific GNC antibodies SI-3524, 25, and 26, with the 330F11 binding domain specific for the kringle domain of ROR1, did not bind.

**Example 2: FACS analysis of binding of tetra-specific GNC antibody to human 41BB transfected CHO cells**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for binding to Chinese hamster ovary cells (CHO) cells stably expressing a full-length human ROR1. Antibodies were prepared at 2X final concentration and titrated 1:5 across 3 wells of a 96 well plate in 50 ul of PBS/2% FBS and then 5,000 ROR1-CHO cells in 50ul PBS/2%FBS were added. This mixture was incubated for 30 minutes on ice, washed once with 200 ul PBS/2%FBS, and then the secondary antibody PE Goat anti-Human IgG Fc at 1:1000 dilution of stock was added, and this mixture was incubated for 30 minutes on ice. Cells were washed 2 x 200 ul PBS/2%FBS, resuspended in 50 ul PBS/2%FBS and analyzed on a BD LSRFORTESSA and the binding profile is shown in FIGURE 5. All of the tetra-specific GNC antibodies except for the control SI-27E12 contain a 41BB binding domain, 460C3, 420H5, or 466F6 and bound to 41BB expressing CHO cells with varying intensity.

**Example 3: FACS analysis of binding of tetra-specific GNC antibody to human PDL1 transfected CHO cells**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for binding to Chinese hamster ovary cells (CHO) cells stably expressing full length human ROR1. Antibodies were prepared at 2X final concentration and titrated 1:5 across 3 wells of a 96 well plate in 50 ul of PBS/2% FBS and then 5,000 ROR1-CHO cells in 50ul PBS/2%FBS were added. This mixture was incubated for 30 minutes on ice, washed once with 200 ul PBS/2%FBS, and then the secondary antibody PE Goat anti-Human IgG Fc at 1:1000 dilution of stock was added, and this mixture was incubated for 30 minutes on ice. Cells were washed 2 x 200 ul PBS/2%FBS, resuspended in 50 ul PBS/2%FBS and analyzed on a BD LSRFORTESSA and the binding profile is shown in FIGURE 6. All of the tetra-specific GNC antibodies except for the control SI-27E15 contain the same PDL1 binding domain, PL230C6, and showed very similar binding intensity to PDL1 expressing CHO cells.

**Example 4: Re-directed T cell cytotoxicity (RTCC) assay with peripheral blood mononuclear cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human peripheral blood mononuclear cells (PBMC) as effectors. The Kasumi 2 target cells, 5 x $10^6$, were labeled with CFSE (Invitrogen, #C34554) at 0.5 uM in 10 ml of culture media for 20 minutes at 37°C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human PBMC were purified by standard ficoll density gradient from a "leukopak" which is an enriched leukapheresis product collected from normal human peripheral blood. In the final destination 96 well plate the target cells, PBMC, and

serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of PBMC (25,000), and 100 ul of each antibody dilution to each well of the assay. The assay plate was incubated at 37°C for approximately 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 7, the tetra-specific GNC antibodies all contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 323H7, and the same CD3 binding domain 284A10, but have one of the 41BB binding domains 460C3, 420H5, and 466F6 and showed greater RTCC activity compared to the controls except for the control SI-27E12 which does not have a 41BB binding domain but appeared to be similarly potent at the tetra-specific GNC antibodies SI-35E18, 19, and 20.

**Example 5: Re-directed T cell cytotoxicity (RTCC) assay with CD8+, CD45RO+ memory T cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLE 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human CD8+, CD45RO+ memory T cells as effectors. The Kasumi 2 target cells, 5 x $10^6$, were labeled with CFSE (Invitrogen, #C34554) at 0.5 uM in 10 ml of culture media for 20 minutes at 37°C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human CD8+, CD45RO+ memory T cells were enriched from PBMC from a normal donor using the EasySep™ Human Memory CD8+ T Cell Enrichment Kit (Stemcell Technologies, #19159) as per the manufacturers protocol. The final cell population was determined to be 98% CD8+, CD45RO+ T cells by FACS analysis. In the final destination 96 well plate the target cells, T cells, and serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of CD8+, CD45RO+ memory T cells (25,000), and 100 ul of each antibody dilution to each well of the assay. The assay plate was incubated at 37C for approximately 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 8, the tetra-specific antibodies all contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 323H7, and the same CD3 binding domain 284A10, but have one of the 41BB binding domains 460C3, 420H5, and 466F6 and showed greater RTCC activity compared to the controls that do not contain one of the 41BB, PDL1, ROR1, or CD3 binding domains.

**Example 6: Re-directed T cell cytotoxicity (RTCC) assay with CD8+, CD45RA+ naive T cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human CD8+, CD45RA+ memory T cells as effectors. The Kasumi 2 target cells, 5 x 10e6, were labeled with CFSE (Invitrogen, #C34554) at 0.5 uM in 10 ml of culture media for 20 minutes at 37C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human CD8+, CD45RA+ memory T cells were enriched from peripheral blood mononuclear cells from a normal donor using the EasySep™ Human Naïve CD8+ T Cell Isolation Kit (Stemcell Technologies, #19258) as per the manufacturers protocol. The final cell population was determined to be 98% CD8+, CD45RA+ T cells by FACS analysis (data not shown). In the final destination 96 well plate the target cells, T cells, and serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of CD8+, CD45RO+ T cells (25,000), and 100 ul of each antibody dilution to each well of the assay. The assay plate was incubated at 37C for approximately 72 hours and then the

contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 9, all tetra-specific GNC antibodies contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 323H7, and the same CD3 binding domain 284A10, but have one of the 41BB binding domains 460C3, 420H5, and 466F6 and showed greater RTCC activity compared to the controls that do not contain one of the 41BB, PDL1, ROR1, or CD3 binding domains.

**Example 7: Re-directed T cell cytotoxicity (RTCC) assay with peripheral blood mononuclear cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human peripheral blood mononuclear cells (PBMC) as effectors. The Kasumi 2 target cells, 5 x $10^6$, were labeled with CFSE (Invitrogen, #C34554) at 0.5 μM in 10 ml of culture media for 20 minutes at 37°C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human PBMC were purified by standard ficoll density gradient from a "leukopak" which is an enriched leukapheresis product collected from normal human peripheral blood. In the final destination 96 well plate the target cells, PBMC, and serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of PBMC (25,000), and 100 ul of each antibody dilution to each well of the assay. The assay plate was incubated at 37°C for approximately 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 10, the tetra-specific GNC antibodies all contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 338H4, and the same CD3 binding domain 284A10, but have one of the 41BB binding domains 460C3, 420H5, and 466F6 and showed greater RTCC activity compared to the controls except for the control SI-35E36 which does not have a 41BB binding domain but appeared to be similarly potent at the tetra-specific GNC antibodies SI-35E18, 19, and 20.

**Example 8: Re-directed T cell cytotoxicity (RTCC) assay with CD8+, CD45RO+ memory T cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human CD8+, CD45RO+ memory T cells as effectors. The Kasumi 2 target cells, 5 x $10^6$, were labeled with CFSE (Invitrogen, #C34554) at 0.5 uM in 10 ml of culture media for 20 minutes at 37°C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human CD8+, CD45RO+ memory T cells were enriched from PBMC from a normal donor using the EasySep™ Human Memory CD8+ T Cell Enrichment Kit (Stemcell Technologies, #19159) as per the manufacturers protocol. The final cell population was determined to be 98% CD8+, CD45RO+ T cells by FACS analysis (data not shown). In the final destination 96 well plate the target cells, T cells, and serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of CD8+, CD45RO+ memory T cells (25,000), and 100 ul of each antibody dilution to each well of the assay. The assay plate was incubated at 37°C for approximately 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 11, the tetra-specific GNC antibodies all contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 338H4, and the same CD3 binding domain 284A10, but have one of the 41BB

binding domains 460C3, 420H5, and 466F6 and showed greater RTCC activity compared to the controls that do not contain one of the 41BB, PDL1, ROR1, or CD3 binding domains.

**Example 9: Re-directed T cell cytotoxicity (RTCC) assay with CD8+, CD45RA+ naive T cells as effectors and B-Acute Lymphoblastic Leukemia (B-ALL) cell line Kasumi-2 as targets**

The tetra-specific GNC antibodies listed in TABLEs 3 and 4 were tested for RTCC activity against the B-ALL cell line Kasumi 2 using human CD8+, CD45RA+ memory T cells as effectors. The Kasumi 2 target cells, 5 x $10^6$, were labeled with CFSE (Invitrogen, #C34554) at 0.5 M in 10 ml of culture media for 20 minutes at 37°C. The cells were washed 3 times with 50 ml of culture media before resuspending in 10 ml then counted again. Antibodies were prepared at 2X final concentration and titrated 1:3 across 10 wells of a 96 well plate in 200 ul of RPMI + 10%FBS. Human CD8+, CD45RA+ memory T cells were enriched from PBMC from a normal donor using the EasySep™ Human Naïve CD8+ T Cell Isolation Kit (Stemcell Technologies, #19258) as per the manufacturers protocol. The final cell population was determined to be 98% CD8+, CD45RA+ T cells by FACS analysis. In the final destination 96 well plate the target cells, T cells, and serially titrated antibodies were combined by adding 100 ul of target cells (5,000), 50 ul of CD8+, CD45RO+ T cells (25,000), and 100 l of each antibody dilution to each well of the assay. The assay plate was incubated at 37°C for approximately 72 hours and then the contents of each assay well were harvested and analyzed for the number of CFSE-labeled target cells remaining. As shown on FIGURE 12, the tetra-specific GNC antibodies all contain the same PDL1 binding domain PL230C6, the same ROR1 binding domain 338H4, and the same CD3 binding domain 284A10, but have one of the 41BB binding domains 460C3, 420H5, and 466F6 but did not show greater RTCC activity compared to the controls that do not contain one of the 41BB, PDL1, ROR1, or CD3 binding domains. This is in contrast to the tetra-specific GNC antibodies described in Example 6 and shown in FIGURE 6 that do show RTCC activity with CD8+, CD45RA+ naïve T cells.

**Example 10: Redirected panT cell cytotoxicity against bladder cancer cell line UM-UC-3-EGFRvIII.**

A set of tetra-specific GNC antibodies listed in TABLE 5 was assessed for their ability to lyse targets cells UM-UC-3-EGFRvIII. PanT cells were isolated with EasySep™ Human Pan T Cell Isolation Kit (Stemcell Technologies). UM-UC-3-EGFRvIII cell line was stably expressing nucleus-localized Red Fluorescent Protein (RFP) delivered via lentiviral transduction (Sartorius). UM-UC-3-EGFRvIII-RFP tumor cells were co-cultured with panT cells. Target cell lysis was assessed with flow cytometry (BD LSRFortessa) via counting the number of live targets left in culture after 96 h co-culture with panT cells. The two tetra-specific antibodies, SI-39E18 and SI-39E29, were the most efficacious at target tumor cell lysis (FIGURE 13). These two molecules are also composed of adjacent binding domains for CD3 and tumor antigen (TABLE 5).

**Example 11: CD8 T cell proliferation in response to treatment with EGFRvIII targeting tetraspecific antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 5 was assessed for their ability to stimulate CD8 T cell proliferation in the presence of targets cells UM-UC-3-EGFRvIII. PanT cells were labeled with CellTrace Violet dye (Thermo Fisher Scientific). UM-UC-3-EGFRvIII-RFP tumor cells were co-cultured with panT cells. CD8 T cell proliferation was assessed with flow cytometry (BD LSRFortessa) via dilution of the CellTrace Violet dye after 96 h of co-culture. The two tetra-specific GNC antibodies, SI-39E18 and SI-39E29, were the most efficacious at stimulating CD8 T cell proliferation in the presence of target cells (FIGURE 14). These two molecules are composed of adjacent binding domains for CD3 and tumor antigen (TABLE

5). Other molecules with the strong T cell stimulatory activity include structures containing adjacent CD3 and PD-L1 domains (TABLE 5).

**Example 12: IFNγ secretion in response to treatment with EGFRvIII targeting tetraspecific antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 5 was assessed for their ability to induce IFNγ secretion by PBMC. PBMC were isolated by Ficoll gradient. PBMC were incubated with the test molecules for 96 h. The supernatants were collected and analyzed for the presence of IFNγ using ELISA (R&D Systems) (FIGURE 15). Tetra-specific GNC antibodies with the strongest activity in this study all contained adjacent CD3 and PD-L1 domains (TABLE 5). The least active group has molecules with adjacent CD3 and tumor antigen or 4-1BB domains. The only exception from this group of tetra-specific GNC antibodies is SI-39E18, which contains adjacent CD3 and tumor antigen domains. This molecule stimulates moderate production of IFNγ that is less than the most active group of the molecules with adjacent CD3 and PD-L1 domains, but more than other molecules with a similar structural arrangement. Moderate production of IFNγ might be beneficial for the anti-tumor activity of this agent.

**Example 13: Redirected naïve T cell cytotoxicity against bladder cancer cell line UM-UC-3-EGFRvIII.**

The tetra-specific GNC antibody, SI-39E18, was tested for its ability to redirect naïve T cells to lyse targets cells UM-UC-3-EGFRvIII. Naïve T cells were isolated with EasySep™ Human Naïve Pan T Cell Isolation Kit (Stemcell Technologies). UM-UC-3-EGFRvIII-RFP tumor cells were co-cultured with naïve or panT cells. Lysis of tumor cells was assessed by counting RFP labeled tumor cell nuclei. Images were acquired on live cell imager IncuCyte (Sartorius). Activity of the antibodies was assessed after 120 hours of incubation. The treatment was tested at lower effector-to-target ratio 2.5-to-1. SI-39E18 was efficacious at redirecting naïve T cells. EC50 was at 22.08 pM for naïve T cells and 0.07 pM for panT cells (FIGURE 16).

**Example 14: Response of PBMC to treatment with EGFRvIII targeting tetra-specific GNC antibodies, proliferation of CD8 T cells.**

A set of tetra-specific GNC antibodies listed in TABLE 1 was assessed for their ability to induce CD8 T cell proliferation in the absence of target cells. PBMC were labeled with CellTrace Violet dye (Thermo Fisher Scientific) and cultured for 96 h with the test molecules. CD8 T cell proliferation was assessed with flow cytometry (BD LSRFortessa) via dilution of the CellTrace Violet dye. The most efficacious in this study molecules shared structural similarities (FIGURE 17). All these molecules contain adjacent CD3 and PD-L1 domains (TABLE 5).

**Example 15. Redirected panT cell activity against bladder cancer cell line UM-UC-3-EGFRvIII in the presence of monocytes.**

A set of tetra-specific GNC antibodies listed in TABLE 5 was assessed for their ability to lyse target cells UM-UC-3-EGFRvIII in the presence of monocytes. Monocytes were isolated from PBMC with EasySep™ Human Monocyte Isolation Kit (Stemcell Technologies). UM-UC-3-EGFRvIII-RFP tumor cells were co-cultured with panT cells and monocytes. Target cell lysis was assessed by counting RFP labeled tumor cell nuclei. Images were acquired on live cell imager IncuCyte (Sartorius). Activity of the antibodies was assessed after 96 hours of incubation. The two tetra-specific GNC antibodies, SI-39E18 and SI-39E29, were the most efficacious at target tumor cell lysis (FIGURE 18) together with molecules containing adjacent CD3 and PD-L1 binding domains (TABLE 5).

**Example 16. Redirected PBMC cytotoxicity against bladder cancer cell line UM-UC-3-EGFRvIII, functional activity of different 4-1BB domains and functional impact of PD-L1 and 4-1BB domains.**

Tetra-specific GNC antibodies listed in TABLE 5 were assessed for their ability to redirect PBMC cancer cell line UM-UC-3- EGFRvIII (UM-UC-3-EGFRvIII). UM-UC-3-EGFRvIII-RFP tumor cells were co-cultured with PBMC. Lysis of tumor cells was assessed by counting RFP labeled tumor cell nuclei. Images were acquired on live cell imager IncuCyte (Sartorius). Activity of the antibodies was assessed after 96 hours of incubation. The tetra-specific GNC antibodies with different 4-1BB domains, SI-39E4, SI-39E2 and SI-39E3, showed similar activity (FIGURE 19). The tetra-specific GNC antibodies with PD-L1 and 4-1BB domains replaced by silent (not functional) FITC domains, SI-39E1 and SI-39E5, showed reduction in lysis activity. This observation confirms functional contribution of 4-1BB and PD-L1 domains.

**Example 17. Granzyme B production by PBMC in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies, the effect of AgBD positions on the value of EC50.**

A set of tetra-specific and EGFRvIII-targeting GNC antibodies listed in TABLE 5 was assessed for their ability to induce Granzyme B secretion by PBMC. PBMC were incubated with the test molecules for 96 h. The supernatants were collected and analyzed for the presence of Granzyme B using ELISA (R&D Systems), and the level of Granzyme B was plotted to determine EC50 for each tetra-specific GNC antibody. TABLE 6 lists the structural position of AgBD in each tetra-specific GNC antibody. As shown in TABLE 6, the most active molecules in this study all contained adjacent CD3 and PD-L1 domains and 4-1BB x TAA (EGFRvIII in this study). Such a high level of Granzyme B secretion may not be desirable as the cytotoxicity *in vivo* may become too high. In this context, next group of molecules, SI-39E29 and SI-39E18, showing modest but at least 20-fold less activities contained adjacent CD3 and TAA (EGFRvIII in this study).

**Example 18. Redirected panT cell activity against Kasumi-2 target cell line in response to treatment with ROR1 targeting tetra-specific GNC antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 7 and SI-35E20 in TABEL 4 was assessed for their ability to lyse target cells Kasumi-2. Kasumi-2 cell line was stably expressing Green Fluorescent Protein (GFP) delivered via lentiviral transduction (Clontech). Kasumi-2 tumor cells were co-cultured with panT cells. Target cell lysis was assessed with flow cytometry (BD LSRFortessa) via counting the number of live targets left in culture after 96 h co-culture with panT cells (FIGURE 20). SI-35E20 was characterized as shown in FIGURE 4-9. This result shows that the efficacy of SI-35E20-mediated redirected panT cell activity against Kasumi-2 target cell line is comparable.

**Example 19. Redirected PBMC T cell activity against Kasumi-2 target cell line in response to treatment with CD19 targeting tetra-specific GNC antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 8 was assessed for their ability to lyse target cells Kasumi-2. Kasumi-2-GFP tumor cells were co-cultured with PBMC. Target cell lysis was assessed with flow cytometry (BD LSRFortessa) via counting the number of live targets left in culture after 8-days of co-culture with PBMC (FIGURE 21). SI-38E17 was among more efficacious molecules in this study.

**Example 20. CD8 T cells proliferation in response to treatment with CD19 targeting tetra-specific GNC antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 8 was assessed for their ability to stimulate CD8 T cell proliferation in the presence of targets cells Kasumi-2. PBMC were labeled with CellTrace Violet dye (Thermo Fisher Scientific). Kasumi-2-GFP tumor cells were co-cultured with PBMC. CD8 T cell proliferation was assessed with flow cytometry (BD LSRFortessa) via dilution of the CellTrace Violet dye after 8-days of co-culture. The two tetra-specific GNC antibodies, SI-38E17 and SI-38E41, were the most

efficacious at stimulating CD8 T cell proliferation in the presence of target cells (FIGURE 22). These two molecules are composed of adjacent binding domains for CD3 and tumor antigen.

**Example 21. IFNγ production by PBMC in response to treatment with CD19 targeting tetraspecific antibodies.**

A set of tetra-specific GNC antibodies listed in TABLE 8 was assessed for their ability to induce IFNγ secretion by PBMC in the presence of target cells Kasumi-2. Target cells and PBMC were incubated with the test molecules for 8 days. The supernatants were collected and analyzed for the presence of IFNγ using ELISA (R&D Systems). Molecules containing adjacent CD3 and PD-L1 domains were the most efficacious at inducing IFNγ production by PBMC followed by antibody SI-38E5. SI-38E17 showed moderate activity in this study (FIGURE 23).

The term "antibody" is used in the broadest sense and specifically covers single monoclonal antibodies (including agonist and antagonist antibodies), antibody compositions with polyepitopic specificity, as well as antibody fragments (e.g., Fab, F(ab')2, and Fv), so long as they exhibit the desired biological activity. In some embodiments, the antibody may be monoclonal, polyclonal, chimeric, single chain, bispecific or bi-effective, simianized, human and humanized antibodies as well as active fragments thereof. Examples of active fragments of molecules that bind to known antigens include Fab, F(ab')2, scFv and Fv fragments, including the products of an Fab immunoglobulin expression library and epitope-binding fragments of any of the antibodies and fragments mentioned above. In some embodiments, antibody may include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e. molecules that contain a binding site that immunospecifically bind an antigen. The immunoglobulin can be of any type (IgG, IgM, IgD, IgE, IgA and IgY) or class (IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclasses of immunoglobulin molecule. In one embodiment, the antibody may be whole antibodies and any antigen-binding fragment derived from the whole antibodies. A typical antibody refers to heterotetrameric protein comprising typically of two heavy (H) chains and two light (L) chains. Each heavy chain is comprised of a heavy chain variable domain (abbreviated as VH) and a heavy chain constant domain. Each light chain is comprised of a light chain variable domain (abbreviated as VL) and a light chain constant domain. The VH and VL regions can be further subdivided into domains of hypervariable complementarity determining regions (CDR), and more conserved regions called framework regions (FR). Each variable domain (either VH or VL) is typically composed of three CDRs and four FRs, arranged in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 from amino-terminus to carboxy-terminus. Within the variable regions of the light and heavy chains there are binding regions that interacts with the antigen.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody

by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler & Milstein, Nature, 256:495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567).

The monoclonal antibodies may include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 [1984]).

Monoclonal antibodies can be produced using various methods including mouse hybridoma or phage display (see Siegel. Transfus. Clin. Biol. 9:15-22 (2002) for a review) or from molecular cloning of antibodies directly from primary B cells (see Tiller. New Biotechnol. 28:453-7 (2011)). In the present disclosure antibodies were created by the immunization of rabbits with both human PD-L1 protein and cells transiently expressing human PD-L1 on the cell surface. Rabbits are known to create antibodies of high affinity, diversity and specificity (Weber et al. Exp. Mol. Med. 49:e305). B cells from immunized animals were cultured in vitro and screened for the production of anti-PD-L1 antibodies. The antibody variable genes were isolated using recombinant DNA techniques and the resulting antibodies were expressed recombinantly and further screened for desired features such as ability to inhibit the binding of PD-L1 to PD-1, the ability to bind to non-human primate PD-L1 and the ability to enhance human T-cell activation. This general method of antibody discovery is similar to that described in Seeber et al. PLOS One. 9:e86184 (2014).

The term "antigen- or epitope-binding portion or fragment" refers to fragments of an antibody that are capable of binding to an antigen (PD-L1 in this case). These fragments may be capable of the antigen-binding function and additional functions of the intact antibody. Examples of binding fragments include, but are not limited to a single-chain Fv fragment (scFv) consisting of the VL and VH domains of a single arm of an antibody connected in a single polypeptide chain by a synthetic linker or a Fab fragment which is a monovalent fragment consisting of the VL, constant light (CL), VH and constant heavy 1 (CH1) domains. Antibody fragments can be even smaller sub-fragments and can consist of domains as small as a single CDR domain, in particular the CDR3 regions from either the VL and/or VH domains (for example see Beiboer et al., J. Mol. Biol. 296:833-49 (2000)). Antibody fragments are produced using conventional methods known to those skilled in the art. The antibody fragments are can be screened for utility using the same techniques employed with intact antibodies.

The "antigen-or epitope-binding fragments" can be derived from an antibody of the present disclosure by a number of art-known techniques. For example, purified monoclonal antibodies can be cleaved with an enzyme, such as pepsin, and subjected to HPLC gel filtration. The appropriate fraction containing Fab fragments can then be collected and concentrated by membrane filtration and the like. For further description of general techniques for the isolation of active fragments of antibodies, see for example, Khaw, B. A. et al. J. Nucl. Med. 23:1011-1019 (1982); Rousseaux et al. Methods Enzymology, 121:663-69, Academic Press, 1986.

Papain digestion of antibodies produces two identical antigen binding fragments, called "Fab" fragments, each with a single antigen binding site, and a residual "Fc" fragment, whose name reflects its

ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen combining sites and is still capable of cross-linking antigen.

The Fab fragment may contain the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')2 antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other, chemical couplings of antibody fragments are also known.

"Fv" is the minimum antibody fragment which contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

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

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG-1, IgG-2, IgG-3, and IgG-4; IgA-1 and IgA-2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, delta, epsilon, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

A "humanized antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity. Methods to obtain "humanized antibodies" are well known to those skilled in the art. (see, e.g., Queen et al., Proc. Natl Acad Sci USA, 86:10029-10032 (1989), Hodgson et al., Bio/Technology, 9:421 (1991)). In one embodiment, the "humanized antibody" may be obtained by genetic engineering approach that enables production of affinity-matured humanlike polyclonal antiboies in large animals such as, for example, rabbits (see, e.g. U.S. Pat. No. 7,129,084).

The terms "polypeptide", "peptide", and "protein", as used herein, are interchangeable and are defined to mean a biomolecule composed of amino acids linked by a peptide bond.

The terms "a", "an" and "the" as used herein are defined to mean "one or more" and include the plural unless the context is inappropriate.

By "isolated" is meant a biological molecule free from at least some of the components with which it naturally occurs. "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.

The term “antigen” refers to an entity or fragment thereof which can induce an immune response in an organism, particularly an animal, more particularly a mammal including a human. The term includes immunogens and regions thereof responsible for antigenicity or antigenic determinants.

Also as used herein, the term “immunogenic” refers to substances which elicit or enhance the production of antibodies, T-cells or other reactive immune cells directed against an immunogenic agent and contribute to an immune response in humans or animals. An immune response occurs when an individual produces sufficient antibodies, T-cells and other reactive immune cells against administered immunogenic compositions of the present disclosure to moderate or alleviate the disorder to be treated.

"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.

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 10-4 M, at least about 10-5 M, at least about 10-6 M, at least about 10-7 M, at least about 10-8 M, at least about 10-9, alternatively at least about 10-10 M, at least about 10-11 M, at least about 10-12 M, or greater, where KD refers to a dissociation rate of a particular antibody-antigen interaction. In some embodiments, 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.

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.

“Homology” between two sequences is determined by sequence identity. If two sequences which are to be compared with each other differ in length, sequence identity preferably relates to the percentage of the nucleotide residues of the shorter sequence which are identical with the nucleotide residues of the longer sequence. Sequence identity can be determined conventionally with the use of computer programs. The deviations appearing in the comparison between a given sequence and the above-described sequences of the disclosure may be caused for instance by addition, deletion, substitution, insertion or recombination.

While the present disclosure has been described with reference to particular embodiments or examples, it may be understood that the embodiments are illustrative and that the disclosure scope is not so limited. Alternative embodiments of the present disclosure may become apparent to those having ordinary skill in the art to which the present disclosure pertains. Such alternate embodiments are considered to be encompassed within the scope of the present disclosure. Accordingly, the scope of the present disclosure is defined by the appended claims and is supported by the foregoing description. All references cited or referred to in this disclosure are hereby incorporated by reference in their entireties.

## TABLES

TABLE 1A. Composition of functional moieties (Moiety 1 and Moiety 2) and antigen binding domains in GNC proteins with T cell binding domains.

| Moiety 1 | | | Moiety 2 |
|---|---|---|---|
| **Activation of T cells** | **Agonist receptor** | **Antagonist receptor** | **Tumor Antigen** |
| **CD3** | **CD28, 41BB, OX40, GITR, CD40L, ICOS, Light, CD27, CD30** | **PDL1, PD1, TIGIT, TIM-3, LAG-3, CTLA4, BTLA, VISTA, PDL2** | **BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2** |

TABLE 1B. Composition of functional moieties (Moiety 1 and Moiety 2) and antigen binding domains in GNC proteins with NK cell binding domains.

| Moiety 1 | | | Moiety 2 |
|---|---|---|---|
| **Activation of NK cell** | **Agonist receptor** | **Antagonist receptor** | **Tumor Antigen** |
| CD16, NKG2D, KIR2DS1, KIR2DS2, KIR2DS4, KIR3DS1, NKG2C, NKG2E, NKG2H | NKp30a, NKp30b, NKp46, NKp80, DNAM-1, CD96, CD160, 4-1BB, GITR, CD27, OX-40, CRTAM | KIR2DL1, KIR2DL2, KIR2DL3, KIR3DL1, KIR3DL2, KIR3DL3, NKG2A, NKp30c, TIGIT, SIGLEC7, SIGLEC9, LILR, LAIR-1, KLRG1, PD-1, CTLA-4, CD161 | BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2 |

TABLE 1C. Composition of functional moieties (Moiety 1 and Moiety 2) and antigen binding domains in GNC proteins with macrophage binding domains.

| Moiety 1 | | | Moiety 2 |
|---|---|---|---|
| **Agonist receptor on macrophage** | **Antagonist receptor on macrophage** | **Other surface receptors** | **Tumor Antigen** |
| TLR2, TLR4, CD16, CD64, CD40, CD80, CD86, TREM-1, TREM-2, ILT-1, ILT-6a, ILT-7, ILT-8, EMR2, Dectin-1, CD69 | CD32b, SIRPα, LAIR-1, VISTA, TIM-3, CD200R, CD300a, CD300f, SIGLEC1, SIGLEC3, SIGLEC5, SIGLEC7, SIGLEC9, ILT-2, ILT-3, ILT-4, ILT-5, LILRB3, LILRB4, DCIR | CSF-1R, LOX-1, CCR2, FRβ, CD163, CR3, DC-SIGN, CD206, SR-A, CD36, MARCO | BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2 |

TABLE 1D. Composition of functional moieties (Moiety 1 and Moiety 2) and antigen binding domains in GNC proteins with DC cell binding domains.

| Moiety 1 | | | Moiety 2 |
|---|---|---|---|
| **Agonist receptor on DC** | **Antagonist receptor on DC** | **Other surface receptors** | **Tumor Antigen** |
| TLR, CD16, CD64, CD40, CD80, CD86, HVEM, CD70 | VISTA, TIM-3, LAG-3, BTLA | CSF-1R, LOX-1, CCR7, DC-SIGN, GM-CSF-R, IL-4R, IL-10R, CD36, CD206, DCIR, RIG-1, CLEC9A, CXCR4 | BCMA, CD19, CD20, CD33, CD123, CD22, CD30, ROR1, CEA, HER2, EGFR, EGFRvIII, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2 |

TABLE 2. Examples of possible combinations of T cell activation, T cell agonist, T cell antagonist, and tumor antigen binding domains in a single GNC protein.

| GNC protein | T cell activation | Tumor antigen | T cell antagonist | T cell agonist | T cell antagonist | T cell antagonist | T cell antagonist | T cell agonist |
|---|---|---|---|---|---|---|---|---|
| **Bi-specific** | **CD3** | **ROR1** | | | | | | |
| **Tri-specific** | **CD3** | **ROR1** | **PD1** | | | | | |
| **Tetra-specific** | **CD3** | **ROR1** | **PD1** | **41BB** | | | | |
| **Penta-specific** | **CD3** | **ROR1** | **PD1** | **41BB** | **LAG3** | | | |
| **Hexa-specific** | **CD3** | **ROR1** | **PD1** | **41BB** | **LAG3** | **TIM3** | | |
| **Hepta-specific** | **CD3** | **ROR1** | **PD1** | **41BB** | **LAG3** | **TIM3** | **TIGIT** | |
| **Octa-specific** | **CD3** | **ROR1** | **PD1** | **41BB** | **LAG3** | **TIM3** | **TIGIT** | **CD28** |

TABLE 3. Specificity of antibody binding domains used in GNC proteins.

| AgBD Specificity | Antibody Name |
|---|---|
| CD3ε | 284A10 |
| | 480C8 |
| 4-1BB | 460C3 |
| | 420H5 |
| | 466F6 |
| FITC | 4420 |
| PD-L1 | PL230C6 |
| CD19 | 21D4 |
| ROR1 IgD Domain | 323H7 |
| Kringle Domain | 330F11 |
| Frizzled Domain | 338H4 |
| | 324C6 |
| EGFRvIII | 806 |

TABLE 4. List of tetra-specific GNC proteins.

| Antibody ID | Domain 1 | Humanized Variant | Domain 2 | Humanized Variant | IgG Fc | Domain 3 | Humanized Variant | Domain 4 | Humanized Variant |
|---|---|---|---|---|---|---|---|---|---|
| | LH-scFv | | Fab | | | LH-scFv | | LH-scFv | |
| SI-35E18 | 460C3 | H1L1 | PL230C6 | H3L3 | n2 | 323H7 | H4L1 | 284A10 | H1L1 |
| SI-35E19 | 420H5 | H3L3 | PL230C6 | H3L3 | n2 | 323H7 | H4L1 | 284A10 | H1L1 |
| SI-35E20 | 466F6 | H2L5 | PL230C6 | H3L3 | n2 | 323H7 | H4L1 | 284A10 | H1L1 |
| SI-35E21 | 460C3 | H1L1 | PL230C6 | H3L3 | n2 | 338H4 | H3L4 | 284A10 | H1L1 |
| SI-35E22 | 420H5 | H3L3 | PL230C6 | H3L3 | n2 | 338H4 | H3L4 | 284A10 | H1L1 |
| SI-35E23 | 466F6 | H2L5 | PL230C6 | H3L3 | n2 | 338H4 | H3L4 | 284A10 | H1L1 |
| SI-35E24 | 460C3 | H1L1 | PL230C6 | H3L3 | n2 | 330F11 | H1L1 | 284A10 | H1L1 |
| SI-35E25 | 420H5 | H3L3 | PL230C6 | H3L3 | n2 | 330F11 | H1L1 | 284A10 | H1L1 |
| SI-35E26 | 466F6 | H2L5 | PL230C6 | H3L3 | n2 | 330F11 | H1L1 | 284A10 | H1L1 |
| SI-27E12 | 4420 | - | PL230C6 | H3L3 | n2 | 324C6 | H2L1 | 480C8 | H1L1 |
| SI-27E15 | 460C3 | H1L1 | 4420 | - | n2 | 324C6 | H2L1 | 480C8 | H1L1 |
| SI-27E13 | 460C3 | H1L1 | PL230C6 | H3L3 | n2 | 4420 | - | 480C8 | H1L1 |
| SI-35E2 | 460C3 | H1L1 | PL230C6 | H3L3 | n2 | 324C6 | H2L1 | 4420 | - |

Table 5. Tetra-specific GNC antibodies with EGFRvIII tumor antigen binding domain.

| GNC ID | AgBD 1 (LH-scFv) | Humanized Variant | AgBD 2 (Fab) | Humanized Variant | IgG1 Fc | AgBD 3 (HL-scFv) | Humanized Variant | AgBD 4 (HL-scFv) | Humanized Variant |
|---|---|---|---|---|---|---|---|---|---|
| SI-39E01 | PL230C6 | L2H3 | 806 | - | n2 | 284A10 | H1L1 | FITC | - |
| SI-39E02 | PL230C6 | L2H3 | 806 | - | n2 | 284A10 | H1L1 | 460C3 | H1L1 |
| SI-39E03 | PL230C6 | L2H3 | 806 | - | n2 | 284A10 | H1L1 | 466F6 | H2L5 |
| SI-39E04 | PL230C6 | L2H3 | 806 | - | n2 | 284A10 | H1L1 | 420H5 | H3L3 |
| SI-39E05 | FITC | - | 806 | - | n2 | 284A10 | H1L1 | 420H5 | H3L3 |
| SI-39E10 | 420H5 | L3H3 | PL230C6 | H3L2 | n2 | 806 | - | 284A10 | H1L1 |
| SI-39E13 | 420H5 | L3H3 | PL230C6 | H3L2 | n2 | 284A10 | H1L1 | 806 | - |
| SI-39E18 | 284A10 | L1H1 | 806 | - | n2 | PL221G5 | H1L1 | 420H5 | H3L3 |
| SI-39E23 | PL230C6 | L2H3 | 806 | - | n2 | 420H5 | H3L3 | 284A10 | H1L1 |
| SI-39E29 | 806 | - | 284A10 | H1L1 | n2 | PL221G5 | H1L1 | 420H5 | H3L3 |
| SI-39E40 | 420H5 | L3H3 | 806 | - | n2 | 284A10 | H1L1 | PL221G5 | H1L1 |
| SI-39E41 | 806 | - | 420H5 | H3L3 | n2 | 284A10 | H1L1 | PL221G5 | H1L1 |
| SI-39E42 | 284A10 | L1H1 | PL230C6 | H3L2 | n2 | 806 | - | 420H5 | H3L3 |
| SI-39E43 | 284A10 | L1H1 | PL230C6 | H3L2 | n2 | 420H5 | H3L3 | 806 | - |
| SI-39E44 | 420H5 | L3H3 | 806 | - | n2 | PL221G5 | H1L1 | 284A10 | H1L1 |
| SI-39E45 | 806 | - | 420H5 | H3L3 | n2 | PL221G5 | H1L1 | 284A10 | H1L1 |
| SI-39E48 | PL230C6 | L2H3 | 284A10 | H1L1 | n2 | 806 | - | 420H5 | H3L3 |
| SI-39E49 | PL230C6 | L2H3 | 284A10 | H1L1 | n2 | 420H5 | H3L3 | 806 | - |

Table 6. Granzyme B production by PBMC in response to treatment with EGFRvIII targeting tetra-specific GNC antibodies, the effect of AgBDs on EC50.

| GNC ID | AgBDs D1 x D2 (Fab) | IgG Fc | AgBDs D3 x D4 | Granzyme B secretion EC50 (pM) |
|---|---|---|---|---|
| SI-39E48 | PD-L1 x CD3 | n2 | 4-1BB x TAA (806) | 0.006 |
| SI-39E49 | PD-L1 x CD3 | n2 | TAA (806) x 4-1BB | 0.050 |
| SI-39E43 | CD3 x PD-L1 | n2 | 4-1BB x TAA (806) | 0.163 |
| SI-39E42 | CD3 x PD-L1 | n2 | TAA (806) x 4-1BB | 0.207 |
| SI-39E45 | TAA (806) x 4-1BB | n2 | PD-L1 x CD3 | 0.285 |
| SI-39E44 | 4-1BB x TAA (806) | n2 | PD-L1 x CD3 | 0.345 |
| SI-39E41 | TAA (806) x 4-1BB | n2 | CD3 x PD-L1 | 0.346 |
| SI-39E40 | 4-1BB x TAA (806) | n2 | CD3 x PD-L1 | 0.355 |
| SI-39E29 | TAA (806) x CD3 | n2 | PD-L1 x 4-1BB | 7.797 |
| SI-39E18 | CD3 x TAA (806) | n2 | PD-L1 x 4-1BB | 14.750 |
| SI-39E4 | PD-L1 x TAA (806) | n2 | CD3 x 4-1BB | 21.930 |
| SI-39E13 | 4-1BB x PD-L1 | n2 | CD3 x TAA (806) | 24.700 |
| SI-39E23 | PD-L1 x TAA (806) | n2 | 4-1BB x CD3 | 35.910 |
| SI-39E10 | 4-1BB x PD-L1 | n2 | TAA (806) x CD3 | 61.680 |

Table 7. Tetra-specific GNC antibodies with ROR1 tumor antigen binding domain.

| GNC ID | AgBD 1 (LH-scFv) | Humanized Variant | AgBD 2 (Fab) | Humanized Variant | IgG1 Fc | AgBD 3 (HL-scFv) | Humanized Variant | AgBD 4 (HL-scFv) | Humanized Variant |
|---|---|---|---|---|---|---|---|---|---|
| SI-35E50 | 466F6 | L5H2 | PL230C6 | H3L2 | n2 | 284A10 | H1L1 | 323H7 | H4L1 |
| SI-35E53 | PL230C6 | L2H3 | 466F6 | H2L5 | n2 | 284A10 | H1L1 | 323H7 | H4L1 |
| SI-35E56 | 284A10 | L1H1 | 323H7 | H4L1 | n2 | 466F6 | H2L5 | PL230C6 | H3L2 |
| SI-35E58 | 284A10 | L1H1 | PL230C6 | H3L2 | n2 | 323H7 | H4L1 | 466F6 | H2L5 |
| SI-35E61 | PL230C6 | L2H3 | 284A10 | H1L1 | n2 | 323H7 | H4L1 | 466F6 | H2L5 |
| SI-35E82 | PL230C6 | L2H3 | 466F6 | H2L5 | n2 | 323H7 | H4L1 | 284A10 | H1L1 |
| SI-35E85 | 466F6 | L5H2 | 323H7 | H4L1 | n2 | PL230C6 | H3L2 | 284A10 | H1L1 |
| SI-35E88 | 284A10 | L1H1 | 323H7 | H4L1 | n2 | PL230C6 | H3L2 | 466F6 | H2L5 |
| SI-35E95 | 466F6 | L5H2 | 323H7 | H4L1 | n2 | 284A10 | H1L1 | PL230C6 | H3L2 |
| SI-35E99 | 284A10 | L1H1 | 323H7 | H4L1 | n2 | PL221G5 | H1L1 | 466F6 | H2L5 |

Table 8. Tetra-specific GNC antibodies with CD19 tumor antigen binding domain.

| GNC ID | AgBD 1 (LH-scFv) | Humanized Variant | AgBD 2 (Fab) | Humanized Variant | IgG1 Fc | AgBD 3 (HL-scFv) | Humanized Variant | AgBD 4 (HL-scFv) | Humanized Variant |
|---|---|---|---|---|---|---|---|---|---|
| SI-38E05 | 466F6 | L5H2 | PL230C6 | H3L2 | n2 | 284A10 | H1L1 | 21D4 | - |
| SI-38E14 | PL230C6 | L2H3 | 466F6 | H2L5 | n2 | 21D4 | - | 284A10 | H1L1 |
| SI-38E17 | 284A10 | H1L1 | 21D4 | - | n2 | PL221G5 | H1L1 | 466F6 | H2L5 |
| SI-38E20 | 466F6 | L5H2 | 21D4 | - | n2 | 284A10 | H1L1 | PL221G5 | H1L1 |
| SI-38E28 | PL230C6 | L2H3 | 284A10 | H1L1 | n2 | 21D4 | - | 466F6 | H2L5 |
| SI-38E33 | 21D4 | - | 284A10 | H1L1 | n2 | PL221G5 | H1L1 | 466F6 | H2L5 |
| SI-38E41 | 284A10 | H1L1 | 21D4 | - | n2 | 460C3 | H1L1 | PL221G5 | H1L1 |

GUIDANCE AND NAVIGATION CONTROL PROTEINS AND METHOD OF MAKING AND USING THEREOF

SEQUENCE LIST

| SEQ ID | Description |
|---|---|
| 1 | anti-CD3 284A10 VHv1 nt |
| 2 | anti-CD3 284A10 VHv1 aa |
| 3 | anti-CD3 284A10 VLv1 nt |
| 4 | anti-CD3 284A10 VLv1 aa |
| 5 | anti-CD3 480C8 VHv1 nt |
| 6 | anti-CD3 480C8 VHv1 aa |
| 7 | anti-CD3 480C8 VLv1 nt |
| 8 | anti-CD3 480C8 VLv1 aa |
| 9 | anti-PD-L1 PL230C6 VHv3 nt |
| 10 | anti-PD-L1 PL230C6 VHv3 aa |
| 11 | anti-PD-L1 PL230C6 VLv2 nt |
| 12 | anti-PD-L1 PL230C6 VLv2 aa |
| 13 | anti-4-1BB 420H5 VHv3 nt |
| 14 | anti-4-1BB 420H5 VHv3 aa |
| 15 | anti-4-1BB 420H5 VLv3 nt |
| 16 | anti-4-1BB 420H5 VHLv3 aa |
| 17 | anti-4-1BB 466F6 VHv2 nt |
| 18 | anti-4-1BB 466F6 VHv2 aa |
| 19 | anti-4-1BB 466F6 VLv5 nt |
| 20 | anti-4-1BB 466F6 VLv5 aa |
| 21 | anti-4-1BB 460C3 VHv1 nt |
| 22 | anti-4-1BB 460C3 VHv1 aa |
| 23 | anti-4-1BB 460C3 VLv1 nt |
| 24 | anti-4-1BB 460C3 VLv1 aa |
| 25 | anti-ROR1 324C6 VHv2 nt |
| 26 | anti-ROR1 324C6 VHv2 aa |
| 27 | anti-ROR1 324C6 VLv1 nt |
| 28 | anti-ROR1 324C6 VLv1 aa |
| 29 | anti-ROR1 323H7 VHv4 nt |
| 30 | anti-ROR1 323H7 VHv4 aa |
| 31 | anti-ROR1 323H7 VLv1 nt |
| 32 | anti-ROR1 323H7 VLv1 aa |
| 33 | anti-ROR1 338H4 VHv3 nt |
| 34 | anti-ROR1 338H4 VHv3 aa |
| 35 | anti-ROR1 338H4 VLv4 nt |
| 36 | anti-ROR1 338H4 VLv4 aa |
| 37 | anti-ROR1 330F11 VHv1 nt |
| 38 | anti-ROR1 330F11 VHv1 aa |

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|---|---|
| 39 | anti-ROR1 330F11 VLv1 nt |
| 40 | anti-ROR1 330F11 VLv1 aa |
| 41 | anti-FITC 4-4-20 VH nt |
| 42 | anti-FITC 4-4-20 VH aa |
| 43 | anti-FITC 4-4-20 VL nt |
| 44 | anti-FITC 4-4-20 VL aa |
| 45 | human IgG1 null2 (G1m-fa with ADCC/CDC null mutations) nt |
| 46 | human IgG1 null2 (G1m-fa with ADCC/CDC null mutations) aa |
| 47 | human Ig Kappa nt |
| 48 | human Ig Kappa aa |
| 49 | SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain nt |
| 50 | SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain aa |
| 51 | SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain nt |
| 52 | SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain aa |
| 53 | anti-CD3 284A10 VHv1b nt |
| 54 | anti-CD3 284A10 VHv1b aa |
| 55 | anti-4-1BB 466F6b VHv2 nt |
| 56 | anti-4-1BB 466F6b VHv2 aa |
| 57 | anti-PD-L1 PL230C6 VHv3b nt |
| 58 | anti-PD-L1 PL230C6 VHv3b aa |
| 59 | anti-huPD-L1 PL221G5 VHv1 nt |
| 60 | anti-huPD-L1 PL221G5 VHv1 aa |
| 61 | anti-huPD-L1 PL221G5 VLv1 nt |
| 62 | anti-huPD-L1 PL221G5 VLv1 aa |
| 63 | anti-huCD19 21D4 VH nt |
| 64 | anti-huCD19 21D4 VH aa |
| 65 | anti-huCD19 21D4 VL nt |
| 66 | anti-huCD19 21D4 VL aa |
| 67 | anti-huEGFRvIII 806 VH nt |
| 68 | anti-huEGFRvIII 806 VH aa |
| 69 | anti-huEGFRvIII 806 VL nt |
| 70 | anti-huEGFRvIII 806 VL aa |
| 71 | GGGGSGGGGSG linker nt |
| 72 | GGGGSGGGGSG linker aa |
| 73 | GGGGSGGGGS linker 01 nt |
| 74 | GGGGSGGGGS linker 01 aa |
| 75 | GGGGSGGGGS linker 02 nt |
| 76 | GGGGSGGGGS linker 02 aa |
| 77 | GGGGSGGGGSGGGGSGGGGS linker nt |
| 78 | GGGGSGGGGSGGGGSGGGGS linker aa |
| 79 | SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain nt |

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|---|---|
| 80 | SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain aa |
| 81 | SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain nt |
| 82 | SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain aa |
| 83 | SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain nt |
| 84 | SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain aa |
| 85 | SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain nt |
| 86 | SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain aa |
| 87 | SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain nt |
| 88 | SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain aa |
| 89 | SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain nt |
| 90 | SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain aa |
| 91 | SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) heavy chain nt |
| 92 | SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) heavy chain aa |
| 93 | SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) light chain nt |
| 94 | SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) light chain aa |
| 95 | SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) heavy chain nt |
| 96 | SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) heavy chain aa |
| 97 | SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain nt |
| 98 | SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain aa |
| 99 | SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt |
| 100 | SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa |
| 101 | SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt |
| 102 | SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa |
| 103 | SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt |
| 104 | SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa |
| 105 | SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt |
| 106 | SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa |
| 107 | SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt |
| 108 | SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa |
| 109 | SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt |
| 110 | SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa |

Sequence listing of tetra-specific GNC antibodies

CDR's underlined in amino acid sequences

>SEQ ID 01 anti-CD3 284A10 VHv1 nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
CCTCTGGATTCACCATCAGTACCAATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTG
GATCGGAGTCATTACTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATT
ACTGTGCGCGCGACGGTGGATCATCTGCTATTACTAGTAACAACATTTGGGGCCAAGGAACTCTGGTCAC
CGTTTCTTCA

>SEQ ID 02 anti-CD3 284A10 VHv1 aa
EVQLVESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCARDGGSSAITSNNIWGQGTLVTVSS

>SEQ ID 03 anti-CD3 284A10 VLv1 nt
GACGTCGTGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCC
AAGCCAGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCTATGAAGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAG
TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCTATTTTTATT
TTATTAGTCGTACTTATGTAAATTCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 04 anti-CD3 284A10 VLv1 aa
DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIK

>SEQ ID 05 anti-CD3 480C8 VHv1 nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
CCTCTGGAATCGACCTCAGTAGCAATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTG
GATCGGAGTCATTACTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATT
ACTGTGCGCGCGACGGTGGATCATCTGCTATTAATAGTAAGAACATTTGGGGCCAAGGAACTCTGGTCAC
CGTTTCTTCA

>SEQ ID 06 anti-CD3 480C8 VHv1 aa
EVQLVESGGGLVQPGGSLRLSCAASGIDLSSNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCARDGGSSAINSKNIWGQGTLVTVSS

>SEQ ID 07 anti-CD3 480C8 VLv1 nt
GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
AAGCCAGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCTATGAAGCATCCAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAG
TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCTATTTTTATT
TTATTAGTCGTACTTATGTAAATGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 08 anti-CD3 480C8 VLv1 aa
DIQMTQSPSTLSASVGDRVTITCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQGYFYFISRTYVNAFGGGTKVEIK

>SEQ ID 09 anti-PD-L1 PL230C6 VHv3 nt
CAGTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCT
CTGGAATCGACCTTAATACCTACGACATGATCTGGGTCCGCCAGGCTCCAGGCAAGGGGCTAGAGTGGGT
TGGAATCATTACTTATAGTGGTAGTAGATACTACGCGAACTGGGCGAAAGGCCGATTCACCATCTCCAAA
GACAATACCAAGAACACGGTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACT
GTGCCAGAGATTATATGAGTGGTTCCCACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCTAGT

>SEQ ID 10 anti-PD-L1 PL230C6 VHv3 aa
QSVEESGGGLVQPGGSLRLSCTASGIDLNTYDMIWVRQAPGKGLEWVGIITYSGSRYYANWAKGRFTISK
DNTKNTVYLQMNSLRAEDTAVYYCARDYMSGSHLWGQGTLVTVSS

>SEQ ID 11 anti-PD-L1 PL230C6 VLv2 nt
GCCTATGATATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCAAGTGTC
AGGCCAGTGAGGACATTTATAGCTTCTTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCCATTCTGCATCCTCTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT
TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGGTTATGGTA
AAAATAATGTTGATAATGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 12 anti-PD-L1 PL230C6 VLv2 aa
AYDMTQSPSSVSASVGDRVTIKCQASEDIYSFLAWYQQKPGKAPKLLIHSASSLASGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIK

>SEQ ID 13 anti-4-1BB 420H5 VHv3 nt
CAGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCT
CTGGATTCTCCTTCAGTAGCAACTACTGGATATGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTG
GATCGCATGCATTTATGTTGGTAGTAGTGGTGACACTTACTACGCGAGCTCCGCGAAAGGCCGGTTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCG
TATATTACTGTGCGAGAGATAGTAGTAGTTATTATATGTTTAACTTGTGGGGCCAGGGAACCCTGGTCAC
CGTCTCGAGC

>SEQ ID 14 anti-4-1BB 420H5 VHv3 aa
QSLVESGGGLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLEWIACIYVGSSGDTYYASSAKGRFT
ISRDNSKNTLYLQMNSLRAEDTAVYYCARDSSSYYMFNLWGQGTLVTVSS

>SEQ ID 15 anti-4-1BB 420H5 VLv3 nt
GCCCTTGTGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCC
AGGCCAGTGAGGACATTGATACCTATTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCTTTTATGCATCCGATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA
TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCGGTTACTATA
CTAGTAGTGCTGATACGAGGGGTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 16 anti-4-1BB 420H5 VLv3 aa
ALVMTQSPSTLSASVGDRVTINCQASEDIDTYLAWYQQKPGKAPKLLIFYASDLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQGGYYTSSADTRGAFGGGTKVEIK

>SEQ ID 17 anti-4-1BB 466F6 VHv2 nt
CGGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCT
CTGGATTCACCATCAGTAGCTACCACATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTACAT
CGGAACCATTAGTAGTGGTGGTAATGTATACTACGCGAGCTCCGCGAGAGGCAGATTCACCATCTCCAGA
CCCTCGTCCAAGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACT
GTGCGAGAGACTCTGGTTATAGTGATCCTATGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 18 anti-4-1BB 466F6 VHv2 aa
RSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLEYIGTISSGGNVYYASSARGRFTISR
PSSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMWGQGTLVTVSS

>SEQ ID 19 anti-4-1BB 466F6 VLv5 nt
GACGTTGTGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCACCTGTC
AGGCCAGTCAGAACATTAGGACTTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCTATGCTGCAGCCAATCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT
TTCACTCTCACCATCAGCGACCTGGAGCCTGGCGATGCTGCAACTTACTATTGTCAGTCTACCTATCTTG
GTACTGATTATGTTGGCGGTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 20 anti-4-1BB 466F6 VLv5 aa
DVVMTQSPSSVSASVGDRVTITCQASQNIRTYLSWYQQKPGKAPKLLIYAAANLASGVPSRFSGSGSGTD
FTLTISDLEPGDAATYYCQSTYLGTDYVGGAFGGGTKVEIK

>SEQ ID 21 anti-4-1BB 460C3 VHv1 nt
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
CCTCTGGAATCGACTTCAGTAGGAGATACTACATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGA
GTGGATCGCATGCATATATACTGGTAGCCGCGATACTCCTCACTACGCGAGCTCCGCGAAAGGCCGGTTC
ACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGG
CCGTATATTACTGTGCGAGAGAAGGTAGCCTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGC

>SEQ ID 22 anti-4-1BB 460C3 VHv1 aa
EVQLLESGGGLVQPGGSLRLSCAASGIDFSRRYYMCWVRQAPGKGLEWIACIYTGSRDTPHYASSAKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCAREGSLWGQGTLVTVSS

>SEQ ID 23 anti-4-1BB 460C3 VLv1 nt
GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
AGTCCAGTCAGAGTGTTTATAGTAACTGGTTCTCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCT
CCTGATCTATTCTGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACA
GAATTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCGCAGGCGGTTACA
ATACTGTTATTGATACTTTTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 24 anti-4-1BB 460C3 VLv1 aa
DIQMTQSPSTLSASVGDRVTITCQSSQSVYSNWFSWYQQKPGKAPKLLIYSASTLASGVPSRFSGSGSGT
EFTLTISSLQPDDFATYYCAGGYNTVIDTFAFGGGTKVEIK

>SEQ ID 25 anti-ROR1 324C6 VHv2 nt
CAGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACTGCCT
CTGGATTCTCCCTCAGTAGGTACTACATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGAT
CGGAACCATTTATACTAGTGGTAGTACATGGTACGCGAGCTGGACAAAAGGCAGATTCACCATCTCCAAA
GACAATACCAAGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACT
GTGCGAGATCCTATTATGGCGGTGATAAGACTGGTTTAGGCATCTGGGGCCAGGGAACTCTGGTTACCGT
CTCTTCA

>SEQ ID 26 anti-ROR1 324C6 VHv2 nt
QSLVESGGGLVQPGGSLRLSCTASGFSLSRYYMTWVRQAPGKGLEWIGTIYTSGSTWYASWTKGRFTISK
DNTKNTVDLQMNSLRAEDTAVYYCARSYYGGDKTGLGIWGQGTLVTVSS

>SEQ ID 27 anti-ROR1 324C6 VLv1 nt
GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
AGGCCAGTCAGAGCATTGATAGTTGGTTATCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT

GATCTATCAGGCATCCACTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAG
TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAATCTGCTTATGGTG
TTAGTGGTACTAGTAGTTATTTATATACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 28 anti-ROR1 324C6 VLv1 aa
DIQMTQSPSTLSASVGDRVTITCQASQSIDSWLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQSAYGVSGTSSYLYTFGGGTKVEIK

>SEQ ID 29 anti-ROR1 323H7 VHv4 nt
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
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GATCGGACATATTTATGTTAATAATGATGACACAGACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATC
TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCACCT
ATTTCTGTGCGAGATTGGATGTTGGTGGTGGTGGTGCTTATATTGGGGACATCTGGGGCCAGGGAACTCT
GGTTACCGTCTCTTCA

>SEQ ID 30 anti-ROR1 323H7 VHv4 aa
EVQLLESGGGLVQPGGSLRLSCAASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDYASSAKGRFTI
SRDNSKNTLYLQMNSLRAEDTATYFCARLDVGGGGAYIGDIWGQGTLVTVSS

>SEQ ID 31 anti-ROR1 323H7 VLv1 nt
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
AGTCCAGTCAGAGTGTTTATAACAACAACGACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAA
GCTCCTGATCTATTATGCTTCCACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGG
ACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTT
ATGATACGGATGGTCTTGATACGTTTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 32 anti-ROR1 323H7 VLv1 aa
DIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAWYQQKPGKVPKLLIYYASTLASGVPSRFSGSGSG
TDFTLTISSLQPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIK

>SEQ ID 33 anti-ROR1 338H4 VHv3 nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACTG
CCTCTGGATTCTCCCTCAGTAGCTATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTG
GATCGGAATCATTTATGCTAGTGGTAGCACATACTACGCGAGCTCGGCGAAAGGCAGATTCACCATCTCC
AAAGACAATACCAAGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATT
ACTGTGCGAGAATTTATGACGGCATGGACCTCTGGGGCCAGGGAACTCTGGTTACCGTCTCTTCA

>SEQ ID 34 anti-ROR1 338H4 VHv3 aa
EVQLVESGGGLVQPGGSLRLSCTASGFSLSSYAMSWVRQAPGRGLEWIGIIYASGSTYYASSAKGRFTIS
KDNTKNTVDLQMNSLRAEDTAVYYCARIYDGMDLWGQGTLVTVSS

>SEQ ID 35 anti-ROR1 338H4 VLv4 nt
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCC
AGGCCAGTCAGAACATTTACAGCTACTTATCCTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCGCCT
GATCTATCTGGCATCTACTCTGGCATCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGAT
TACACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAAAGCAATTATAACG
GTAATTATGGTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 36 anti-ROR1 338H4 VLv4 aa
DIQMTQSPSSLSASVGDRVTINCQASQNIYSYLSWYQQKPGKVPKRLIYLASTLASGVPSRFSGSGSGTD
YTLTISSLQPEDVATYYCQSNYNGNYGFGGGTKVEIK

>SEQ ID 37 anti-ROR1 330F11 VHv1 nt
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
CCTCTGGATTCTCCCTCAATAACTACTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTG
GATCGGAACCATTAGTAGTGGTGCGTATACATGGTTCGCCACCTGGGCGACAGGCAGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATT
ACTGTGCGAGATATTCTTCTACTACTGATTGGACCTACTTTAACATCTGGGGCCAGGGAACTCTGGTTAC
CGTCTCTTCA

>SEQ ID 38 anti-ROR1 330F11 VHv1 aa
EVQLVESGGGLVQPGGSLRLSCAASGFSLNNYWMSWVRQAPGKGLEWIGTISSGAYTWFATWATGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCARYSSTTDWTYFNIWGQGTLVTVSS

>SEQ ID 39 anti-ROR1 330F11 VLv1 nt
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AGGCCAGTCAGAGCATTAATAACTACTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
GATCTATAGGGCATCCACTCTGGAATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAA
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TTGGTAGGACTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 40 anti-ROR1 330F11 VLv1 aa
DIQMTQSPSTLSASVGDRVTITCQASQSINNYLAWYQQKPGKAPKLLIYRASTLESGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQSYNGVGRTAFGGGTKVEIK

>SEQ ID 41 anti-FITC 4-4-20 VH nt
GAGGTGAAGCTGGATGAGACTGGAGGAGGCTTGGTGCAACCTGGGAGGCCCATGAAACTCTCCTGTGTTG
CCTCTGGATTCACTTTTAGTGACTACTGGATGAACTGGGTCCGCCAGTCTCCAGAGAAAGGACTGGAGTG
GGTAGCACAAATTAGAAACAAACCTTATAATTATGAAACATATTATTCAGATTCTGTGAAAGGCAGATTC
ACCATCTCAAGAGATGATTCCAAAAGTAGTGTCTACCTGCAAATGAACAACTTAAGAGTTGAAGACATGG
GTATCTATTACTGTACGGGTTCTTACTATGGTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTC
CTCA

>SEQ ID 42 anti-FITC 4-4-20 VH aa
EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWVRQSPEKGLEWVAQIRNKPYNYETYYSDSVKGRF
TISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSS

>SEQ ID 43 anti-FITC 4-4-20 VL nt
GATGTCGTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTCCATCTCTTGCA
GATCTAGTCAGAGCCTTGTACACAGTAATGGAAACACCTATTTACGTTGGTACCTGCAGAAGCCAGGCCA
GTCTCCAAAGGTCCTGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGT
GGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTATTTCTGCT
CTCAAAGTACACATGTTCCGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAA

>SEQ ID 44 anti-FITC 4-4-20 VL aa
DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLRWYLQKPGQSPKVLIYKVSNRFSGVPDRFSGS
GSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIK

>SEQ ID 45 human IgG1 null (G1m-fa with ADCC/CDC null mutations) nt
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CAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC
GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG

TGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGC
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GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
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CGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCC
CTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCC
TGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC
CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG
CTGGACTCCGACGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGA
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TCCGGGT

>SEQ ID 46 human IgG1 null (G1m-fa with ADCC/CDC null mutations) aa
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
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EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

>SEQ ID 47 human Ig Kappa nt
CGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCT
CTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCT
CCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC
ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCC
TGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT

>SEQ ID 48 human Ig Kappa aa
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS
TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>SEQ ID 49 SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x
284A10-H1L1-scFv) heavy chain nt

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
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GAATTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCGCAGGCGGTTACA
ATACTGTTATTGATACTTTTGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAAGGCGGTGGCGGTAGTGG
GGGAGGCGGTTCTGGCGGCGGAGGGTCCGGCGGTGGAGGATCAGAGGTGCAGCTGTTGGAGTCTGGGGGA
GGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGAATCGACTTCAGTAGGAGAT
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CCGCGATACTCCTCACTACGCGAGCTCCGCGAAAGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAAC
ACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGAGAGAAGGTA
GCCTGTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGCGGCGGTGGAGGGTCCGGCGGTGGTGGATCCCA
GTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCT
GGAATCGACCTTAATACCTACGACATGATCTGGGTCCGCCAGGCTCCAGGCAAGGGGCTAGAGTGGGTTG
GAATCATTACTTATAGTGGTAGTAGATACTACGCGAACTGGGCGAAAGGCCGATTCACCATCTCCAAAGA
CAATACCAAGAACACGGTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGT
GCCAGAGATTATATGAGTGGTTCCCACTTGTGGGGCCAGGGAACCCTGGTCACCGTCTCTAGTGCTAGCA
CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGC
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CCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAA
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GCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA
CATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
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ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCAACAAAGCCCTCCCAG
CCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTATACCCTGCCCCC
ATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGAC
ATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACT
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CTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCAGTCCAGTCAGAGTGTTTATAACAACAACGACTT
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GGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGC
CTGAAGATGTTGCAACTTATTACTGTGCAGGCGGTTATGATACGGATGGTCTTGATACGTTTGCTTTCGG
CGGAGGGACCAAGGTGGAGATCAAAGGCGGTGGAGGGTCCGGCGGTGGTGGATCCGAGGTGCAGCTGGTG
GAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCA
TCAGTACCAATGCAATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATCGGAGTCATTAC
TGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCCAGAGACAATTCCAAG
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CAAACTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATC
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>SEQ ID 50 SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain aa

DIQMTQSPSTLSASVGDRVTITCQSSQSVYSNWFSWYQQKPGKAPKLLIYSASTLASGVPSRFSGSGSGT
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TLYLQMNSLRAEDTAVYYCAREGSLWGQGTLVTVSSGGGGSGGGGSQSVEESGGGLVQPGGSLRLSCTAS
GIDLNTYDMIWVRQAPGKGLEWVGIITYSGSRYYANWAKGRFTISKDNTKNTVYLQMNSLRAEDTAVYYC
ARDYMSGSHLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAG
APSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
GGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTISRYHMTWVRQAPGKGLEWIGHIYVNNDDTDY
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GSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCQSSQSVYNNNDLAWYQQKPGKVPKLLIYYASTLAS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCAGGYDTDGLDTFAFGGGTKVEIKGGGGSGGGGSEVQLV

ESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTISRDNSK
NTLYLQMNSLRAEDTAVYYCARDGGSSAITSNNIWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDVVMT
QSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTEFTLTI
SSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIK

>SEQ ID 51 SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain nt

GCCTATGATATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTCACCATCAAGTGTC
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GATCCATTCTGCATCCTCTCTGGCATCTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAT
TTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGGTTATGGTA
AAAATAATGTTGATAATGCTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGCACCATC
TGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAAT
AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGG
AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGC
AGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAG
AGCTTCAACAGGGGAGAGTGT

>SEQ ID 52 SI-35E18 (460C3-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain aa

AYDMTQSPSSVSASVGDRVTIKCQASEDIYSFLAWYQQKPGKAPKLLIHSASSLASGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQGYGKNNVDNAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC

>SEQ ID 53 anti-CD3 284A10 VHv1b nt

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAG
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GATCGGAGTCATTACTGGTCGTGATATCACATACTACGCGAGCTGGGCGAAAGGCAGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATT
ACTGTGCGAGAGACGGTGGTTCTTCTGCTATTACTAGTAACAACATTTGGGGCCAGGGAACCCTGGTCAC
CGTGTCGACA

>SEQ ID 54 anti-CD3 284A10 VHv1b aa

EVQLVESGGGLVQPGGSLRLSCAASGFTISTNAMSWVRQAPGKGLEWIGVITGRDITYYASWAKGRFTIS
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>SEQ ID 55 anti-4-1BB 466F6b VHv2 nt

CGGTCGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCT
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CGGAACCATTAGTAGTGGTGGTAATGTATACTACGCAAGCTCCGCTAGAGGCAGATTCACCATCTCCAGA
CCCTCGTCCAAGAACACGGTGGATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACT
GTGCGAGAGACTCTGGTTATAGTGATCCTATGTGGGGCCAGGGAACCCTGGTCACCGTGTCGACA

>SEQ ID 56 anti-4-1BB 466F6b VHv2 aa

RSLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLEYIGTISSGGNVYYASSARGRFTISR
PSSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMWGQGTLVTVST

>SEQ ID 57 anti-PD-L1 PL230C6 VHv3b nt

CAGTCGGTGGAGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACCGCCT
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TGGAATCATTACTTATAGTGGTAGTAGATACTACGCGAACTGGGCGAAAGGCCGATTCACCATCTCCAAA
GACAATACCAAGAACACGGTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACT
GTGCGAGAGATTATATGAGTGGTTCCCACTTGTGGGGCCAGGGAACCCTGGTCACCGTGTCGACA

>SEQ ID 58 anti-PD-L1 PL230C6 VHv3b aa

QSVEESGGGLVQPGGSLRLSCTASGIDLNTYDMIWVRQAPGKGLEWVGIITYSGSRYYANWAKGRFTISK
DNTKNTVYLQMNSLRAEDTAVYYCARDYMSGSHLWGQGTLVTVST

>SEQ ID 59 anti-huPD-L1 PL221G5 VHv1 nt

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GTGGATCGCATGCATTGCTGCTGGTAGTGCTGGTATCACTTACGACGCGAACTGGGCGAAAGGCCGGTTC
ACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGG
CCGTATATTACTGTGCGAGATCGGCGTTTTCGTTCGACTACGCCATGGACCTCTGGGGCCAGGGAACCCT
GGTCACCGTCTCGAGC

>SEQ ID 60 anti-huPD-L1 PL221G5 VHv1 aa
EVQLLESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWIACIAAGSAGITYDANWAKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQGTLVTVSS

>SEQ ID 61 anti-huPD-L1 PL221G5 VLv1 nt

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCC
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TTTACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGGGTTATAGTT
GGGGTAATGTTGATAATGTTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

>SEQ ID 62 anti-huPD-L1 PL221G5 VLv1 aa
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>SEQ ID 63 anti-huCD19 21D4 VH nt

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GATGGGGATCATCTATCCTGATGACTCTGATACCAGATACAGTCCATCCTTCCAAGGCCAGGTCACCATC
TCAGCCGACAAGTCCATCAGGACTGCCTACCTGCAGTGGAGTAGCCTGAAGGCCTCGGACACCGCTATGT
ATTACTGTGCGAGACATGTTACTATGATTTGGGGAGTTATTATTGACTTCTGGGGCCAGGGAACCCTGGT
CACCGTCTCCTCA
>SEQ ID 64 anti-huCD19 21D4 VH aa

EVQLVQSGAEVKKPGESLKISCKGSGYSFSSSWIGWVRQAPGKGLEWMGIIYPDDSDTRYSPSFQGQVTI
SADKSIRTAYLQWSSLKASDTAMYYCARHVTMIWGVIIDFWGQGTLVTVSS

>SEQ ID 65 anti-huCD19 21D4 VL nt

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ACCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA

>SEQ ID 66 anti-huCD19 21D4 VL aa

AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTD
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>SEQ ID 67 anti-huEGFRvIII 806 VH nt

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GTGGATGGGCTACATAAGTTATAGTGGTAACACTAGGTACAACCCATCTCTCAAAAGTCGAATCTCTATC
ACTCGCGACACATCCAAGAACCAATTCTTCCTGCAGTTGAACTCTGTGACTATTGAGGACACAGCCACAT
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>SEQ ID 68 anti-huEGFRvIII 806 VH aa

DVQLQESGPSLVKPSQSLSLTCTVTGYSITSDFAWNWIRQFPGNKLEWMGYISYSGNTRYNPSLKSRISI
TRDTSKNQFFLQLNSVTIEDTATYYCVTAGRGFPYWGQGTLVTVSA

>SEQ ID 69 anti-huEGFRvIII 806 VL nt

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GATCTATCATGGAACCAACTTGGACGATGAAGTTCCATCAAGGTTCAGTGGCAGTGGATCTGGAGCCGAT
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>SEQ ID 70 anti-huEGFRvIII 806 VL aa

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YSLTISSLESEDFADYYCVQYAQFPWTFGGGTKLEIK

>SEQ ID 71 GGGGSGGGGSG linker nt

GGCGGTGGAGGGTCCGGCGGTGGTGGCTCCGGA

>SEQ ID 72 GGGGSGGGGSG linker aa

GGGGSGGGGSG

>SEQ ID 73 GGGGSGGGGS linker 01 nt

GGCGGTGGAGGGTCCGGCGGTGGTGGATCA

>SEQ ID 74 GGGGSGGGGS linker 01 aa

GGGGSGGGGS

>SEQ ID 75 GGGGSGGGGS linker 02 nt

GGCGGTGGAGGGTCCGGCGGTGGTGGATCC

>SEQ ID 76 GGGGSGGGGS linker 02 aa

GGGGSGGGGS

>SEQ ID 77 GGGGSGGGGSGGGGSGGGGS linker nt

GGCGGTGGCGGTAGTGGGGGAGGCGGTTCTGGCGGCGGAGGGTCCGGCGGTGGAGGATCA

>SEQ ID 78 GGGGSGGGGSGGGGSGGGGS linker aa

GGGGSGGGGSGGGGSGGGGS

>SEQ ID 79 SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain nt

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AAGCCAGTGAGAGCATTAGCAGTTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT
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TTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAAGGCTATTTTTATT
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GGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCATCAGTACCA
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CGGCGGTGGTGGATCCGATGTGCAGCTTCAGGAGTCGGGACCTAGCCTGGTGAAACCTTCTCAGTCTCTG
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TCACTGTCTCTGCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTC
TGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAC
TCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCA
GCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCC
CAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAAGCCGCGGGGGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAA
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TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGG
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>SEQ ID 80 SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain aa

DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTE
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EDTATYYCVTAGRGFPYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC
PAPEAAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
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SLVESGGGLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLEWIACIYVGSSGDTYYASSAKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCARDSSSYYMFNLWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSA
LVMTQSPSTLSASVGDRVTINCQASEDIDTYLAWYQQKPGKAPKLLIFYASDLASGVPSRFSGSGSGTEF
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>SEQ ID 81 SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain nt

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TATTCTCTCACCATCAGCAGCCTGGAATCTGAAGATTTTGCAGACTATTACTGTGTACAGTATGCTCAGT
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CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGA
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>SEQ ID 82 SI-39E18 (284A10-L1H1-scFv x 806-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain aa

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YSLTISSLESEDFADYYCVQYAQFPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC

>SEQ ID 83 SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain nt

GACATCCTGATGACCCAATCTCCATCCTCCATGTCTGTATCTCTGGGAGACACAGTCAGCATCACTTGCC
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TATTCTCTCACCATCAGCAGCCTGGAATCTGAAGATTTTGCAGACTATTACTGTGTACAGTATGCTCAGT
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TGGCGGCGGAGGGTCCGGCGGTGGAGGATCAGATGTGCAGCTTCAGGAGTCGGGACCTAGCCTGGTGAAA
CCTTCTCAGTCTCTGTCCCTCACCTGCACTGTCACTGGCTACTCAATCACCAGTGATTTTGCCTGGAACT
GGATTCGGCAGTTTCCAGGAAACAAGCTGGAGTGGATGGGCTACATAAGTTATAGTGGTAACACTAGGTA
CAACCCATCTCTCAAAAGTCGAATCTCTATCACTCGCGACACATCCAAGAACCAATTCTTCCTGCAGTTG
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TCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT
GCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC
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>SEQ ID 84 SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) heavy chain aa

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DGGSSAITSNNIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEA
AGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
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ITYDANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQGTLVTVSSGGGGSG
GGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCQASQSISSHLNWYQQKPGKAPKLLIYKASTLAS
GVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQGYSWGNVDNVFGGGTKVEIKGGGGSGGGGSQSLVES
GGGLVQPGGSLRLSCAASGFSFSSNYWICWVRQAPGKGLEWIACIYVGSSGDTYYASSAKGRFTISRDNS
KNTLYLQMNSLRAEDTAVYYCARDSSSYYMFNLWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSALVMTQ
SPSTLSASVGDRVTINCQASEDIDTYLAWYQQKPGKAPKLLIFYASDLASGVPSRFSGSGSGTEFTLTIS
SLQPDDFATYYCQGGYYTSSADTRGAFGGGTKVEIK

>SEQ ID 85 SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain nt

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TTATTAGTCGTACTTATGTAAATTCTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCTGC
ACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTG
CTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC
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>SEQ ID 86 SI-39E29 (806-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 420H5-H3L3-scFv) light chain aa

DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV
TKSFNRGEC

>SEQ ID 87 SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain nt

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CAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACTCTGGTTATAGTGATC
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>SEQ ID 88 SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) heavy chain aa

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FTLTISDLEPGDAATYYCQSTYLGTDYVGGAFGGGTKVEIKGGGGSGGGGSGGGGSGGGGSRSLVESGGG
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>SEQ ID 89 SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain nt

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>SEQ ID 90 SI-35E20 (466F6-L5H2-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 284A10-H1L1-scFv) light chain aa

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>SEQ ID 91 SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 92 SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 93 SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) light chain nt

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>SEQ ID 94 SI-35E58 (284A10-L1H1-scFv x PL230C6-Fab x 323H7-H4L1-scFv x 466F6-H2L5-scFv) light chain aa

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SFNRGEC

>SEQ ID 95 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 96 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 97 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain nt

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>SEQ ID 98 SI-35E88 (284A10-L1H1-scFv x 323H7-Fab x PL230C6-H3L2-scFv x 466F6-H2L5-scFv) light chain aa

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>SEQ ID 99 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 100 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 101 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt

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>SEQ ID 102 SI-35E99 (284A10-L1H1-scFv x 323H7-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa

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>SEQ ID 103 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 104 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa

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>SEQ ID 105 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt

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>SEQ ID 106 SI-38E17 (284A10-L1H1-scFv x 21D4-Fab x PL221G5-H1L1-scFv
x 466F6-H2L5-scFv) light chain aa

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>SEQ ID 107 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x
466F6-H2L5-scFv) heavy chain nt

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>SEQ ID 108 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) heavy chain aa

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YRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFSFSSGYDMCWVRQAPGKGLEWIACIA
AGSAGITYDANWAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSAFSFDYAMDLWGQGTLVTVSSG
GGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCQASQSISSHLNWYQQKPGKAPKLLIYKA
STLASGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQQGYSWGNVDNVFGGGTKVEIKGGGGSGGGGSR
SLVESGGGLVQPGGSLRLSCTASGFTISSYHMQWVRQAPGKGLEYIGTISSGGNVYYASSARGRFTISRP
SSKNTVDLQMNSLRAEDTAVYYCARDSGYSDPMWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQ
SPSSVSASVGDRVTITCQASQNIRTYLSWYQQKPGKAPKLLIYAAANLASGVPSRFSGSGSGTDFTLTIS
DLEPGDAATYYCQSTYLGTDYVGGAFGGGTKVEIK

SEQ ID 109 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain nt

GACGTCGTGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAATTGCC
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CTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACT
CCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG

CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC
ACAAAGAGCTTCAACAGGGGAGAGTGT

SEQ ID 110 SI-38E33 (21D4-LH-scFv x 284A10-Fab x PL221G5-H1L1-scFv x 466F6-H2L5-scFv) light chain aa

DVVMTQSPSTLSASVGDRVTINCQASESISSWLAWYQQKPGKAPKLLIYEASKLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQGYFYFISRTYVNSFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV
TKSFNRGEC

CLAIMS

What we claim is:

1. A guidance and navigation control (GNC) protein, comprising,
a binding domain for a T cell activating receptor,
a binding domain for a tumor associated antigen,
a bind domain for an immune checkpoint receptor, and
a binding domain for a T cell co-stimulating receptor,
wherein the binding domain for the tumor associated antigen is not adjacent to the binding domain for the T cell co-stimulating receptor.

2. The guidance and navigation control (GNC) protein of Claim 1, wherein the binding domain for the T cell activating receptor is adjacent to the binding domain for the tumor associated antigen (TAA).

3. The guidance and navigation control (GNC) protein of Claim 1, wherein T cell activating receptor comprises CD3.

4. The guidance and navigation control (GNC) protein of Claim 1, wherein an immune checkpoint receptor comprises PD-L1, PD-1, TIGIT, TIM-3, LAG-3, CTLA4, BTLA, VISTA, PDL2, CD160, LOX-1, siglec-15, CD47, or a combination thereof.

5. The guidance and navigation control (GNC) protein of Claim 1, wherein T cell co-stimulating receptor comprises 4-1BB, CD28, OX40, GITR, CD40L, ICOS, Light, CD27, CD30, or a combination thereof.

6. The guidance and navigation control (GNC) protein of Claim 1, wherein a tumor associated antigen comprises ROR1, CD19, EGRFVIII, BCMA, CD20, CD33, CD123, CD22, CD30, CEA, HER2, EGFR, LMP1, LMP2A, Mesothelin, PSMA, EpCAM, glypican-3, gpA33, GD2, TROP2, or a combination thereof.

7. The guidance and navigation control (GNC) protein of Claim 1, wherein the tumor associated antigen is a receptor on a lung cancer cell, a liver cancer cell, a breast cancer cell, a colorectal cancer cell, an anal cancer cell, a pancreatic cancer cell, a gallbladder cancer cell, a bile duct cancer cell, a head and neck cancer cell, a nasopharyngeal cancer cell, a skin cancer cell, a melanoma cell, an ovarian cancer cell, a prostate cancer cell, a urethral cancer cell, a lung cancer cell, a non-small lung cell cancer cell, a small cell lung cancer cell, a brain tumour cell, a glioma cell, a neuroblastoma cell, an esophageal cancer cell, a gastric cancer cell, a liver cancer cell, a kidney cancer cell, a bladder cancer cell, a cervical cancer cell, an endometrial cancer cell, a thyroid cancer cell, an eye cancer cell, a sarcoma cell, a bone cancer cell, a leukemia cell, a myeloma cell, a lymphoma cell, or a combination thereof.

8. The guidance and navigation control (GNC) protein of Claim 1, wherein the protein is a tri- or tetra-specific antibody comprising a Fc domain.

9. The guidance and navigation control (GNC) protein of Claim 8, wherein the T cell activating receptor comprises CD3, and wherein the binding domain for CD3 is linked to the binding domain for the tumor associated (TAA) antigen through a peptide linker to form a CD3-TAA pair, wherein the peptide linker has length not exceeding 100 amino acids.

10. The guidance and navigation control (GNC) protein of Claim 9, wherein the peptide linker has a length not exceeding 20 amino acids.

11. The guidance and navigation control (GNC) protein of Claim 9, wherein the peptide linker has a length not exceeding 10 amino acids.

12. The guidance and navigation control (GNC) protein of Claim 9, wherein the peptide linker has a length from about 2 amino acids to about 10 amino acids.

13. The guidance and navigation control (GNC) protein of Claim 9, wherein the tumor associated antigen comprises ROR1, CD19, or EGRFVIII.

14. The guidance and navigation control (GNC) protein of Claim 9, wherein the IgG Fc domain intermediates the CD3-TAA pair and the binding domain for the immune checkpoint receptor.

15. The guidance and navigation control (GNC) protein of Claim 14, wherein the immune checkpoint receptor comprises PD-L1.

16. The guidance and navigation control (GNC) protein of Claim 9 having a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal,

the binding domain for CD3,

the binding domain for EGFRVIII,

IgG Fc domain,

the bind domain for PD-L1, and

the binding domain for 41-BB.

17. The guidance and navigation control (GNC) protein of Claim 16, comprising an amino acid sequence having a percentage homology to SEQ ID NO. 80 and 82, wherein the percentage homology is not less than 98%.

18. The guidance and navigation control (GNC) protein of Claim 9 having a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal,

the binding domain for 4-1BB,

the binding domain for PD-L1,

IgG Fc domain,

the bind domain for ROR1, and

the binding domain for CD3.

19. The guidance and navigation control (GNC) protein of Claim 18, comprising an amino acid sequence having a percentage homology to SEQ ID NO. 88 and 90, wherein the percentage homology is not less than 98%.

20. The guidance and navigation control (GNC) protein of Claim 9 having a N-terminal and a C-terminal, comprising in tandem from the N-terminal to the C-terminal,

the binding domain for CD3,

the binding domain for CD19,

IgG Fc domain,

the bind domain for PD-L1, and

the binding domain for 4-1BB.

21. The guidance and navigation control (GNC) protein of Claim 20, comprising an amino acid sequence having a percentage homology to SEQ ID NO. 104 and 106, wherein the percentage homology is not less than 98%.

22. The GNC protein of Claim 1, comprising an amino acid having a percentage homology to SEQ ID NO. 50, 52, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108 and 110, wherein the percentage homology is not less than 98%.

23. A nucleic acid, encoding the GNC protein of Claim 1.

24. The nucleic acid of Claim 23 having a percentage homology to SEQ ID NO. 49, 51, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, and 109, wherein the percentage homology is not less than 98%.

25. A cytotoxic cell, comprising,

a T cell having a T cell activating receptor and a T cell co-stimulating receptor, and

the GNC protein of Claim 1 bound to the T cell through interaction with the T cell activating receptor, the T cell co-stimulating receptor, or a combination there.

26. A cancer cell, comprising

a cancer cell having a tumor associated antigen, and

the GNC protein of Claim 1 bound to cancer cell through the interaction with the tumor associated antigen.

27. A biological complex, comprising,

a T cell having a T cell activating receptor and a T cell co-stimulating receptor,

a cancer cell having a tumor associated antigen, and

the GNC protein of Claim 1, wherein the GNC protein is bound to the T cell through the interaction with the T cell activating receptor, the T cell co-stimulating receptor, or a combination thereof and wherein the GNC protein is bound to the cancer cell through the interaction with the tumor associated antigen.

28. A pharmaceutical composition, comprising

the GNC protein of Claim 1, 9, 16, 18, or 20, or the cytotoxic cell of 25, or a combination thereof, and

a pharmaceutically acceptable carrier.

29. A method of treating a subject having a cancer, comprising administering to the subject an effective amount of the pharmaceutical composition of 28.