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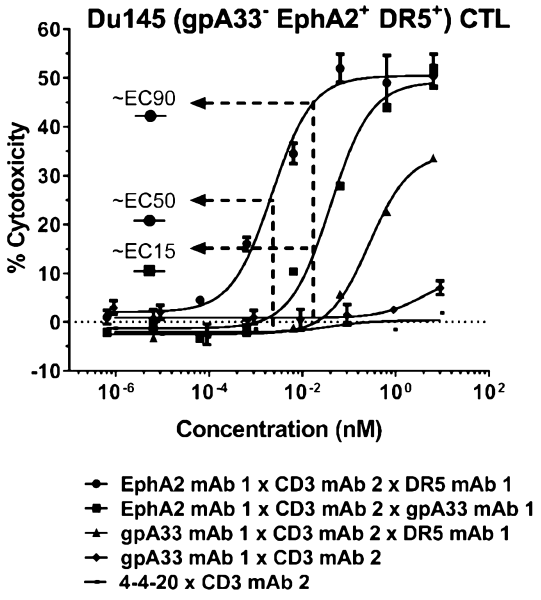


Figure 10C

(57) Abstract: The present invention relates to Tri-Specific Binding Molecules, which are multi-chain polypeptide molecules that possess three Binding Domains and are thus capable of mediating coordinated binding to three epitopes. The Tri-Specific Binding Molecule is preferably characterized in possessing binding domains that permit it to immunospecifically bind to: (1) an epitope of a first Cancer Antigen, (2) an epitope of a second Cancer Antigen, and (3) an epitope of a molecule that is expressed on the surface of an immune system effector cell, and are thus capable of localizing an immune system effector cell to a cell that expresses a Cancer Antigen, so as to thereby facilitate the killing of such cancer cell.

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Title of the Invention:

Tri-Specific Binding Molecules That Specifically Bind to Multiple Cancer Antigens and Methods of Use Thereof

Cross-Reference to Related Applications

[0001] This application claims priority to United States Patent Applications No. 62/107,824 (filed January 26, 2015), 62/008,229 (filed June 5, 2014; pending), and 62/004,571 (filed May 29, 2014; pending), each of which applications is herein incorporated by reference in its entirety.

Reference to Sequence Listing:

[0002] This application includes one or more Sequence Listings pursuant to 37 C.F.R. 1.821 et seq., which are disclosed in computer-readable media (file name: 1301_0119PCT_Sequence_Listing_ST25.txt, created on 18 May 2015, and having a size of 416,408 bytes), which file is herein incorporated by reference in its entirety.

Background of the Invention:

Field of the Invention:

[0003] The present invention relates to Tri-Specific Binding Molecules, which are multi-chain polypeptide molecules that possess three Binding Domains and are thus capable of mediating coordinated binding to three epitopes. The Tri-Specific Binding Molecule is preferably characterized in possessing binding domains that permit it to immunospecifically bind to: (1) an epitope of a first Cancer Antigen, (2) an epitope of a second Cancer Antigen, and (3) an epitope of a molecule that is expressed on the surface of an immune system effector cell, and are thus capable of localizing an immune system effector cell to a cell that expresses a Cancer Antigen, so as to thereby facilitate the killing of such cancer cell.

Description of Related Art:

I. The Mammalian Immune System

[0004] The mammalian immune system serves as a defense against a variety of conditions, including, *e.g.*, injury, infection and neoplasia. The efficiency with which humans and other mammals develop an immunological response to pathogens, foreign substances and cancer antigens rests on two characteristics: the exquisite specificity of the immune response for antigen recognition, and the immunological memory that allows for faster and more vigorous responses upon re-activation with the same antigen (Portolés, P. *et al.* (2009) "*The TCR/CD3 Complex: Opening the Gate to Successful Vaccination*," Current Pharmaceutical Design 15:3290-3300; Guy, C.S. *et al.* (2009) "*Organization of Proximal Signal Initiation at the TCR:CD3 Complex*," Immunol Rev. 232(1):7-21).

[0005] The mammalian immune system is mediated by two separate but interrelated systems: the cellular and humoral immune systems. Generally speaking, the humoral system is mediated by soluble products (antibodies or immunoglobulins) that have the ability to combine with and neutralize products recognized by the system as being foreign to the body. In contrast, the cellular immune system involves the mobilization of certain cells, termed "T cells," that serve a variety of therapeutic roles. T cells are lymphocytes that are derived from the thymus and circulate between the tissues, lymphatic system and the circulatory system. In response to the presence and recognition of foreign structures (antigens), T cells become "**activated**" to initiate an immune response. In many instances these foreign antigens are expressed on host cells as a result of neoplasia or infection. Although T cells do not themselves secrete antibodies, they are usually required for antibody secretion by the second class of lymphocytes, B cells (which derive from bone marrow). Critically, T cells exhibit extraordinary immunological specificity so as to be capable of discerning one antigen from another). Two types of T cells, "T helper cells" and "cytotoxic T cells," are of particular relevance.

[0006] T helper cells are characterized by their expression of the glycoprotein, **CD4** (i.e., they are "$CD4^+$"). $CD4^+$ T cells are the essential organizers of most mammalian immune and autoimmune responses (Dong, C. *et al.* (2003) "*Immune*

Regulation by Novel Costimulatory Molecules," Immunolog. Res. 28(1):39-48). The activation of $CD4^+$ T cells has been found to be mediated through co-stimulatory interactions between an antigen:major histocompability class II (**MHC II**) molecule complex that is arrayed on the surface of an Antigen Presenting Cell (such as a B cell, a macrophage or a dendritic cell) and a complex of two molecules, the T Cell Receptor ("**TCR**") and a **CD3** cell surface receptor ligand, that are arrayed on surface of a naive $CD4^+$ T cell. Activated T helper cells are capable of proliferating into Th1 cells that are capable of mediating an inflammatory response to the target cell.

[0007] Cytotoxic T cells are characterized by their expression of **CD8** (i.e., they are "CD8+" as well as $CD3^+$). The activation of $CD8^+$ T cells has been found to be mediated through co-stimulatory interactions between an antigen:major histocompability class I (**MHC I**) molecule complex that is arrayed on the surface of a target cell and a complex of CD8 and the T Cell Receptor, that are arrayed on surface of the $CD8^+$ T cell. Unlike MHC II molecules, which are expressed by only certain immune system cells, MHC I molecules are very widely expressed. Thus, cytotoxic T cells are capable of binding to a wide variety of cell types. Activated cytotoxic T cells mediate cell killing through their release of the cytotoxins perforin, granzymes, and granulysin. Through the action of perforin, granzymes enter the cytoplasm of the target cell and their serine protease function triggers the caspase cascade, which is a series of cysteine proteases that eventually lead to apoptosis (programmed cell death) of targeted cells.

[0008] The T cell receptor ("TCR") is a covalently linked heterodimer of α and β chains ("TCRαβ"). These chains are class I membrane polypeptides of 259 (α) and 296 (β) amino acids in length. The CD3 molecule is a T cell co-receptor composed of five distinct polypeptide chains (a CD3 γ chain, a CD3 δ chain, two CD3 ε chains and two zeta chains). The individual polypeptide chains associate to form a complex of three dimers (εγ, εδ, ζζ) (Wucherpfennig, K.W. *et al.* (2010) "*Structural Biology Of The T Cell Receptor: Insights into Receptor Assembly, Ligand Recognition, And Initiation of Signaling*," Cold Spring Harb. Perspect. Biol. 2(4):a005140; pages 1-14; Chetty, R. *et al.* (1994) "*CD3: Structure, Function And The Role Of Immunostaining In Clinical Practice*," J. Pathol. 173:303-307; Guy, C.S. *et al.* (2009) "*Organization*

of Proximal Signal Initiation at the TCR:CD3 Complex," Immunol Rev. 232(1):7-21; Call, M.E. *et al.* (2007) "*Common Themes In The Assembly And Architecture Of Activating Immune Receptors*," Nat. Rev. Immunol. 7:841-850; Weiss, A. (1993) "*T Cell Antigen Receptor Signal Transduction: A Tale Of Tails And Cytoplasmic Protein-Tyrosine Kinases*," Cell 73:209-212). The CD3 complex associates with TCR in order to generate an activation signal in T lymphocytes. In the absence of CD3, TCRs do not assemble properly and are degraded (Thomas, S. *et al.* (2010) "*Molecular Immunology Lessons From Therapeutic T Cell Receptor Gene Transfer*," Immunology 129(2):170–177). CD3 is found bound to the membranes of all mature T cells, and in virtually no other cell type (see, Janeway, C.A. *et al.* (2005) In: IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE," 6th ed. Garland Science Publishing, NY, pp. 214-216; Sun, Z. J. *et al.* (2001) "*Mechanisms Contributing To T Cell Receptor Signaling And Assembly Revealed By The Solution Structure Of An Ectodomain Fragment Of The CD3ε:γ Heterodimer*," Cell 105(7):913-923; Kuhns, M.S. *et al.* (2006) "*Deconstructing The Form And Function Of The TCR/CD3 Complex*," Immunity. 2006 Feb;24(2):133-139).

[0009] The TCR and CD3 complex, along with the CD3 ζ chain zeta chain (also known as T cell receptor T3 zeta chain or CD247) comprise the TCR complex (van der Merwe, P.A. *etc.* (epub Dec. 3, 2010) "*Mechanisms For T Cell Receptor Triggering*," Nat. Rev. Immunol. 11:47-55; Wucherpfennig, K.W. *et al.* (2010) "*Structural Biology of the T cell Receptor: Insights into Receptor Assembly, Ligand Recognition, and Initiation of Signaling*," Cold Spring Harb. Perspect. Biol. 2:a005140). The complex is particularly significant since it contains a large number (ten) of immunoreceptor tyrosine-based activation motifs (ITAMs).

[0010] Two interactions are required for T cell activation (Viglietta, V. *et al.* (2007) "*Modulating Co-Stimulation*," Neurotherapeutics 4:666-675; Korman, A.J. *et al.* (2007) "*Checkpoint Blockade in Cancer Immunotherapy*," Adv. Immunol. 90:297-339). In the first interaction, a Cell must display the relevant target antigen bound to the cell's major histocompatibility complex so that it can bind to the T cell Receptor ("TCR") of a naive T lymphocyte. In the second interaction, a ligand of the Cell must bind to a co-receptor of the T lymphocyte (Dong, C. *et al.* (2003) "*Immune*

Regulation by Novel Costimulatory Molecules," Immunolog. Res. 28(1):39-48; Lindley, P.S. *et al.* (2009) "*The Clinical Utility Of Inhibiting CD28-Mediated Costimulation*," Immunol. Rev. 229:307-321). T cells experiencing both stimulatory signals are then capable of responding to cytokines (such as Interleukin-2 and Interleukin-12). In the absence of both co-stimulatory signals during TCR engagement, T cells enter a functionally unresponsive state, referred to as clonal anergy (Khawli, L.A. *et al.* (2008) "*Cytokine, Chemokine, and Co-Stimulatory Fusion Proteins for the Immunotherapy of Solid Tumors*," Exper. Pharmacol. 181:291-328). In pathologic states, T cells are the key players of various organ-specific autoimmune diseases, such as type I diabetes, rheumatoid arthritis, and multiple sclerosis (Dong, C. *et al.* (2003) "*Immune Regulation by Novel Costimulatory Molecules*," Immunolog. Res. 28(1):39-48).

[0011] The need for two signals to activate T cells such that they achieve an adaptive immune response is believed to provide a mechanism for avoiding responses to self-antigens that may be present on an Antigen Presenting Cell at locations in the system where it can be recognized by a T cell. Where contact of a T cell with a Cell results in the generation of only one of two required signals, the T cell does not become activated and an adaptive immune response does not occur.

II. Antibodies and Other Epitope-Binding Molecules

A. Antibodies

[0012] "**Antibodies**" are immunoglobulin molecules capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, *etc.*, through at least one antigen recognition site, located in the Variable Domain of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, camelized antibodies, single-chain antibodies, and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id and anti-anti-Id antibodies to antibodies of the invention), but also mutants thereof, naturally occurring variants, fusion proteins comprising an antibody portion with an antigen recognition site of the required specificity, humanized antibodies, and chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity. Throughout this

application, the numbering of amino acid residues of the light and heavy chains of antibodies is according to the EU index as in Kabat *et al.* (1992) SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST, National Institutes of Health Publication No. 91-3242. As used herein, an "antigen-binding fragment of an antibody" is a portion of an antibody that possesses an at least one antigen recognition site. As used herein, the term encompasses fragments (*e.g.*, Fab, Fab', $F(ab')_2$ Fv), disulfide-linked bispecific Fvs (sdFv), intrabodies, and single-chain molecules (*e.g.*, scFv). In particular, antibodies include immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, i.e., molecules that contain an antigen-binding site. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

[0013] Natural antibodies (such as IgG antibodies) are composed of two **Light Chains** complexed with two **Heavy Chains**. Each Light Chain contains a Variable Domain (**VL**) and a Constant Domain (**CL**). Each heavy chain contains a Variable Domain (**VH**), three Constant Domains (**CH1**, **CH2** and **CH3**), and a Hinge Domain located between the **CH1** and **CH2** Domains. The basic structural unit of naturally occurring immunoglobulins (*e.g.*, IgG) is thus a tetramer having two light chains and two heavy chains, usually expressed as a glycoprotein of about 150,000 Da. The amino-terminal ("N") portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal ("C") portion of each chain defines a constant region, with light chains having a single Constant Domain and heavy chains usually having three Constant Domains and a hinge region. Thus, the structure of the light chains of an IgG molecule is n-VL-CL-c and the structure of the IgG heavy chains is n-VH-CH1-H-CH2-CH3-c (where H is the hinge region, and n and c represent, respectively, the N-terminus and the C-terminus of the polypeptide).

[0014] The ability of an intact, unmodified antibody (*e.g.*, an IgG antibody) to bind an epitope of an antigen depends upon the presence of Variable Domains on the immunoglobulin light and heavy chains (*i.e.*, the VL Domain and VH Domain, respectively). Interaction of an antibody Light Chain and an antibody heavy chain and, in particular, interaction of its VL and VH Domains forms one of the epitope-

binding sites of the antibody. The variable regions of an IgG molecule consist of the complementarity determining regions (**CDR**), which contain the residues in contact with epitope, and non-CDR segments, referred to as framework segments (**FR**), which in general maintain the structure and determine the positioning of the CDR loops so as to permit such contacting (although certain framework residues may also contact antigen). Thus, the VL and VH Domains have the structure n-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4-c. Polypeptides that are (or may serve as) the first, second and third CDR of an antibody Light Chain are herein respectively designated **CDR_L1 Domain**, **CDR_L2 Domain**, and **CDR_L3 Domain**. Similarly, polypeptides that are (or may serve as) the first, second and third CDR of an antibody heavy chain are herein respectively designated **CDR_H1 Domain**, **CDR_H2 Domain**, and **CDR_H3 Domain**. Thus, the terms CDR_L1 Domain, CDR_L2 Domain, CDR_L3 Domain, CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are directed to polypeptides that when incorporated into a protein cause that protein to be able to bind to an specific epitope regardless of whether such protein is an antibody having light and heavy chains or a diabody or a single-chain binding molecule (*e.g.*, an scFv, a BiTe, *etc.*), or is another type of protein. In contrast to such antibodies, the scFv construct comprises a VL and VH Domain of an antibody contained in a single polypeptide chain wherein the Domains are separated by a flexible linker of sufficient length to allow self-assembly of the two Domains into a functional epitope-binding site. Where self-assembly of the VL and VH Domains is rendered impossible due to a linker of insufficient length (less than about 12 amino acid residues), two of the scFv constructs may interact with one another other to form a bivalent molecule in which the VL of one chain associates with the VH of the other (reviewed in Marvin *et al.* (2005) *"Recombinant Approaches To IgG-Like Bispecific Antibodies,"* Acta Pharmacol. Sin. 26:649-658).

[0015] In addition to their known uses in diagnostics, antibodies have been shown to be useful as therapeutic agents. The last few decades have seen a revival of interest in the therapeutic potential of antibodies, and antibodies have become one of the leading classes of biotechnology-derived drugs (Chan, C.E. *et al.* (2009) "*The Use Of Antibodies In The Treatment Of Infectious Diseases*," Singapore Med. J. 50(7):663-666). Nearly 200 antibody-based drugs have been approved for use or are under development.

[0016] The term "**monoclonal antibody**" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an antigen. Monoclonal antibodies are highly specific, being directed against a single epitope (or antigenic site). The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$ Fv), single-chain (scFv), mutants thereof, fusion proteins comprising an antibody portion, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity and the ability to bind to an antigen. It is not intended to be limited as regards to the source of the antibody or the manner in which it is made (*e.g.*, by hybridoma, phage selection, recombinant expression, transgenic animals, *etc.*). The term includes whole immunoglobulins as well as the fragments *etc.* described above under the definition of "antibody." Methods of making monoclonal antibodies are known in the art. One method which may be employed is the method of Kohler, G. *et al.* (1975) "*Continuous Cultures Of Fused Cells Secreting Antibody Of Predefined Specificity*," Nature 256:495-497 or a modification thereof. Typically, monoclonal antibodies are developed in mice, rats or rabbits. The antibodies are produced by immunizing an animal with an immunogenic amount of cells, cell extracts, or protein preparations that contain the desired epitope. The immunogen can be, but is not limited to, primary cells, cultured cell lines, cancerous cells, proteins, peptides, nucleic acids, or tissue. Cells used for immunization may be cultured for a period of time (*e.g.*, at least 24 hours) prior to their use as an immunogen. Cells may be used as immunogens by themselves or in combination with a non-denaturing adjuvant, such as Ribi (see, *e.g.*, Jennings, V.M. (1995) "*Review of Selected Adjuvants Used in Antibody Production*," ILAR J. 37(3):119-125).

[0017] In general, cells should be kept intact and preferably viable when used as immunogens. Intact cells may allow antigens to be better detected than ruptured cells by the immunized animal. Use of denaturing or harsh adjuvants, *e.g.*, Freud's adjuvant, may rupture cells and therefore is discouraged. The immunogen may be administered multiple times at periodic intervals such as, bi weekly, or weekly, or

may be administered in such a way as to maintain viability in the animal (*e.g.*, in a tissue recombinant). Alternatively, existing monoclonal antibodies and any other equivalent antibodies that are immunospecific for a desired pathogenic epitope can be sequenced and produced recombinantly by any means known in the art. In one embodiment, such an antibody is sequenced and the polynucleotide sequence is then cloned into a vector for expression or propagation. The sequence encoding the antibody of interest may be maintained in a vector in a host cell and the host cell can then be expanded and frozen for future use. The polynucleotide sequence of such antibodies may be used for genetic manipulation to generate a chimeric antibody, a humanized antibody, or a caninized antibody, or to improve the affinity, or other characteristics of the antibody. The term "**humanized**" antibody refer to a chimeric molecule, generally prepared using recombinant techniques, having an antigen-binding site derived from an immunoglobulin from a non-human species and the remaining immunoglobulin structure of the molecule based upon the structure and /or sequence of a human immunoglobulin. The polynucleotide sequence of the variable domains of such antibodies may be used for genetic manipulation to generate such derivatives and to improve the affinity, or other characteristics of such antibodies. The general principle in humanizing an antibody involves retaining the basic sequence of the antigen-binding portion of the antibody, while swapping the non-human remainder of the antibody with human antibody sequences. There are four general steps to humanize a monoclonal antibody. These are: (1) determining the nucleotide and predicted amino acid sequence of the starting antibody light and heavy variable Domains (2) designing the humanized antibody or caninized antibody, *i.e.*, deciding which antibody framework region to use during the humanizing or canonizing process (3) the actual humanizing or caninizing methodologies/techniques and (4) the transfection and expression of the humanized antibody. See, for example, U.S. Patents Nos. 4,816,567; 5,807,715; 5,866,692; and 6,331,415.

[0018] The epitope-binding domain of such antibodies may comprise either complete Variable Domains fused onto Constant Domains or only the complementarity determining regions (CDRs) grafted onto appropriate framework regions in the Variable Domains. Antigen-binding sites may be wild-type or modified by one or more amino acid substitutions. This eliminates the constant region as an

immunogen in human individuals, but the possibility of an immune response to the foreign variable region remains (LoBuglio, A.F. *et al.* (1989) "*Mouse/Human Chimeric Monoclonal Antibody In Man: Kinetics And Immune Response*," Proc. Natl. Acad. Sci. (U.S.A.) 86:4220-4224). Another approach focuses not only on providing human-derived constant regions, but modifying the variable regions as well so as to reshape them as closely as possible to human form. It is known that the variable regions of both heavy and light chains contain three complementarity determining regions (CDRs) which vary in response to the antigens in question and determine binding capability, flanked by four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When non-human antibodies are prepared with respect to a particular antigen, the variable regions can be "reshaped" or "humanized" by grafting CDRs derived from non-human antibody on the FRs present in the human antibody to be modified. Application of this approach to various antibodies has been reported by Sato, K. *et al.* (1993) Cancer Res 53:851-856. Riechmann, L. *et al.* (1988) "*Reshaping Human Antibodies for Therapy*," Nature 332:323-327; Verhoeyen, M. *et al.* (1988) "*Reshaping Human Antibodies: Grafting An Antilysozyme Activity*," Science 239:1534-1536; Kettleborough, C. A. *et al.* (1991) "*Humanization Of A Mouse Monoclonal Antibody By CDR-Grafting: The Importance Of Framework Residues On Loop Conformation*," Protein Engineering 4:773-3783; Maeda, H. *et al.* (1991) "*Construction Of Reshaped Human Antibodies With HIV-Neutralizing Activity*," Human Antibodies Hybridoma 2:124-134; Gorman, S. D. *et al.* (1991) "*Reshaping A Therapeutic CD4 Antibody*," Proc. Natl. Acad. Sci. (U.S.A.) 88:4181-4185; Tempest, P.R. *et al.* (1991) "*Reshaping A Human Monoclonal Antibody To Inhibit Human Respiratory Syncytial Virus Infection in vivo*," Bio/Technology 9:266-271; Co, M. S. *et al.* (1991) "*Humanized Antibodies For Antiviral Therapy*," Proc. Natl. Acad. Sci. (U.S.A.) 88:2869-2873; Carter, P. *et al.* (1992) "*Humanization Of An Anti-p185her2 Antibody For Human Cancer Therapy*," Proc. Natl. Acad. Sci. (U.S.A.) 89:4285-4289; and Co, M.S. *et al.* (1992) "*Chimeric And Humanized Antibodies With Specificity For The CD33 Antigen*," J. Immunol. 148:1149-1154. In some embodiments, humanized antibodies preserve all CDR sequences (for example, a humanized mouse antibody which contains all six CDRs from the mouse antibodies).

In other embodiments, humanized antibodies have one or more CDRs (one, two, three, four, five, or six) which differ in sequence relative to the original antibody.

[0019] A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent or modified rodent V regions and their associated complementarity determining regions (CDRs) fused to human constant domains (see, for example, Winter *et al.* (1991) "*Man-made Antibodies*," Nature 349:293-299; Lobuglio *et al.* (1989) "*Mouse/Human Chimeric Monoclonal Antibody In Man: Kinetics And Immune Response*," Proc. Natl. Acad. Sci. (U.S.A.) 86:4220-4224 (1989), Shaw *et al.* (1987) "*Characterization Of A Mouse/Human Chimeric Monoclonal Antibody (17-1A) To A Colon Cancer Tumor-Associated Antigen*," J. Immunol. 138:4534-4538, and Brown *et al.* (1987) "*Tumor-Specific Genetically Engineered Murine/Human Chimeric Monoclonal Antibody*," Cancer Res. 47:3577-3583). Other references describe rodent CDRs grafted into a human supporting framework region (FR) prior to fusion with an appropriate human antibody constant domain (see, for example, Riechmann, L. *et al.* (1988) "*Reshaping Human Antibodies for Therapy*," Nature 332:323-327; Verhoeyen, M. *et al.* (1988) "*Reshaping Human Antibodies: Grafting An Antilysozyme Activity*," Science 239:1534-1536; and Jones *et al.* (1986) "*Replacing The Complementarity-Determining Regions In A Human Antibody With Those From A Mouse*," Nature 321:522-525). Another reference describes rodent CDRs supported by recombinantly veneered rodent framework regions. See, for example, European Patent Publication No. 519,596. These "humanized" molecules are designed to minimize unwanted immunological response toward rodent anti-human antibody molecules, which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients. Other methods of humanizing antibodies that may also be utilized are disclosed by Daugherty *et al.* (1991) "*Polymerase Chain Reaction Facilitates The Cloning, CDR-Grafting, And Rapid Expression Of A Murine Monoclonal Antibody Directed Against The CD18 Component Of Leukocyte Integrins*," Nucl. Acids Res. 19:2471-2476 and in U.S. Patents Nos. 6,180,377; 6,054,297; 5,997,867; and 5,866,692.

B. Bi-Specific Antibodies, Multi-Specific Diabodies and DART™ Diabodies

[0020] Natural antibodies are capable of binding to only one epitope species (*i.e.*, they are "mono-specific"), although they may be able to bind multiple copies of that species (*i.e.*, they may exhibit bi-valency or multi-valency). A wide variety of recombinant bi-specific antibody formats have been developed (see, *e.g.*, PCT Publication Nos. WO 2008/003116, WO 2009/132876, WO 2008/003103, WO 2007/146968, WO 2007/146968, WO 2009/018386, WO 2012/009544, WO 2013/070565), most of which use linker peptides either to fuse the antibody core (IgA, IgD, IgE, IgG or IgM) to a further binding protein (*e.g.*, scFv, VL VH, *etc.*) to, or within, the antibody core, or to fuse multiple antibody portions or to fuse (*e.g.* two Fab fragments or scFv) to a Heterodimerization-Promoting Domain such as the CH2-CH3 Domain or alternative polypeptides (WO 2005/070966, WO 2006/107786A WO 2006/107617A, WO 2007/046893). Typically, such approaches involve compromises and trade-offs. For example, PCT Publications Nos. WO 2013/174873, WO 2011/133886 and WO 2010/136172 disclose that the use of linkers may cause problems in therapeutic settings, and teaches a tri-specific antibody in which the CL and CH1 Domains are switched from their respective natural positions and the VL and VH Domains have been diversified (WO 2008/027236; WO 2010/108127) to allow them to bind to more than one antigen. Thus, the molecules disclosed in these documents trade binding specificity for the ability to bind additional antigen species. PCT Publications Nos. WO 2013/163427 and WO 2013/119903 disclose modifying the CH2 Domain to contain a fusion protein adduct comprising a binding domain. The document notes that the CH2 Domain likely plays only a minimal role in mediating effector function. PCT Publications Nos. WO 2010/028797, WO2010028796 and WO 2010/028795 disclose recombinant antibodies whose Fc Domains have been replaced with additional VL and VH Domains, so as to form tri-valent binding molecules. PCT Publications Nos. WO 2003/025018 and WO2003012069 disclose recombinant diabodies whose individual chains contain scFv domains. PCT Publications No. WO 2013/006544 discloses multi-valent Fab molecules that are synthesized as a single polypeptide chain and then subjected to proteolysis to yield heterodimeric structures. Thus, the molecules disclosed in these

documents trade all or some of the capability of mediating effector function for the ability to bind additional antigen species. PCT Publications Nos. WO 2014/022540, WO 2013/003652, WO 2012/162583, WO 2012/156430, WO 2011/086091, WO 2007/075270, WO 1998/002463, WO 1992/022583 and WO 1991/003493 disclose adding additional Binding Domains or functional groups to an antibody or an antibody portion (*e.g.*, adding a diabody to the antibody's Light Chain, or adding additional VL and VH Domains to the antibody's light and heavy chains, or adding a heterologous fusion protein or chaining multiple Fab Domains to one another). Thus, the molecules disclosed in these documents trade native antibody structure for the ability to bind additional antigen species.

[0021] The art has additionally noted the capability to produce **diabodies** that differ from such natural antibodies in being capable of binding two or more different epitope species (*i.e.*, exhibiting bi-specificity or multispecificity in addition to bi-valency or multi-valency) (see, *e.g.*, Holliger *et al.* (1993) "*'Diabodies': Small Bivalent And Bispecific Antibody Fragments,*" Proc. Natl. Acad. Sci. (U.S.A.) 90:6444-6448; US 2004/0058400 (Hollinger *et al.*); US 2004/0220388 (Mertens *et al.*); Alt *et al.* (1999) FEBS Lett. 454(1-2):90-94; Lu, D. *et al.* (2005) "*A Fully Human Recombinant IgG-Like Bispecific Antibody To Both The Epidermal Growth Factor Receptor And The Insulin-Like Growth Factor Receptor For Enhanced Antitumor Activity*," J. Biol. Chem. 280(20):19665-19672; WO 02/02781 (Mertens *et al.*); Olafsen, T. *et al.* (2004) "*Covalent Disulfide-Linked Anti-CEA Diabody Allows Site-Specific Conjugation And Radiolabeling For Tumor Targeting Applications*," Protein Eng Des Sel. 17(1):21-27; Wu, A. *et al.* (2001) "*Multimerization Of A Chimeric Anti-CD20 Single-chain Fv-Fv Fusion Protein Is Mediated Through Variable Domain Exchange*," Protein Engineering 14(2):1025-1033; Asano *et al.* (2004) "*A Diabody For Cancer Immunotherapy And Its Functional Enhancement By Fusion Of Human Fc Domain*," Abstract 3P-683, J. Biochem. 76(8):992; Takemura, S. *et al.* (2000) "*Construction Of A Diabody (Small Recombinant Bispecific Antibody) Using A Refolding System,*" Protein Eng. 13(8):583-588; Baeuerle, P.A. *et al.* (2009) "*Bispecific T-Cell Engaging Antibodies For Cancer Therapy*," Cancer Res. 69(12):4941-4944).

[0022] The design of a diabody is based on the structure of single-chain Variable Domain fragments (**scFv**). Such molecules are made by linking light and/ or Heavy Chain Variable Domains to one another via a short linking peptide. Bird *et al.* (1988) ("*Single-Chain Antigen-Binding Proteins*," Science 242:423-426) describes an example of linking peptides which bridge approximately 3.5 nm between the carboxy terminus of one Variable Domain and the amino terminus of the other Variable Domain. Linkers of other sequences have been designed and used (Bird *et al.* (1988) "*Single-Chain Antigen-Binding Proteins*," Science 242:423-426). Linkers can in turn be modified for additional functions, such as attachment of drugs or attachment to solid supports. The single-chain variants can be produced either recombinantly or synthetically. For synthetic production of scFv, an automated synthesizer can be used. For recombinant production of scFv, a suitable plasmid containing polynucleotide that encodes the scFv can be introduced into a suitable host cell, either eukaryotic, such as yeast, plant, insect or mammalian cells, or prokaryotic, such as *E. coli*. Polynucleotides encoding the scFv of interest can be made by routine manipulations such as ligation of polynucleotides. The resultant scFv can be isolated using standard protein purification techniques known in the art.

[0023] United States Patent No. 7,585,952 and United States Patent Publication No. 2010-0173978 concern scFv molecules that are immunospecific for ErbB2. Bi-specific T cell engagers ("**BiTEs**"), a type of scFv molecule has been described (WO 05/061547; Baeuerle, P *et al.* (2008) "*BiTE: A New Class Of Antibodies That Recruit T Cells*," Drugs of the Future 33: 137-147; Bargou, *et al.* 2008) "*Tumor Regression in Cancer Patients by Very Low* Doses of a T Cell-Engaging Antibody," Science 321: 974-977). Such molecules are composed of a single polypeptide chain molecule having two Antigen-Binding Domains, one of which immunospecifically binds to a CD3 epitope and the second of which immunospecifically binds to an antigen present on the surface of a target cell.

[0024] The provision of non-mono-specific diabodies provides a significant advantage: the capacity to co-ligate and co-localize cells that express different epitopes. Bivalent diabodies thus have wide-ranging applications including therapy and immunodiagnosis. Bi-valency allows for great flexibility in the design and

engineering of the diabody in various applications, providing enhanced avidity to multimeric antigens, the cross-linking of differing antigens, and directed targeting to specific cell types relying on the presence of both target antigens. Due to their increased valency, low dissociation rates and rapid clearance from the circulation (for diabodies of small size, at or below ~50 kDa), diabody molecules known in the art have also shown particular use in the field of tumor imaging (Fitzgerald *et al.* (1997) *"Improved Tumour Targeting By Disulphide Stabilized Diabodies Expressed In Pichia pastoris,"* Protein Eng. 10:1221). Of particular importance is the co-ligating of differing cells, for example, the cross-linking of cytotoxic T cells to tumor cells (Staerz *et al.* (1985) *"Hybrid Antibodies Can Target Sites For Attack By T Cells,"* Nature 314:628-631, and Holliger *et al.* (1996) *"Specific Killing Of Lymphoma Cells By Cytotoxic T-Cells Mediated By A Bispecific Diabody,"* Protein Eng. 9:299-305).

[0025] Diabody epitope-binding domains may be directed to a surface determinant of any immune effector cell such as CD3, CD16, CD32, CD64, *etc.*, which are expressed on T lymphocytes, Natural Killer (NK) cells or other mononuclear cells. In many studies, diabody binding to effector cell determinants, *e.g.*, Fcγ receptors (FcγR), was also found to activate the effector cell (Holliger *et al.* (1996) *"Specific Killing Of Lymphoma Cells By Cytotoxic T-Cells Mediated By A Bispecific Diabody,"* Protein Eng. 9:299-305; Holliger *et al.* (1999) *"Carcinoembryonic Antigen (CEA)-Specific T-cell Activation In Colon Carcinoma Induced By Anti-CD3 x Anti-CEA Bispecific Diabodies And B7 x Anti-CEA Bispecific Fusion Proteins,"* Cancer Res. 59:2909-2916; WO 2006/113665; WO 2008/157379; WO 2010/080538; WO 2012/018687; WO 2012/162068). Normally, effector cell activation is triggered by the binding of an antigen bound antibody to an effector cell via Fc-FcγR interaction; thus, in this regard, diabody molecules may exhibit Ig-like functionality independent of whether they comprise an Fc Domain (*e.g.,* as assayed in any effector function assay known in the art or exemplified herein (*e.g.*, ADCC assay)). By cross-linking tumor and effector cells, the diabody not only brings the effector cell within the proximity of the tumor cells but leads to effective tumor killing (see *e.g.*, Cao *et al.* (2003) *"Bispecific Antibody Conjugates In Therapeutics,"* Adv. Drug. Deliv. Rev. 55:171-197).

[0026] For example, United States Patent No. 6,171,586, concerns the production of bi-specific antibodies by proteolytically cleaving two antibodies to obtain their $F(ab')_2$ fragments, reducing such fragments under conditions for preventing intermolecular disulfide bond formation, and then mixing the fragments to generate the bi-specific antibody). United States Patents No. 6,551,592; 6,994,853 and 8,277,806 and PCT Publications Nos. WO 2012/156430, WO 2002/020039, WO 2000/018806 and WO 1998/003670 concern the production of tri-specific antibodies capable of simultaneously binding to T cells and other antigens on a tumor cell, and, via the Fc portion of the bi-specific antibody, to the Fc receptor of cells possessing such a receptor. PCT Publications Nos. WO 2000/018806, WO 1998/003670 and WO 2006/072152 concern the production of tri-specific antibodies capable of simultaneously binding to T cells and other antigens. United States Patent Publication No. 2008-0057054 discloses bi-specific conjugates specific for a binding element against amyloid beta oligomers and a binding element against transmembrane protein telencephalin. United States Patent Publication No. 2010-0291112 concerns bi-specific and tri-specific single-chain Fv molecules that specifically bind to a one (or two) tumor antigen(s) and an effector cell antigen (such as CD3, CD16 CD32, CD64, *etc.*).

[0027] PCT Publication Nos. WO 1999/042597 and WO 1998/006749 disclose antibody derivatives that comprise human Major Histocompatibility Complex binding domains, with or without bound MHC binding peptides. PCT Publication No. WO 02/072141 concerns multi-specific binding molecules whose on-rates (rates at which they bind to target molecules) and off-rates (rates at which they release target molecules) differ so as to preferentially bind to one target compared to their binding to the other such target molecule. Tri-specific molecules, for example molecules having a monovalent first portion which is an Anti-CD3 or anti-CD28 antibody, and a second portion comprising a divalent immune function exerting moiety which immunospecifically binds to one or more target ligands on a target diseased cell or immune cell.

[0028] United States Patent No. 7,695,936 and Patent Publication 2007/ 0196363 concern bi-specific antibodies that are formed from the heavy chains of two

antibodies, one of which possess a protuberance engineered into its heavy chain and the second of which possess a complementary cavity engineered into its heavy chain. The presence of such complementary "knobs" and "holes" is taught to preferentially form bi-specific hetero-antibodies (having one heavy chain of each such antibody) relative to mono-specific homo-antibodies that contain two heavy chains of the same antibody. Various bi-specific hetero-antibodies are proposed, including those that are immunospecific for CD3 and a tumor cell antigen. Various tri-specific hetero-antibodies are also proposed, including some that are immunospecific for CD3, CD8 and CD37 (a transmembrane protein expressed predominantly on B cells that is involved the regulation of T cell proliferation (Robak, T. *et al.* (2014) "Anti-*CD37 Antibodies For Chronic Lymphocytic Leukemia*," Expert Opin. Biol. Ther. 14(5):651-661), however, no mechanism for their production and no disclosure of their structure is provided.

[0029] PCT Publication WO2012-162561 concerns bi-specific, tetravalent binding molecules that comprise two polypeptides, each of which comprises two diabody structures, separated by an intervening CH2-CH3 Domain. The document also concerns tetravalent binding molecules composed of four polypeptide chains in which two of the polypeptide chains contain variable light and variable heavy Domains for two antigens, and in which the other two polypeptide chains contain the complementary variable heavy and variable light Domains for the antigens and a terminal CH2-CH3 Domain. The bi-specific, tetravalent binding molecules form through the association of their respective CH2-CH3 Domains. In the four polypeptide chain construct, the "light" chains are not covalently bound to the heavy chains, thus leading to instability (see, Lu, D. *et al.* (2005) "*A Fully Human Recombinant IgG-like Bispecific Antibody To Both The Epidermal Growth Factor Receptor And The Insulin-Like Growth Factor Receptor For Enhanced Antitumor Activity*," J. Biol. Chem. 280(20):19665-19672). The document discloses a third construct in which the chains are altered to provide such covalent bonding, but at the cost of eliminating their bi-specificity (*i.e.*, the molecules are mono-specific). Molecules having specificity for CD2, CD3, CD4, CD8, CD161, a chemokine receptor, CD95, CCR5, *etc.* are disclosed. A bi-specific molecule capable of binding to both CD3 and CD8 is not disclosed.

[0030] However, the above advantages come at salient cost. The formation of such *non*-mono-specific diabodies requires the successful assembly of two or more distinct and different polypeptides (*i.e.*, such formation requires that the diabodies be formed through the heterodimerization of different polypeptide chain species). This fact is in contrast to mono-specific diabodies, which are formed through the homodimerization of identical polypeptide chains. Because at least two dissimilar polypeptides (*i.e.*, two polypeptide species) must be provided in order to form a non-mono-specific diabody, and because homodimerization of such polypeptides leads to inactive molecules (Takemura, S. *et al.* (2000) "*Construction Of A Diabody (Small Recombinant Bispecific Antibody) Using A Refolding System,*" Protein Eng. 13(8):583-588), the production of such polypeptides must be accomplished in such a way as to prevent covalent bonding between polypeptides of the same species (Takemura, S. *et al.* (2000) "*Construction Of A Diabody (Small Recombinant Bispecific Antibody) Using A Refolding System,*" Protein Eng. 13(8):583-588). The art has therefore taught the non-covalent association of such polypeptides (see, *e.g.*, Olafsen *et al.* (2004) *"Covalent Disulfide-Linked Anti-CEA Diabody Allows Site-Specific Conjugation And Radiolabeling For Tumor Targeting Applications,"* Prot. Engr. Des. Sel. 17:21-27; Asano *et al.* (2004) "*A Diabody For Cancer Immunotherapy And Its Functional Enhancement By Fusion Of Human Fc Domain*," Abstract 3P-683, J. Biochem. 76(8):992; Takemura, S. *et al.* (2000) "*Construction Of A Diabody (Small Recombinant Bispecific Antibody) Using A Refolding System,*" Protein Eng. 13(8):583-588; Lu, D. *et al.* (2005) "*A Fully Human Recombinant IgG-Like Bispecific Antibody To Both The Epidermal Growth Factor Receptor And The Insulin-Like Growth Factor Receptor For Enhanced Antitumor Activity*," J. Biol. Chem. 280(20):19665-19672).

[0031] However, the art has recognized that bi-specific diabodies composed of non-covalently associated polypeptides are unstable and readily dissociate into non-functional monomers (see, *e.g.*, Lu, D. *et al.* (2005) "*A Fully Human Recombinant IgG-Like Bispecific Antibody To Both The Epidermal Growth Factor Receptor And The Insulin-Like Growth Factor Receptor For Enhanced Antitumor Activity*," J. Biol. Chem. 280(20):19665-19672).

[0032] In the face of this challenge, the art has succeeded in developing stable, covalently bonded heterodimeric non-mono-specific diabodies, termed **DARTs™** (see, *e.g.*, United States Patent Publications No. 2013-0295121; 2010-0174053 and 2009-0060910; European Patent Publication No. EP 2714079; EP 2601216; EP 2376109; EP 2158221 and PCT Publications No. WO 2012/162068; WO 2012/018687; WO 2010/080538; and Moore, P.A. *et al.* (2011) "*Application Of Dual Affinity Retargeting Molecules To Achieve Optimal Redirected T-Cell Killing Of B-Cell Lymphoma*," Blood 117(17):4542-4551; Veri, M.C. *et al.* (2010) "*Therapeutic Control Of B Cell Activation Via Recruitment Of Fcgamma Receptor IIb (CD32B) Inhibitory Function With A Novel Bispecific Antibody Scaffold*," Arthritis Rheum. 62(7):1933-1943; Johnson, S. *et al.* (2010) "*Effector Cell Recruitment With Novel Fv-Based Dual-Affinity Re-Targeting Protein Leads To Potent Tumor Cytolysis And in vivo B-Cell Depletion*," J. Mol. Biol. 399(3):436-449). Such diabodies comprise two or more covalently complexed polypeptides and involve engineering one or more cysteine residues into each of the employed polypeptide species that permit disulfide bonds to form and thereby covalently bond two polypeptide chains. For example, the addition of a cysteine residue to the C-terminus of such constructs has been shown to allow disulfide bonding between the polypeptide chains, stabilizing the resulting heterodimer without interfering with the binding characteristics of the bivalent molecule.

[0033] There are many DART™ embodiments. Each of the two polypeptides of the simplest DART™ embodiment comprises three Domains (**Figure 1**). The first polypeptide comprises: (i) a first domain that comprises a binding region of a Light Chain Variable Domain of the a first immunoglobulin (VL1), (ii) a second domain that comprises a binding region of a Heavy Chain Variable Domain of a second immunoglobulin (VH2), and (iii) a third domain that contains a cysteine residue (or a Cysteine-Containing Domain) and a Heterodimerization-Promoting Domain that serves to promote heterodimerization with the second polypeptide chain. The cysteine residue (or a Cysteine-Containing Domain) of the third domain serves to promote the covalent bonding of the first polypeptide chain to the second polypeptide chain of the diabody. The second polypeptide contains: (i) a complementary first domain (a VL2-containing Domain), (ii) a complementary second domain (a VH1-

containing Domain) and (iii) a third domain that contains a cysteine residue (or a Cysteine-Containing Domain) and, optionally, a complementary Heterodimerization-Promoting Domain that complexes with the Heterodimerization-Promoting Domain of the first polypeptide chain in order to promote heterodimerization with the first polypeptide chain. The cysteine residue (or a Cysteine-Containing Domain) of the third domain of the second polypeptide chain serves to promote the covalent bonding of the second polypeptide chain to the first polypeptide chain of the diabody. Such molecules are stable, potent and have the ability to simultaneously bind two or more antigens. They are able to promote re-directed T cell mediated killing of cells expressing target antigens.

[0034] In one embodiment, the third domains of the first and second polypeptides each contain a cysteine residue, which serves to bind the polypeptides together via a disulfide bond. The third domain of one or both of the polypeptides may additionally possesses the sequence of a CH2-CH3 Domain, such that complexing of the diabody polypeptides forms an Fc Domain that is capable of binding to the Fc receptor of cells (such as B lymphocytes, dendritic cells, Natural Killer cells, macrophages, neutrophils, eosinophils, basophils and mast cells) (**Figures 2A-2B**).

[0035] Many variations of such molecules have been described (see, *e.g.*, United States Patent Publications No. 2013-0295121; 2010-0174053 and 2009-0060910; European Patent Publication No. EP 2714079; EP 2601216; EP 2376109; EP 2158221 and PCT Publications No. WO 2012/162068; WO 2012/018687; WO 2010/080538). These Fc-bearing DARTs may comprise three polypeptide chains (*e.g.*, **Figure 2B**). The first polypeptide chain of such a diabody contains three domains: (i) a VL1-containing Domain, (ii) a VH2-containing Domain and (iii) a domain containing a cysteine residue (or a Cysteine-Containing Domain) and a Heterodimerization-Promoting Domain, and (iv) a cysteine residue (or a Cysteine-Containing Domain and a CH2-CH3 Domain. The second polypeptide chain of such DART™ contains: (i) a VL2-containing Domain, (ii) a VH1-containing Domain and (iii) a Domain that contains a cysteine residue (or a Cysteine-Containing Domain) and a Heterodimerization-Promoting Domain that promotes heterodimerization with the first polypeptide chain. The cysteine residue (or a Cysteine-Containing Domain) of

the third domain of the second polypeptide chain serves to promote the covalent bonding of the second polypeptide chain to the first polypeptide chain of the diabody. The third polypeptide of such DART™ comprises a cysteine residue (or a Cysteine-Containing Domain) and a CH2-CH3 Domain. Thus, the first and second polypeptide chains of such DART™ associate together to form a VL1/VH1 binding site that is capable of binding to the epitope, as well as a VL2/VH2 binding site that is capable of binding to the second epitope. The first and second polypeptides are bonded to one another through a disulfide bond involving cysteine residues in their respective third domains. Notably, the first and third polypeptide chains complex with one another to form an Fc Domain that is stabilized via a disulfide bond. Such diabodies have enhanced potency. Such Fc-bearing **DARTs™** may have either of two orientations (**Table 1**):

Table 1

First Orientation	3rd Chain	NH_2-CH2-CH3-COOH
	1st Chain	NH_2-VL1-VH2-Cys-Heterodimer-Promoting Domain-CH2-CH3-COOH
	2nd Chain	NH_2-VL2-VH1-Cys-Heterodimer-Promoting Domain-COOH
Second Orientation	3rd Chain	NH_2-CH2-CH3-COOH
	1st Chain	NH_2-CH2-CH3-VL1-VH2-Cys-Heterodimer-Promoting Domain-COOH
	2nd Chain	NH_2-VL2-VH1-Cys-Heterodimer-Promoting Domain-COOH

[0036] Even more complex DART™ diabodies, termed **Ig-DART™** (**Figures 3A-3B**) and **Fc-DART™** diabodies (**Figure 3C**) have been described (WO 2012/018687). Fc-DARTs™ have four polypeptide chains. The first and third polypeptide chains of such a diabody contain three Domains: (i) a VL1-containing Domain, (ii) a VH2-containing Domain and (iii) a Domain containing a CH2-CH3 sequence. The second and fourth polypeptide of the Fc-DART™ contain: (i) a VL2-containing Domain, (ii) a VH1-containing Domain and (iii) a Domain that promotes heterodimerization and covalent bonding with the Fc-DART's™ first polypeptide chain. The third and fourth, and the first and second polypeptide chains may be the same or different so as to permit tetravalent binding that is either mono-specific, bi-specific or tetra-specific. Such more complex DART™ molecules also possess Cysteine-Containing Domains which function to form a covalently bonded complex. Fc-DART™ diabodies contain CH1 and CL Domains.

[0037] Alternative constructs are known in the art for applications where a tetravalent molecule is desirable but an Fc is not required including, but not limited to, tetravalent tandem antibodies, also referred to as "**TandAbs**" (see, *e.g.* United States Patent Publications Nos. 2005-0079170, 2007-0031436, 2010-0099853, 2011-020667 2013-0189263; European Patent Publication Nos. EP 1078004, EP 2371866, EP 2361936 and EP 1293514; PCT Publications Nos. WO 1999/057150, WO 2003/025018, and WO 2013/013700) which are formed by the homo-dimerization of two identical chains each possessing a VH1, VL2, VH2, and VL2 Domain.

[0038] However, despite all prior advances, a need remains for compositions that could provide improved therapeutic value to patients suffering from cancer or other diseases and conditions. The present invention is directed to this and other goals.

Summary of the Invention:

[0039] The present invention relates to Tri-Specific Binding Molecules, which are multi-chain polypeptide molecules that possess three Binding Domains and are thus capable of mediating coordinated binding to three epitopes. The Tri-Specific Binding Molecule is preferably characterized in possessing binding domains that permit it to immunospecifically bind to: (1) an epitope of a first Cancer Antigen, (2) an epitope of a second Cancer Antigen, and (3) an epitope of a molecule that is expressed on the surface of an immune system effector cell, and are thus capable of localizing an immune system effector cell to a cell that expresses a Cancer Antigen, so as to thereby facilitate the killing of such cancer cell.

[0040] In detail, the invention provides a Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, said Epitopes being Epitope I, Epitope II, and Epitope III, wherein two of three epitopes are epitopes of Cancer Antigen(s), and the third of said epitopes is an epitope of an Effector Cell Antigen.

[0041] The invention particularly concerns the embodiment of such Tri-Specific Binding Molecule wherein the molecule comprises four different polypeptide chains covalently complexed together and comprises:

(I) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that

is capable of immunospecifically binding to an Epitope II present on a second antigen, wherein the Antigen-Binding Domain I and the Antigen-Binding Domain II are both Diabody-Type Binding Domains;

(II) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(III) an Fc Domain that is formed by the complexing of two CH2-CH3 Domains to one another;

wherein one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and the third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen, and wherein the Antigen-Binding Domains I, II and III of the Binding Molecules mediate coordinated binding of an immune system effector cell expressing the Effector Cell Antigen and a cancer cell expressing the first and second Cancer Antigens.

[0042] The invention particularly concerns the embodiment of such Tri-Specific Binding Molecules wherein the Fc Domain is capable of binding to an Fc Receptor arrayed on the surface of a cell.

[0043] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the Effector Cell Antigen is arrayed on the surface of an effector cell and wherein the Cancer Antigens are arrayed on the surface of a cancer cell, and wherein the immunospecific binding is sufficient to co-localize the Effector Cell Antigen, and the Cancer Antigens, thereby facilitating the activation of the effector cell against the cancer cell.

[0044] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the Effector Cell Antigen is selected from the group consisting of: CD2, CD3, CD16, CD19, CD20, CD22, CD32B, CD64, the B cell Receptor (BCR), the T cell Receptor (TCR), and the NKG2D Receptor.

[0045] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the first and second Cancer Antigens are independently selected from the group consisting of: colon cancer antigen 19.9; a gastric cancer

mucin; antigen 4.2; glycoprotein A33 (gpA33); ADAM-9; gastric cancer antigen AH6; ALCAM; malignant human lymphocyte antigen APO-1; cancer antigen B1; B7-H3; beta-catenin; blood group ALe^b/Le^y; Burkitt's lymphoma antigen-38.13, colonic adenocarcinoma antigen C14; ovarian carcinoma antigen CA125; Carboxypeptidase M; CD5; CD19; CD20; CD22; CD23; CD25; CD27; CD30 ; CD33; CD36; CD45; CD46; CD52; CD79a/CD79b; CD103; CD317; CDK4; carcinoembryonic antigen (CEA); CEACAM5; CEACAM6; CO17-1A; CO-43 (blood group Le^b); CO-514 (blood group Le^a); CTA-1; CTLA4; Cytokeratin 8; antigen D1.1; antigen $D_1$56-22; DR5; E_1 series (blood group B); EGFR (Epidermal Growth Factor Receptor); Ephrin receptor A2 (EphA2); ErbB1; ErbB3; ErbB4; GAGE-1; GAGE-2; GD2/GD3/GM2; lung adenocarcinoma antigen F3; antigen FC10.2; G49, ganglioside GD2; ganglioside GD3; ganglioside GM2; ganglioside GM3; G_{D2}; G_{D3}; GICA 19-9; G_{M2}; gp100; human leukemia T cell antigen Gp37; melanoma antigen gp75; gpA33; HER2 antigen ($p185^{HER2}$); human milk fat globule antigen (HMFG); human papillomavirus-E6/human papillomavirus-E7; high molecular weight melanoma antigen (HMW-MAA); I antigen (differentiation antigen) I(Ma); Integrin Alpha-V-Beta-6 Integrinβ6 (ITGB6); Interleukin-13; Receptor α2 (IL13Rα2); JAM-3; KID3; KID31; KS 1/4 pan-carcinoma antigen; human lung carcinoma antigens L6 and L20; LEA; LUCA-2; M1:22:25:8; M18; M39; MAGE-1; MAGE-3; MART; MUC-1; MUM-1; Myl; N-acetylglucosaminyltransferase; neoglycoprotein; NS-10; OFA-1; OFA-2; Oncostatin M; p15; melanoma-associated antigen p97; polymorphic epithelial mucin (PEM); polymorphic epithelial mucin antigen (PEMA); PIPA; prostate-specific antigen (PSA); prostate-specific membrane antigen (PSMA); prostatic acid phosphate; R_{24}; ROR1; sphingolipids; SSEA-1; SSEA-3; SSEA-4; sTn; T cell receptor derived peptide; T_5A_7; TAG-72; TL5 (blood group A); TNF-α receptor; TNF-ß receptor; TNF-γ receptor; TRA-1-85 (blood group H); Transferrin Receptor; tumor-specific transplantation antigen (TSTA), oncofetal antigen-alpha-fetoprotein (AFP); VEGF; VEGFR, VEP8; VEP9; VIM-D5; and Y hapten, Le^y.

[0046] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the first and second Cancer Antigens are selected from the group consisting of: CD2, CD317, CEACAM5, CEACAM6, DR5, EphA2, gpA33, Her2, B7-H3; EGF, EGFR, VEGF and VEGFR.

[0047] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the Non-Diabody-Type Binding Domain III comprises the Fab-Type Binding Domain (VL_{III}/VH_{III}) that is capable of immunospecifically binding to an Epitope III, wherein the molecule comprises:

(A) a first polypeptide chain that comprises in the N-terminus to C-terminus direction:

(1) a light chain variable Domain of an immunoglobulin capable of binding to a first of the three epitopes (VL_I);

(2) a heavy chain variable Domain of an immunoglobulin capable of binding to a second of the three epitopes (VH_{II});

(3) a Heterodimer-Promoting Domain; and

(4) CH2 and CH3 Domains of an IgG;

(B) a second polypeptide chain that comprises, in the N-terminus to C-terminus direction:

(1) a light chain variable Domain of an immunoglobulin capable of binding to the second of the three epitopes (VL_{II});

(2) a heavy chain variable Domain of an immunoglobulin capable of binding to the first of the three epitopes (VH_I); and

(3) a complementary Heterodimer-Promoting Domain;

(C) a third polypeptide chain that comprises, in the N-terminus to C-terminus direction:

(1) a heavy chain variable Domain of an immunoglobulin capable of binding to a third of the three epitopes (VH_{III}); and

(2) a CH1 Domain, a Hinge Domain, and a CH2-CH3 Domain of an IgG;

and

(D) a fourth polypeptide chain that comprises, in the N-terminus to C-terminus direction:

(1) a light chain variable Domain of an immunoglobulin capable of binding to the third of the three epitopes (VL_{III}); and

(2) a light chain constant Domain (CL);

wherein:

(i) the VL_I and VH_I Domains associate to form a Domain capable of binding the first epitope;

(ii) the VL_{II} and VH_{II} Domains associate to form a Domain capable of binding the second epitope;

(iii) the VL_{III} and VH_{III} Domains associate to form a Domain capable of binding the third epitope;

(iv) the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form an Fc Domain;

(v) the first and second polypeptide chains are covalently bonded to one another;

(vi) the first and third polypeptide chains are covalently bonded to one another; and

(vii) the third and fourth polypeptide chains are covalently bonded to one another.

[0048] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein:

(A) the Heterodimer-Promoting Domain is an E-coil and the complementary Heterodimer-Promoting Domain is a K-coil; or

(B) the Heterodimer-Promoting Domain is a K-coil and the complementary Heterodimer-Promoting Domain is an E-coil.

[0049] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein:

(A) the CH2-CH3 Domains of the first and third polypeptide chains each have the sequence of **SEQ ID NO:1**, such that the Fc Domain formed from their association exhibits normal FcγR-mediated effector function; or

(B) the CH2-CH3 Domain of the first and third polypeptide chains comprise at least one amino acid substitution, relative to the sequence of **SEQ ID NO:1**, such that the Fc Domain formed from their association exhibits altered FcγR-mediated effector function.

[0050] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the at least one amino acid substitution comprises at least one amino acid substitution selected from the group consisting of: L235V, F243L, R292P, Y300L, V305I, and P396L, wherein the numbering is that of the EU index as in Kabat.

[0051] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the at least one amino acid substitution comprises:

(A) at least one substitution selected from the group consisting of F243L, R292P, Y300L, V305I, and P396L;

(B) at least two substitutions selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P; and

(3) R292P and V305I;

(C) at least three substitutions selected from the group consisting of:

(1) F243L, R292P and Y300L;

(2) F243L, R292P and V305I;

(3) F243L, R292P and P396L; and

(4) R292P, V305I and P396L;

(D) at least four substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L and P396L; and

(2) F243L, R292P, V305I and P396L;

or

(E) at least the five substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L, V305I and P396L; and

(2) L235V, F243L, R292P, Y300L and P396L.

[0052] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the CH2-CH3 Domain of the first and third polypeptide chains differ from one another and have an amino acid sequence selected from the group consisting of **SEQ ID NO:52** and **SEQ ID NO:53**.

[0053] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein:

(A) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the second Cancer Antigen and an epitope of the Effector Cell Antigen;

(B) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the second Cancer Antigen;

(C) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of second Cancer Antigen, an epitope of the first Cancer Antigen, and an epitope of the Effector Cell Antigen;

(D) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the second Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the first Cancer Antigen;

(E) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of the first Cancer Antigen, and an epitope of the second Cancer Antigen;

and

(F) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of second Cancer Antigen, and an epitope of the first Cancer Antigen.

[0054] The invention additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein:

(A) the epitope of an Effector Cell Antigen is a CD2 epitope recognized by antibody Lo-CD2a;

(B) the epitope of an Effector Cell Antigen is a CD3 epitope recognized by antibody OKT3, M291, YTH12.5, Anti-CD3 mAb 1 or Anti-CD3 mAb 2;

(C) the epitope of an Effector Cell Antigen is a CD16 epitope recognized by antibody 3G8 or A9;

(D) the epitope of an Effector Cell Antigen is a CD19 epitope recognized by antibody MD1342, MEDI-551, blinatumomab or HD37;

(E) the epitope of an Effector Cell Antigen is a CD20 epitope recognized by antibody rituximab, ibritumomab, ofatumumab, and tositumomab;

(F) the epitope of an Effector Cell Antigen is a CD22 epitope recognized by antibody epratuzumab;

(G) the epitope of an Effector Cell Antigen is a CD32B epitope recognized by antibody CD32B mAb 1;

(H) the epitope of an Effector Cell Antigen is a CD64 epitope recognized by antibody CD64 mAb 1;

(I) the epitope of an Effector Cell Antigen is a BCR/CD79 epitope recognized by antibody CD79 mAb 1;

(J) the epitope of an Effector Cell Antigen is a TCR epitope recognized by antibody BMA 031;

or

(K) the epitope of an Effector Cell Antigen is a NKG2D Receptor epitope recognized by antibody KYK-2.0.

[0055] The invention additionally concerns a pharmaceutical composition that comprises any of the above-described Tri-Specific Binding Molecules, and a pharmaceutically acceptable carrier, excipient or diluent.

[0056] The invention additionally concerns the embodiment of such pharmaceutical composition or of any such Tri-Specific Binding Molecules wherein the Tri-Specific Binding Molecule is used in the treatment of cancer.

[0057] The invention additionally concerns the embodiment of such pharmaceutical compositions or such Tri-Specific Binding Molecules wherein the cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma,

a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0058] The invention additionally concerns the embodiment of such pharmaceutical compositions or such Tri-Specific Binding Molecules wherein the cancer is acolorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer or a rectal cancer.

[0059] The invention additionally concerns the embodiment of such pharmaceutical compositions or such Tri-Specific Binding Molecules the cancer is acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphomas (NHL), including mantel cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.

Brief Description of the Drawings:

[0060] **Figures 1A-1B** show diagrammatic representation of the Domains of DART™ diabodies. **Figure 1A** shows a diagrammatic representation of the Domains of a basic DART™ diabody. **Figure 1B** provides a schematic of a covalently bonded diabody composed of two polypeptide chains, each having a Heterodimer-Promoting Domain VL and VH domains that recognize the same epitope are shown using the same shading.

[0061] **Figures 2A-2B** provide a schematic of covalently bonded diabodies composed of two polypeptide chains, each having a CH2 and CH3 Domain (**Figure 2A**) or in which only one has a CH2 and CH3 Domain (**Figure 2B**), such that the associated chains form an Fc Domain that comprises all or part of a naturally occurring Fc Domain. VL and VH domains that recognize the same epitope are shown using the same shading.

[0062] **Figures 3A-3C** provide schematics showing tetravalent diabodies composed of two pairs of polypeptide chains. The pairs are different, thus resulting in a bi-specific molecule that is bivalent with respect to each of two epitopes, in which one is an epitope of DR5 and the other is an epitope of a molecule present on the surface of an effector cell. One polypeptide of each pair possesses a CH2 and CH3 Domain, such that the associated chains form an Fc Domain that comprises all or part of a naturally occurring Fc Domain. VL and VH domains that recognize the same epitope are shown using the same shading. Only one pair of epitopes (shown with the same shading) is capable of binding to DR5. **Figure 3A** shows an Ig diabody. **Figure 3B** shows an Ig diabody, which contains E-coil and K-coil heterodimer-promoting domains. **Figure 3C**, shows an Fc-DART™ diabody that contains antibody CH1 and CL domains. The notation "**VL1**" and "**VH1**" denote respectively, the Variable Light Chain Domain and Variable Heavy Chain Domain that bind the "first" epitope. Similarly, the notation "**VL2**" and "**VH2**"denote respectively, the Variable Light Chain Domain and Variable Heavy Chain Domain that bind the "second" epitope.

[0063] **Figures 4A-4G** provide a diagrammatic representation of the Domains of preferred Tri-Specific Binding Molecules of the present invention. The Figures illustrate schematically the order and orientation of the Domains of embodiments of the preferred Tri-Specific Binding Molecules of the present invention. **Figures 4A**, **4B** and **4G** illustrate embodiments in which the Tri-Specific Binding Molecule is composed of four polypeptide chains. **Figures 4C**, **4D**, **4E** and **4F** illustrate embodiments in which the binding molecule is composed of three polypeptide chains. The molecule may possess Hinge and/or CL domains (**Figures 4A**, **4B**, **4C**, **4E**) or may contain an alternative linker peptide (**Figure 4D**, **4F**, **4G**).

[0064] **Figures 5A-5E** provide a diagrammatic representation of the Domains of an alternative embodiment of the Tri-Specific Binding Molecules of the present invention, in which the Effector Cell-Binding Domain is composed of an Effector Cell Receptor-Type Binding Domai rather than a Diabody-Type Binding Domain or a Fab-Type Binding Domain. **Figures 5A** and **5B** illustrate embodiments in which the Tri-Specific Binding Molecule is composed of four polypeptide chains. **Figure 5C** and **Figure 5E** illustrate an embodiment in which the binding molecule is composed of three polypeptide chains. **Figure 5D** illustrates an embodiment in which the binding molecule is composed of five polypeptide chains. The molecule may possess Hinge and/or CL domains or may contain alternative linker peptides.

[0065] **Figure 6** shows the ability of anti-human DR5 monoclonal antibodies DR5 mAb 1 and DR5 mAb 2 to bind to human DR5 and to the DR5 of cynomolgus monkey.

[0066] **Figure 7, Panels A-H**, show the kinetics of binding of DR5 mAb 1 (**Panels A** and **E**), DR5 mAb 2 (**Panels B and F**), DR5 mAb 3 (**Panels C and G**) and DR5 mAb 4 (**Panels D and H**) for human DR 5 (**Panels A-D**) and for cynomolgus monkey DR5 (**Panels E-H**).

[0067] **Figure 8** shows the unexpected superiority of DR5 mAb 1 and DR5 mAb 2. Superiority was assessed by comparing the ability of DR5 x CD3 diabodies having the VL and VH Domains of DR5 mAb 1, DR5 mAb 2, DR5 mAb 3, or DR5 mAb 4,

to mediate the cytotoxicity of A549 adenocarcinomic human alveolar basal epithelial tumor cells.

[0068] **Figures 9A-9C** demonstrate the synergistic enhancement in target cell binding that is attained when both of the two Cancer Antigen-Binding Domains of a Tri-Specific Binding Molecule of the present invention are able to bind to a target cell. **Figure 9A** shows the binding obtained when trispecific molecules: EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1; EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1; and gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 are incubated in the presence of EphA2-expressing CHO cells. **Figure 9B** shows the binding obtained when such trispecific molecules are incubated in the presence of DR5-expressing CHO cells. **Figure 9C** shows the binding obtained when such trispecific molecules are incubated in the presence of DU145 human prostate cells that express EphA2 and DR5, but not gpA33.

[0069] **Figures 10A-10C** demonstrate the synergistic enhancement in target cell cytotoxicity that is attained when both of the two Cancer Antigen-Binding Domains of a Tri-Specific Binding Molecule of the present invention are able to bind to a target cell. **Figure 10A** shows the percent cytotoxicity obtained by incubating trispecific molecules: EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1; EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1; and gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 are incubated in the presence of EphA2-expressing CHO cells and cytotoxic lymphocytes. **Figure 10B** shows the percent cytotoxicity obtained when such trispecific molecules are incubated in the presence of DR5-expressing CHO cells and cytotoxic lymphocytes. **Figure 10C** shows the cytotoxicity obtained when such trispecific molecules are incubated in the presence of DU145 human prostate cells and cytotoxic lymphocytes. DU145 cells express EphA2 and DR5, but not gpA33. Cytotoxicity was measured by the increase in luminescence caused by the release of luciferase upon cell lysis.

Detailed Description of the Invention:

[0070] The present invention relates to Tri-Specific Binding Molecules, which are multi-chain polypeptide molecules that possess three Binding Domains and are thus capable of mediating coordinated binding to three epitopes. The Tri-Specific Binding

Molecule is preferably characterized in possessing binding domains that permit it to immunospecifically bind to: (1) an epitope of a first Cancer Antigen, (2) an epitope of a second Cancer Antigen, and (3) an epitope of a molecule that is expressed on the surface of an immune system effector cell, and are thus capable of localizing an immune system effector cell to a cell that expresses a Cancer Antigen, so as to thereby facilitate the killing of such cancer cell.

[0071] The Tri-Specific Binding Molecules of the present invention may include Epitope-Binding Domains of humanized, chimeric or caninized derivatives of the above-discussed antibodies, for example, DR5 mAb 1 or DR5 mAb 2.

I. General Techniques and General Definitions

[0072] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, MOLECULAR CLONING: A LABORATORY MANUAL, Third Edition (Sambrook *et al.* Eds., 2001) Cold Spring Harbor Press, Cold Spring Harbor, NY; OLIGONUCLEOTIDE SYNTHESIS: METHODS AND APPLICATIONS (Methods in Molecular Biology), Herdewijn, P., Ed., Humana Press, Totowa, NJ; OLIGONUCLEOTIDE SYNTHESIS (Gait, M.J., Ed., 1984); METHODS IN MOLECULAR BIOLOGY, Humana Press, Totowa, NJ; CELL BIOLOGY: A LABORATORY NOTEBOOK (Cellis, J.E., Ed., 1998) Academic Press, New York, NY; ANIMAL CELL CULTURE (Freshney, R.I., Ed., 1987); INTRODUCTION TO CELL AND TISSUE CULTURE (Mather, J.P. and Roberts, P.E., Eds., 1998) Plenum Press, New York, NY; CELL AND TISSUE CULTURE: LABORATORY PROCEDURES (Doyle, A. *et al.*, Eds., 1993-8) John Wiley and Sons, Hoboken, NJ; METHODS IN ENZYMOLOGY (Academic Press, Inc.) New York, NY; WEIR'S HANDBOOK OF EXPERIMENTAL IMMUNOLOGY (Herzenberg, L.A. *et al.* Eds. 1997) Wiley-Blackwell Publishers, New York, NY; GENE TRANSFER VECTORS FOR MAMMALIAN CELLS (Miller, J.M. *et al.* Eds., 1987) Cold Spring Harbor Press, Cold Spring Harbor, NY; CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, F.M. *et al.*, Eds., 1987) Greene Pub. Associates, New York, NY; PCR: THE POLYMERASE CHAIN REACTION, (Mullis, K. *et al.*, Eds., 1994) Birkhäuser, Boston MA; CURRENT PROTOCOLS IN

IMMUNOLOGY (Coligan, J.E. *et al.*, eds., 1991) John Wiley and Sons, Hoboken, NJ; SHORT PROTOCOLS IN MOLECULAR BIOLOGY (John Wiley and Sons, 1999) Hoboken, NJ; IMMUNOBIOLOGY 7 (Janeway, C.A. *et al.* 2007) Garland Science, London, UK; Antibodies (P. Finch, 1997) Stride Publications, Devoran, UK; ANTIBODIES: A PRACTICAL APPROACH (D. Catty., ed., 1989) Oxford University Press, USA, New York NY); MONOCLONAL ANTIBODIES: A PRACTICAL APPROACH (Shepherd, P. *et al.* Eds., 2000) Oxford University Press, USA, New York NY; USING ANTIBODIES: A LABORATORY MANUAL (Harlow, E. *et al.* Eds., 1998) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; THE ANTIBODIES (Zanetti, M. *et al.* Eds. 1995) Harwood Academic Publishers, London, UK); and DEVITA, HELLMAN, AND ROSENBERG'S CANCER: PRINCIPLES & PRACTICE OF ONCOLOGY, EIGHTH EDITION, DeVita, V. *et al.* Eds. 2008, Lippincott Williams & Wilkins, Philadelphia, PA.

II. Preferred Tri-Specific Binding Molecules of the Present Invention

A. Binding Capabilities

[0073] The preferred Tri-Specific Binding Molecules of the present invention are able to coordinately and simultaneously bind to three different epitopes. The preferred Tri-Specific Binding Molecules of the present invention comprise:

(I) a "**Binding Domain I**" that is capable of immunospecifically binding to an "**Epitope I**" present on a first antigen, and a "**Binding Domain II**" that is capable of immunospecifically binding to an "**Epitope II**" present on a second antigen, wherein said **Binding Domain I** and said **Binding Domain II** are both "**Diabody-Type Binding Domains;**"

(II) a "**Binding Domain III**" that is capable of immunospecifically binding to an "**Epitope III**" present on a third antigen; and

(III) an **Fc Domain** that is formed by the complexing of two **CH2-CH3 Domains** to one another;

wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of a first "**Cancer Antigen**" Cancer Antigen;

(B) a second of Epitope I, Epitope II or Epitope III is an epitope of a second **Cancer Antigen**; and

(C) the third of Epitope I, Epitope II or Epitope III is an epitope of a molecule expressed on the surface of an immune system effector cell (**"Effector Cell Antigen"**);

and wherein the Binding Domains I, II and III of the binding molecules mediate coordinated binding of the immune system effector cell and a cell expressing both the first and second Cancer Antigens to thereby co-localize such cells.

[0074] Diabody Epitope-Binding Domains may also be directed to a surface determinant of a B cell, such as CD19, CD20, CD22, CD30, CD37, CD40, and CD74 (Moore, P.A. *et al.* (2011) "*Application Of Dual Affinity Retargeting Molecules To Achieve Optimal Redirected T-Cell Killing Of B-Cell Lymphoma*," Blood 117(17):4542-4551; Cheson, B.D. *et al.* (2008) "Monoclonal *Antibody Therapy For B-Cell Non-Hodgkin's Lymphoma*," N. Engl. J. Med. 359(6):613-626; Castillo, J. *et al.* (2008) "Newer monoclonal antibodies for hematological malignancies," Exp. Hematol. 36(7):755-768. In many studies, diabody binding to effector cell determinants, *e.g.*, Fcγ receptors (FcγR), was also found to activate the effector cell (Holliger *et al.* (1996) *"Specific* Killing *Of Lymphoma Cells By Cytotoxic T-Cells Mediated By A Bi-specific Diabody,"* Protein Eng. 9:299-305; Holliger *et al.* (1999) *"Carcinoembryonic Antigen (CEA)-Specific T-Cell Activation In Colon Carcinoma Induced By Anti-CD3 x Anti-CEA Bi-specific Diabodies And B7 x Anti-CEA Bi-specific Fusion Proteins,"* Cancer Res. 59:2909-2916; WO 2006/113665; WO 2008/157379; WO 2010/080538; WO 2012/018687; WO 2012/162068). Normally, effector cell activation is triggered by the binding of an antigen bound antibody to an effector cell via Fc-FcγR interaction; thus, in this regard, diabody molecules may exhibit Ig-like functionality independent of whether they comprise an Fc Domain (*e.g.,* as assayed in any effector function assay known in the art or exemplified herein (*e.g.*, ADCC assay)). By cross-linking tumor and effector cells, the diabody not only brings the effector cell within the proximity of the tumor cells but leads to effective tumor killing (see *e.g.*, Cao *et al.* (2003) *"Bi-specific Antibody Conjugates In Therapeutics,"* Adv. Drug. Deliv. Rev. 55:171-197).

[0075] Although such Tri-Specific Binding Molecules are particularly preferred, the invention additionally specifically contemplates Tri-Specific Binding Molecules

that comprise any combination of Binding Domains sufficient to produce a molecule having three binding specificities, of which two are binding specificities directed against Cancer Antigens, and one is a binding specificity directed against an Effector Cell Antigen. Thus, for example, the invention contemplates: a Tri-Specific Binding Molecule that comprises three Fab-Type Binding Domains, a Tri-Specific Binding Molecule that comprises one bivalent, bi-specific antibody domain (formed for example, by complexing two different light chains and two different heavy chains) and one Fab-Type Binding Domain, a Tri-Specific Binding Molecule that comprises two bivalent, bi-specific antibody domains (formed for example, by complexing four different light chains and two different heavy chains), but in which one of antibodiy domains has been rendered inactive, *etc.*

[0076] The terms "**polypeptide**," "**polypeptide chain**," and "**peptide**" are used interchangeably herein to refer to polymers of amino acids of any length, but especially lengths greater than 3, 5, 10, 15, 20 or 25 amino acid residues, in which two, and more preferably all, amino acid residues are joined via an amide (peptide) bond (-NH-C(O)-). The polymer may however be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, *etc.*), as well as other modifications known in the art. The polypeptides of this invention can occur as single-chains or as complexed chains.

[0077] A **"Diabody-Type Binding Domain**" is the Epitope-Binding Domain of a diabody, and especially, a DART® diabody. The terms "**diabody**" and "**DART® diabody**" has been discussed above, and refers to a molecule that comprises at least two polypeptide chains that preferably complex with one another through a covalent interaction to form at least two epitope binding sites, which may recognize the same or different epitopes. Two of the polypeptide chains of a diabody or DART® diabody

each comprise immunoglobulin Light Chain Variable Region and an immunoglobulin Heavy Chain Variable Region, but these regions do not interact to form an epitope binding site (*i.e.*, they are not mutually "**complementary**"). Rather, the immunoglobulin Heavy Chain Variable Region of one (*e.g.*, the first) of the diabody, or DART® diabody, chains interacts with the immunoglobulin Light Chain Variable Region of a different (*e.g.*, the second) diabody or, DART® diabody, polypeptide chain to form an epitope binding site. Similarly, the immunoglobulin Light Chain Variable Region of one (*e.g.*, the first) of the diabody, or DART® diabody, polypeptide chains interacts with the immunoglobulin Heavy Chain Variable Region of a different (*e.g.*, the second) diabody, or DART® diabody, polypeptide chain to form an epitope binding site. DART® diabody molecules are disclosed in United States Patent Publications No. 2013-0295121; 2010-0174053 and 2009-0060910; European Patent Publication No. EP 2714079; EP 2601216; EP 2376109; EP 2158221 and PCT Publications No. WO 2012/162068; WO 2012/018687; WO 2010/080538; WO 2006/113665, WO 2008/157379 and Moore, P.A. *et al.* (2011) "*Application Of Dual Affinity Retargeting Molecules To Achieve Optimal Redirected T-Cell Killing Of B-Cell Lymphoma*," Blood 117(17):4542-4551; Veri, M.C. *et al.* (2010) "*Therapeutic Control Of B Cell Activation Via Recruitment Of Fcgamma Receptor IIb (CD32B) Inhibitory Function With A Novel Bi-specific Antibody Scaffold*," Arthritis Rheum. 62(7):1933-1943; and Johnson, S. *et al.* (2010) "*Effector Cell Recruitment With Novel Fv-Based Dual-Affinity Re-Targeting Protein Leads To Potent Tumor Cytolysis And in vivo B-Cell Depletion*," J. Mol. Biol. 399(3):436-449.

[0078] **Binding Domain III** is preferably a "**Non-Diabody-Type" Binding Domain**, which is intended to denote that Binding Domain III does not have the structure of a Diabody-Type Binding Domain. Preferably, Binding Domain III is a Non-Diabody-Type Binding Domain that is a **Fab-Type Binding Domain** or an **Effector Cell Receptor-Type Binding Domain**. Thus, in one embodiment, exemplified in **Figures 4A-4G**, the Binding Domain III is a Fab-Type Binding Domain. **Figures 5A-5E** exemplify the embodiment in which Binding Domain III is an Effecotr Cell Receptor-Type Binding Domain. As used herein, the term an "**Fab-Type Binding Domain**" refers to an epitope Binding Domain that is formed by the interaction of the VL Domain of an immunoglobulin light chain and a complementing

VH Domain of an immunoglobulin heavy chain. Fab-Type Binding Domains differ from Diabody-Type Binding Domain in that the two polypeptide chains that form a Fab-Type Binding Domain comprise only a single epitope Binding Domain, whereas the two polypeptide chains that form a Diabody-Type Binding Domain comprise at least two epitope Binding Domains. Thus, as used herein Fab-Type Binding Domains are distinct from Diabody-Type Binding Domain. When a binding domain is a Fab-Type Binding Domain or a Diabody-Type Binding Domain, it will be composed of a VL Domain and a VH Domain, which may be located on the same or on different polypetide chains. The selection of such VL and VH domains is coordinated, such that the domains form an epitope binding domain. As used herein, the term "**Effector Cell Receptor-Type Binding Domain**" refers to an epitope binding domain that is formed by the interaction of a variable domain of a T Cell Receptor alpha chain and a variable domain of a T Cell Receptor beta chain. Such receptors recognize peptides displayed in the context of MHC and are thus capable of recognizing intracellular epitopes.

[0079] The Tri-Specific Binding Molecules of the present invention are thus distinguished from tetravalent binding molecules, such as those produced from the dimerization of a bivalent antibody, and preferably possess three and not four Binding Domains. As discussed below, the trispecific molecules of the present invention may possess additional binding domains (such as an Albumin-Binding Domain, an FcγR-Binding Domain, *etc.*). Such additional Binding Domains are not intended to be considered or counted as being one of the three Binding Domains of the Tri-Specific Binding Molecules of the present invention.

[0080] As used herein, the terms "**association**" or "**associating**," with regard to polypeptides (*e.g.*, one diabody polypeptide to another, an immunoglobulin light chain to an immunoglobulin heavy chain, one CH2-CH3 Domain to another CH2-CH3 Domain, *etc.*) is intended to denote a non-covalent combining of the polypeptides. The terms "**complexes**" or "**complexing**" are intended to denote a covalent combining of the polypeptides.

[0081] As used herein, Binding Domains of a Binding Molecule of the invention is said to mediate "**coordinated binding**" if at least two of its Binding Domains and preferably all of its Binding Domains, are capable of concurrently being bound to their respective recognized epitopes or binding ligand. Such binding may be simultaneous. However, one aspect of the present invention relates to modifying the "on" and/or "off" rates with which such Binding Domains bind to their recognized epitopes. As used here, the "**on rate**" of binding is a measure of the affinity with which such Binding Domains recognize and initiate binding to their recognized epitopes. In contrast, the "**off rate**" of binding is a measure of the degree of stability of the Binding Domain:epitope complex. The "on" and/or "off" rates of binding can be modified by altering the amino acid sequence of the CDRs of a Binding Domain. As discussed below, independent of any CDR modifications, the extent of coordinated binding of the molecules of the present invention may be modulated by changing the configuration of the their Binding Domains so that a particular Binding Domain (*i.e.*, a VLx/VHx Domain) is present as Binding Domain III or as an internal or external Diabody-Type Binding Domain relative to Binding Domain III (discussed in detail below).

[0082] The on- and off-rates of the Binding Domains of the Binding Molecules of the present invention can be readily measured by methods well-known in the art, for example by Biacore® analysis (Jason-Moller, L. *et al.* (2006) "*Overview Of Biacore Systems And Their Applications*," Curr. Protoc. Protein Sci. Chapter 19:Unit 19.13; Swanson, S.J. (2005) "*Characterization Of An Immune Response*," Dev. Biol. (Basel). 122:95-101; Buijs, J. *et al.* (2005) "*SPR-MS In Functional Proteomics*," Brief Funct. Genomic Proteomic. 4(1):39-47; Karlsson, R. *et al.* (2004) "*SPR For Molecular Interaction Analysis: A Review Of Emerging Application Areas*," J. Mol. Recognit. 17(3):151-161; Van Regenmortel, M.H. (2003) "*Improving The Quality Of BIACORE-Based Affinity Measurements*," Dev. Biol. (Basel) 112:141-151; Malmqvist, M. (1999) "*BIACORE: An Affinity Biosensor System For Characterization Of Biomolecular Interactions*," Biochem. Soc. Trans. 27(2):335-340; Malmqvist, M. *et al.* (1997) "*Biomolecular Interaction Analysis: Affinity Biosensor Technologies For Functional Analysis Of Proteins*," Curr. Opin. Chem. Biol. 1(3):378-383; Fivash, M. *et al.* (1998) "*Biacore For Macromolecular*

Interaction," Curr. Opin. Biotechnol. 9(1):97-101; Malmborg, A.C. *et al.* (1995) "*Biacore As A Tool In Antibody Engineering*," J. Immunol. Methods. 183(1):7-13). The on- and off-rates of the Binding Domains of the Binding Molecules of the present invention can be readily altered by random or directed mutagenesis of nucleic acid molecules that encode such Binding Domains, followed by the routine screening of recovered nucleic acid molecules for their ability to encode mutated proteins that exhibit such altered binding kinetics.

[0083] The Binding Domains of the the Tri-Sprecific Binding Molecules of the present invention bind to epitopes in an "**immunospecific**" manner. As used herein, an antibody, diabody or other epitope binding molecule is said to "**immunospecifically**" bind a region of another molecule (*i.e.*, an epitope) if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with that epitope relative to alternative epitopes. For example, an antibody that immunospecifically binds to a viral epitope is an antibody that binds this viral epitope with greater affinity, avidity, more readily, and /or with greater duration than it immunospecifically binds to other viral epitopes or non-viral epitopes. It is also understood by reading this definition that, for example, an antibody (or moiety or epitope) that immunospecifically binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means "specific" binding. Two molecules are said to be capable of binding to one another in a "**physiospecific**" manner, if such binding exhibits the specificity with which receptors bind to their respective ligands.

[0084] The functionality of antibodies can be enhanced by generating multispecific antibody-based molecules that can simultaneously bind two separate and distinct antigens (or different epitopes of the same antigen) and/or by generating antibody-based molecule having higher valency (*i.e.*, more than two binding sites) for the same epitope and/or antigen.

[0085] Thus, in their simplest embodiment, the preferred binding molecules of the present invention are at least trispecific. Significantly, such molecules have at least

three Sites that are capable of binding antigen: an "**external**" Diabody-Type Binding Domain that is located furthest from Binding Domain III, an "internal" Diabody-Type Binding Domain that is located nearest to Binding Domain III, and Binding Domain III itself. The positions of such Domains are respectively designated as "**Site A**," **Site B**" and "**Site C**" (**Figures 4A-4G**; **Figures 5A-5E**).

[0086] The Tri-Specific Binding Molecules of the present invention are able to coordinately bind to three different epitopes by comprising three binding domains. Two of the binding domains of such molecules are capable of binding to epitopes of "**Cancer Antigens**," such that the molecule is capable of binding to two different Cancer Antigens. The third binding domain of such molecules is capable of binding to an epitope of a molecule expressed on the surface of an immune system effector cell (*i.e.*, an **"Effector Cell Antigen"**). Thus, the Tri-Specific Binding Molecules of the present invention are able to mediate coordinated and simultaneous binding to a cancer cell expressing two Cancer Antigens and to an immune system effector cell expressing the **Effector Cell Antigen**. The epitopes recognized by the Tri-Specific Binding Molecules of the present invention may be continuous or discontinuous (*e.g.*, conformational).

[0087] The first and second Cancer Antigens that are bound by the Cancer Antigen-Binding Domains of the trispecific binding moleules of the present invention may be selected from any molecule that is characteristically present on the surface of a cancer cell. One aspect of the present invention relates to the ability to target "**Low Expression Cancer Antigens**" (*i.e.*, a Cancer Antigen that may be expressed on a cancer cell at a level too low to permit a monospecific binding molecule to provide an effective cancer therapy). In contrast to such monospecific binding molecules, the Tri-Specific Binding Molecules of the present invention, by targeting two Cancer Antigens instead of one, exhibit synergistic and cooperative enhanced binding avidity that may compensate for low affinity of binding and thus may be advantageously used to target cancers characterized even by a Low Expression Cancer Antigen. A second aspect of the present invention relates to the ability to target "**Low Specificity Cancer Antigens**" (*i.e.*, a Cancer Antigen that may be expressed on a normal cell in addition to being expressed on a cancer cell). The Tri-Specific Binding Molecules of the

present invention, by providing synergistic and cooperative enhanced binding avidity to two Cancer Antigens, exhibits higher avidity of binding even for Low Specificity Cancer Antigens and thus provides a means for treating cancers that are characterized by such Cancer Antigens. Thus, the Tri-Specific Binding Molecules of the present invention may be used to impart an anti-cancer therapy even in circumstances where one or both of the target Cancer Antigens is ineffective on its own to provide such therapy.

[0088] For example, CD32B (the FcγRIIB receptor) is widely expressed on hematopoietic cells, including monocytes, macrophages, B cells, NK cells, neutrophils, mast cells, and platelets. Upon binding to IgG Fc Domain, CD32B inhibits the host immune system to thereby depress an ongoing immune response. Although such inhibition is desirable in helping the host recover from inflammatory reactions, it serves to exacerbate the immune deficiencies of subjects suffering from cancer or infectious disease. Antibodies that bind to CD32B, so as to block the binding of IgG Fc molecules, serve to prevent such inhibition and thus have utility as adjunct molecules in the treatment of cancer and infectious disease (Veri, M.C. *et al.* (2007) "*Monoclonal Antibodies Capable Of Discriminating The Human Inhibitory Fcgamma-Receptor IIB (CD32B) From The Activating Fcgamma-Receptor IIA (CD32A): Biochemical, Biological And Functional Characterization*," Immunology 121(3):392-404). Unfortunately, CD32B is also expressed on liver sinusoidal endothelial cells ("**LSE cells**") (Shahani, T. *et al.* (2014) "*Human Liver Sinusoidal Endothelial Cells But Not Hepatocytes Contain Factor VIII*," J. Thromb. Haemost. 12(1):36-42; Géraud, C. *et al.* (2013) "*Endothelial Transdifferentiation In Hepatocellular Carcinoma: Loss Of Stabilin-2 Expression In Peri-Tumourous Liver Correlates With Increased Survival*," Liver Int. 33(9):1428-1440; Takabe, Y. *et al.* (2012) "*Immunomagnetic Exclusion Of E-Cadherin-Positive Hepatoblasts In Fetal Mouse Liver Cell Cultures Impairs Morphogenesis And Gene Expression Of Sinusoidal Endothelial Cells*," J. Anat. 221(3):229-239). Thus, antibodies that bind CD32B attack LSE cells. However, by forming a Tri-Specific Binding Molecule of the present invention that binds to CD32B and to antigens (*i.e.*, the first and second Cancer Antigens) that are not expressed on LSE cells, or are expressed at low levels by such cells (*i.e.*, Low Expression Cancer Antigen(s)), or are expressed with low

specificity on cancer cells and such LSE cells (*i.e.*, Low Specificity Cancer Antigen(s)), the present invention provides compositions and methods that would be used to depress CD32B-mediated immune system inhibition.

B. Exemplary Cancer Antigen-Binding Domains

[0089] Examples of suitable Cancer Antigens include: **19.9** as found in colon cancer, gastric cancer mucins; **4.2**; **A33** (a colorectal carcinoma antigen; Almqvist, Y. 2006, *Nucl Med Biol.* Nov;33(8):991-998); **ADAM-9** (United States Patent Publication No. 2006/0172350; PCT Publication No. WO 06/084075); **AH6** as found in gastric cancer; **ALCAM** (PCT Publication No. WO 03/093443); **APO-1 (malignant human lymphocyte antigen)** (Trauth *et al.* (1989) *"Monoclonal Antibody-Mediated Tumor Regression By Induction Of Apoptosis,"* Science 245:301-304); **B1** (Egloff, A.M. *et al.* 2006, *Cancer Res.* 66(1):6-9); BAGE (Bodey, B. 2002 *Expert Opin Biol Ther.* 2(6):577-84); **B7-H3**; **beta-catenin** (Prange W. *et al.* 2003 *J Pathol.* 201(2):250-9); **blood group ALe^b/Le^y** as found in colonic adenocarcinoma; **Burkitt's lymphoma antigen-38.13**, **C14** as found in colonic adenocarcinoma; **CA125 (ovarian carcinoma antigen)** (Bast, R.C. Jr. *et al.* 2005 *Int J Gynecol Cancer* 15 Suppl 3:274-81 ; Yu *et al.* (1991) *"Coexpression Of Different Antigenic Markers On Moieties That Bear CA 125 Determinants,"* Cancer Res. 51(2):468-475); **Carboxypeptidase M** (United States Patent Publication No. 2006/0166291); **CD5** (Calin, G.A. *et al.* 2006 *Semin Oncol.* 33(2):167-73; **CD19** (Ghetie *et al.* (1994) *"Anti-CD19 Inhibits The Growth Of Human B-Cell Tumor Lines In Vitro And Of Daudi Cells In SCID Mice By Inducing Cell Cycle Arrest,"* Blood 83:1329-1336; Troussard, X. *et al.* 1998 *Hematol Cell Ther.* 40(4):139-48); **CD20** (Thomas, D.A. *et al.* 2006 Hematol Oncol Clin North Am. 20(5):1125-36); **CD22** (Kreitman, R.J. 2006 AAPS J. 18;8(3):E532-51); **CD23** (Rosati, S. *et al.* 2005 *Curr Top Microbiol Immunol.* 5;294:91-107); **CD25** (Troussard, X. *et al.* 1998 *Hematol Cell Ther.* 40(4):139-48); **CD27** (Bataille, R. 2006 *Haematologica* 91(9):1234-40); CD28 (Bataille, R. 2006 *Haematologica* 91(9):1234-40); **CD33** (Sgouros *et al.* (1993) *"Modeling And Dosimetry Of Monoclonal Antibody M195 (Anti-CD33) In Acute Myelogenous Leukemia,"* J. Nucl. Med. 34:422-430); **CD36** (Ge, Y. 2005 *Lab Hematol.* 11(1):31-7); CD40/CD154 (Messmer, D. *et al.* 2005 *Ann N Y Acad Sci.*

1062:51-60); **CD45** (Jurcic, J.G. 2005 *Curr Oncol Rep.* 7(5):339-46); CD56 (Bataille, R. 2006 *Haematologica* 91(9):1234-40); **CD46** (United States Patent No. 7,148,038; PCT Publication No. WO 03/032814); **CD79a/CD79b** (Troussard, X. *et al.* 1998 *Hematol Cell Ther.* 40(4):139-48; Chu, P.G. *et al.* 2001 Appl Immunohistochem Mol Morphol. 9(2):97-106); **CD103** (Troussard, X. *et al.* 1998 *Hematol Cell Ther.* 40(4):139-48); **CDK4** (Lee, Y.M. *et al.* 2006 *Cell Cycle* 5(18):2110-4); **CEA (carcinoembryonic antigen)** (Foon *et al.* (1995) *"Immune Response To The Carcinoembryonic Antigen In Patients Treated With An Anti-Idiotype Antibody Vaccine,"* J. Clin. Invest. 96(1):334-42); **CEA** (carcinoembryonic antigen; Mathelin, C. 2006 *Gynecol Obstet Fertil.* 34(7-8):638-46; Tellez-Avila, F.I. *et al.* 2005 *Rev Invest Clin.* 57(6):814-9); **CO17-1A** (Ragnhammar *et al.* (1993) *"Effect Of Monoclonal Antibody 17-1A And GM-CSF In Patients With Advanced Colorectal Carcinoma - Long-Lasting, Complete Remissions Can Be Induced,"* Int. J. Cancer 53:751-758); **CO-43** (blood group Le^b); **CO-514** (blood group Le^a) as found in adenocarcinoma; **CTA-1**; **CTLA4** (Peggs, K.S. *et al.* 2006 *Curr Opin Immunol.* 18(2):206-13); **Cytokeratin 8** (PCT Publication No. WO 03/024191); **D1.1**; **$D_1$56-22**; **DR5** (Abdulghani, J. *et al.* (2010) "*TRAIL Receptor Signaling And Therapeutics*," Expert Opin. Ther. Targets 14(10):1091-1108; Andera, L. (2009) "*Signaling Activated By The Death Receptors Of The TNFR Family*," Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub. 153(3):173-180; Carlo-Stella, C. *et al.* (2007) "*Targeting TRAIL Agonistic Receptors for Cancer Therapy*," Clin, Cancer 13(8):2313-2317; Chaudhari, B.R. *et al.* (2006) "*Following the TRAIL to Apoptosis*," Immunologic Res. 35(3):249-262); **E_1** series (blood group B) as found in pancreatic cancer; **EGFR (Epidermal Growth Factor Receptor)** (Adenis, A. *et al.* 2003 *Bull Cancer.* 90 Spec No:S228-32); **Ephrin receptors** (and in particular **EphA2** (United States Patent No. 7,569,672; PCT Publication No. WO 06/084226); **Erb** (ErbB1; ErbB3; ErbB4; Zhou, H. *et al.* 2002 *Oncogene* 21(57):8732-8740; Rimon, E. *et al.* 2004 Int J Oncol. 24(5):1325-1338); **GAGE** (GAGE-1; GAGE-2; Akcakanat, A. *et al.* 2006 *Int J Cancer.* 118(1):123-128); **GD2/GD3/GM2** (Livingston, P.O. *et al.* 2005 Cancer Immunol Immunother. 54(10):1018-1025); **F3** as found in lung adenocarcinoma; **FC10.2** as found in embryonal carcinoma cells and gastric adenocarcinoma; **G49**, **ganglioside GD2** (Saleh *et al.* (1993) *"Generation Of A*

Human Anti-Idiotypic Antibody That Mimics The GD2 Antigen," J.Immunol., 151, 3390-3398); **ganglioside GD3** (Shitara *et al.* (1993) *"A Mouse/Human Chimeric Anti-(Ganglioside GD3) Antibody With Enhanced Antitumor Activities,"* Cancer Immunol. Immunother. 36:373-380); **ganglioside GM2** (Livingston *et al.* (1994) *"Improved Survival In Stage III Melanoma Patients With GM2 Antibodies: A Randomized Trial Of Adjuvant Vaccination With GM2 Ganglioside,"* J. Clin. Oncol. 12:1036-1044); **ganglioside GM3** (Hoon *et al.* (1993) *"Molecular Cloning Of A Human Monoclonal Antibody Reactive To Ganglioside GM3 Antigen On Human Cancers,"* Cancer Res. 53:5244-5250); **G_{D2}**; **G_{D3}**; **GICA 19-9** (Herlyn *et al.* (1982) *"Monoclonal Antibody Detection Of A Circulating Tumor-Associated Antigen. I. Presence Of Antigen In Sera Of Patients With Colorectal, Gastric, And Pancreatic Carcinoma,"* J. Clin. Immunol. 2:135-140); **G_{M2}**; **gp100** (Lotem, M. *et al.* 2006 *J Immunother.* 29(6):616-27); **Gp37 (human leukemia T cell antigen)** (Bhattacharya-Chatterjee *et al.* (1988) *"Idiotype Vaccines Against Human T Cell Leukemia. II. Generation And Characterization Of A Monoclonal Idiotype Cascade (Ab1, Ab2, and Ab3),"* J. Immunol. 141:1398-1403); **gp75 (melanoma antigen)** (Vijayasardahl *et al.* (1990) *"The Melanoma Antigen Gp75 Is The Human Homologue Of The Mouse B (Brown) Locus Gene Product,"* J. Exp. Med. 171(4):1375-1380); **gpA33**; **HER2 antigen ($p185^{HER2}$)** (Kumar, Pal S *et al.* 2006 Semin Oncol. 33(4):386-91); **human B-lymphoma antigen-CD20** (Reff *et al.* (1994) *"Depletion Of B Cells In Vivo By A Chimeric Mouse Human Monoclonal Antibody To CD20,"* Blood 83:435-445); **human milk fat globule antigen**; **human papillomavirus-E6/human papillomavirus-E7** (DiMaio, D. *et al.* 2006 *Adv Virus Res.* 66:125-59; **HMW-MAA (high molecular weight melanoma antigen)** (Natali *et al.* (1987) *"Immunohistochemical Detection Of Antigen In Human Primary And Metastatic Melanomas By The Monoclonal Antibody 140.240 And Its Possible Prognostic Significance,"* Cancer 59:55-63; Mittelman *et al.* (1990) *"Active Specific Immunotherapy In Patients With Melanoma. A Clinical Trial With Mouse Antiidiotypic Monoclonal Antibodies Elicited With Syngeneic Anti-High-Molecular-Weight-Melanoma-Associated Antigen Monoclonal Antibodies,"* J. Clin. Invest. 86:2136-2144); **I antigen (differentiation antigen)** (Feizi (1985) *"Demonstration By Monoclonal Antibodies That Carbohydrate Structures Of Glycoproteins And Glycolipids Are Onco-Developmental Antigens,"* Nature 314:53-57) such as **I(Ma)** as

found in gastric adenocarcinomas; **Integrin Alpha-V-Beta-6** (PCT Publication No. WO 03/087340); **JAM-3** (PCT Publication No. WO 06/084078); **KID3** (PCT Publication No. WO 05/028498); **KID31** (PCT Publication No. WO 06/076584); **KS 1/4 pan-carcinoma antigen** (Perez *et al.* (1989) *"Isolation And Characterization Of A cDNA Encoding The Ks1/4 Epithelial Carcinoma Marker,"* J. Immunol. 142:3662-3667; Möller *et al.* (1991) *"Bi-specific-Monoclonal-Antibody-Directed Lysis Of Ovarian Carcinoma Cells By Activated Human T Lymphocytes,"* Cancer Immunol. Immunother. 33(4):210-216; Ragupathi, G. 2005 *Cancer Treat Res.* 123:157-80); **L6** and **L20 (human lung carcinoma antigens)** (Hellström *et al.* (1986) *"Monoclonal Mouse Antibodies Raised Against Human Lung Carcinoma,"* Cancer Res. 46:3917-3923); **LEA**; **LUCA-2** (United States Patent Publication No. 2006/0172349; PCT Publication No. WO 06/083852); **M1:22:25:8**; **M18**; **M39**; **MAGE** (MAGE-1; MAGE-3; (Bodey, B. 2002 *Expert Opin Biol Ther.* 2(6):577-84); **MART** (Kounalakis, N. *et al.* 2005 *Curr Oncol Rep.* 7(5):377-82; **MUC-1** (Mathelin, C. 2006 *Gynecol Obstet Fertil.* 34(7-8):638-46); **MUM-1** (Castelli, C. *et al.* 2000 *J Cell Physiol.* 182(3):323-31); **Myl**; **N-acetylglucosaminyltransferase** (Dennis, J.W. 1999 *Biochim Biophys Acta.* 6;1473(1):21-34); **neoglycoprotein**; **NS-10** as found in adenocarcinomas; **OFA-1**; **OFA-2**; **Oncostatin M** (Oncostatin Receptor Beta) (United States Patent No. 7,572,896; PCT Publication No. WO 06/084092); **p15** (Gil, J. *et al.* 2006 *Nat Rev Mol Cell Biol.* 7(9):667-77); **p97 (melanoma-associated antigen)** (Estin *et al.* (1989) *"Transfected Mouse Melanoma Lines That Express Various Levels Of Human Melanoma-Associated Antigen p97,"* J. Natl. Cancer Instit. 81(6):445-454); **PEM (polymorphic epithelial mucin**) (Hilkens *et al.* (1992) *"Cell Membrane-Associated Mucins And Their Adhesion-Modulating Property,"* Trends in Biochem. Sci. 17:359-363); **PEMA (polymorphic epithelial mucin antigen)**; **PIPA** (United States Patent No. 7,405,061; PCT Publication No. WO 04/043239); **PSA (prostate-specific antigen)** (Henttu *et al.* (1989) *"cDNA Coding For The Entire Human Prostate Specific Antigen Shows High Homologies To The Human Tissue Kallikrein Genes,"* Biochem. Biophys. Res. Comm. 10(2):903-910; Israeli *et al.* (1993) *"Molecular Cloning Of A Complementary DNA Encoding A Prostate-Specific Membrane Antigen,"* Cancer Res. 53:227-230; Cracco, C.M. *et al.* 2005 *Minerva Urol Nefrol.* 57(4):301-11); **PSMA (prostate-specific membrane antigen)**

(Ragupathi, G. 2005 *Cancer Treat Res.* 123:157-180); **prostatic acid phosphate** (Tailor *et al.* (1990) *"Nucleotide Sequence Of Human Prostatic Acid Phosphatase Determined From A Full-Length cDNA Clone,"* Nucl. Acids Res. 18(16):4928); **R_{24}** as found in melanoma; **ROR1** (United States Patent No. 5,843,749); **sphingolipids**; **SSEA-1**; **SSEA-3**; **SSEA-4**; **sTn** (Holmberg, L.A. 2001 *Expert Opin Biol Ther.* 1(5):881-91); **T cell receptor derived peptide** from a cutaneous T cell lymphoma (*see* Edelson (1998) *"Cutaneous T-Cell Lymphoma: A Model For Selective Immunotherapy,"* Cancer J Sci Am. 4:62-71); **T_5A_7** found in myeloid cells; **TAG-72** (Yokota *et al.* (1992) *"Rapid Tumor Penetration Of A Single-Chain Fv And Comparison With Other Immunoglobulin Forms,"* Cancer Res. 52:3402-3408); **TL5** (blood group A); **TNF-receptor** (TNF-α receptor, TNF-ß receptor; **TNF-γ receptor** (van Horssen, R. *et al.* 2006 *Oncologist.* 11(4):397-408; Gardnerova, M. *et al.* 2000 *Curr Drug Targets.* 1(4):327-64); **TRA-1-85** (blood group H); **Transferrin Receptor** (United States Patent No. 7,572,895; PCT Publication No. WO 05/121179); **TSTA (tumor-specific transplantation antigen)** such as virally-induced tumor antigens including T-antigen DNA tumor viruses and envelope antigens of RNA tumor viruses, oncofetal antigen-alpha-fetoprotein such as CEA of colon, bladder tumor oncofetal antigen (Hellström *et al.* (1985) *"Monoclonal Antibodies To Cell Surface Antigens Shared By Chemically Induced Mouse Bladder Carcinomas,"* Cancer. Res. 45:2210-2188); **VEGF** receptor (O'Dwyer. P.J. 2006 *Oncologist.* 11(9):992-998); **VEP8**; **VEP9**; **VIM-D5**; and **Y hapten**, **Le^y** as found in embryonal carcinoma cells.

1. Campath-1 (CD52) Binding Domain (Alemtuzumab)

[0090] The amino acid sequence of the VL Domain of the humanized anti-CD52 antibody "**Alemtuzumab**" (**SEQ ID NO:205**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITC**KASQNID KYLN**WYQQKP GKAPKLLIY**N**
TNNLQTGVPS RFSGSGSGTD FTFTISSLQP EDIATYYC**LQ HISRPRT**FGQ
GTKVEIKR

[0091] The amino acid sequence of the VH Domain of the humanized anti-CD52 antibody "**Alemtuzumab**" (**SEQ ID NO:206**) is shown below (CDR residues are shown underlined):

QVQLQESGPG LVRPSQTLSL TCTVS**GFTFT DFYMN**WVRQP PGRGLEWIG**F**
IRDKAKGYTT EYNPSVKGRV TMLVDTSKNQ FSLRLSSVTA ADTAVYYCAR
EGHTAAPFDY WGQGSLVTVS S

2. CD317 (BMST2)-Binding Domains

[0092] CD317 (also known as Bone Marrow Stromal Cell Antigen 2; BMST) is overexpressed on various cancer cells isolated from breast, lung, kidney, endometrium, and skin (Kawai, S. *et al.* (2008) "Interferon-α enhances CD317 expression and the antitumor activity of anti-CD317 monoclonal antibody in renal cell carcinoma xenograft models," Cancer Science 99(12):2461-2466; Cai, D. *et al.* (2009) "*Up-Regulation Of Bone Marrow Stromal Protein 2 (BST2) In Breast Cancer With Bone Metastasis*," BMC Cancer 9:102, pp. 1-10; Wang, W. *et al.* (2009) *HM1.24 (CD317) Is A Novel Target Against Lung Cancer For Immunotherapy Using Anti-HM1.24 Antibody*," Cancer Immunology, Immunotherapy 58(6):967-976; Wang, W. *et al.* (2009) "*Chimeric And Humanized Anti-HM1.24 Antibodies Mediate Antibody-Dependent Cellular Cytotoxicity Against Lung Cancer Cells. Lung Cancer*," 63(1):23-31; Sayeed, A. *et al.* (2013) "*Aberrant Regulation Of The BST2 (Tetherin) Promoter Enhances Cell Proliferation And Apoptosis Evasion In High Grade Breast Cancer Cells*," PLoS ONE 8(6)e67191, pp. 1-10; Yi, E.H. *et al.* (2013) "*BST-2 Is A Potential Activator Of Invasion And Migration In Tamoxifen-Resistant Breast Cancer Cells*," Biochem. Biophys. Res. Commun. 435(4):685-690; Staudinger, M. (2014) "*The Novel Immunotoxin HM1.24-ETA' Induces Apoptosis In Multiple Myeloma Cells*," Blood Cancer J. 13;4:e219, pp. 1-11). Antibodies that immunospecifically bind to CD317 are commercially available (Novus Biologicals LLC; BioLegend, Inc.; see also U.S. Patent No. 8,834,876, which references the deposit of the heavy and light chains of antibody HM1.24 as FERM BP-5644 and FERM BP-5646; see also U.S. Patent No. 8,394,374). The amino acid sequence of the VL Domain of the anti-CD317 antibody "HM1.24" (**SEQ ID NO:302**) is shown below (CDR residues are shown underlined):

DIVMTQSHKF MSTSVGDRVS ITCK**KASQDV NTAVA**WYQQK PGQSPKLLIY **SASNRYT**GVP DRITGSGSGT DFTFTISSVQ AEDLALTTC**Q QHYSTPFT**FG SGTKLEIK

[0093] The amino acid sequence of the VH Domain of the anti-CD317 antibody "HM1.24" (**SEQ ID NO:303**) is shown below (CDR residues are shown underlined):

QVQLQQSGAE LARPGASVKL SCKASGYTFT **PYWMQ**WVKQR PGQGLEWIG**S IFPGDGDTRY SQKFKG**KATL TADKSSSTAY MQLSILAFED SAVYYCAR**GL RRGGYYFDY**W GQGTTLTVSS

3. CEACAM5- and CEACAM6-Binding Domains

[0094] Carcinoembryonic Antigen-Related Cell Adhesion Molecules 5 (CEACAM5) and 6 (CEACAM6) have been found to be associated with various types of cancers including medullary thyroid cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, lung cancer, head and neck cancers, urinary bladder cancer, prostate cancer, uterine cancer, endometrial cancer, breast cancer, hematopoietic cancer, leukemia and ovarian cancer (PCT Pubmication No. WO 2011/034660), and particularly colorectal, gastrointestinal, pancreatic, non-small cell lung cancer (NSCL), breast, thyroid, stomach, ovarian and uterine carcinomas (Zheng, C. *et al.* (2011) "*A Novel Anti-CEACAM5 Monoclonal Antibody, CC4, Suppresses Colorectal Tumor Growth and Enhances NK Cells-Mediated Tumor Immunity*," PLoS One 6(6):e21146, pp. 1-11).

[0095] CEACAM5 has been found to be overexpressed in 90% of gastrointestinal, colorectal and pancreatic cancers, 70% of non-small cell lung cancer cells and 50% of breast cancers (Thompson, J.A. *et al.* (1991) "*Carcinoembryonic Antigen Gene Family: Molecular Biology And Clinical Perspectives*," J. Clin. Lab. Anal. 5:344-366).

[0096] Overexpressed carcinoembryonic antigen-related cellular adhesion molecule 6 (CEACAM6) plays important roles in the invasion and metastasis of a variety of human cancers, including medullary thyroid cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, gastric cancer, lung cancer, head and neck cancers, urinary bladder cancer, prostate cancer, uterine cancer, endometrial cancer, breast cancer, hematopoietic cancer, leukemia and ovarian cancer (PCT Pubmication No. WO 2011/034660; Deng, X. *et al.* (2014) "*Expression Profiling Of*

CEACAM6 Associated With The Tumorigenesis And Progression In Gastric Adenocarcinoma," Genet. Mol. Res. 13(3):7686-7697; Cameron, S. *et al.* (2012) "*Focal Overexpression Of CEACAM6 Contributes To Enhanced Tumourigenesis In Head And Neck Cancer Via Suppression Of Apoptosis*," Mol. Cancer 11:74, pp. 1-11; Chapin, C. *et al.* (2012) "*Distribution And Surfactant Association Of Carcinoembryonic Cell Adhesion Molecule 6 In Human Lung*," Amer. J. Physiol. Lung Cell. Mol. Physiol. 302(2):L216-L25; Riley, C.J. *et al.* (2009) "*Design And Activity Of A Murine And Humanized Anti-CEACAM6 Single-Chain Variable Fragment In The Treatment Of Pancreatic Cancer*," Cancer Res. 69(5):1933-1940; Lewis-Wambi, J.S. *et al.* (2008) "*Overexpression Of CEACAM6 Promotes Migration And Invasion Of Oestrogen-Deprived Breast Cancer Cells*," Eur. J. Cancer 44(12):1770-1779; Blumenthal, R.D. *et al.* (2007) "*Expression Patterns Of CEACAM5 And CEACAM6 In Primary And Metastatic Cancers*," BMC Cancer. 7:2, pp. 1-15). Antibodies that immunospecifically bind to CEACAM5 and CEACAM6 are commercially available (Santa Cruz Biotechnology, Inc., Novus Biologicals LLC; Abnova Corporation). The amino acid sequence of the VL Domain of the humanized anti-CEACAM5 / ANTI-CEACAM6 antibody 16C3 (EP 2585476) (**SEQ ID NO:304**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITC**GASENIY GALN**WYQRKP GKSPKLLIW**G**
ASNLADGMPS RFSGSGSGRQ YTLTISSLQP EDVATYY**CQN VLSSPYT**FGG
GTKLEIK

[0097] The amino acid sequence of the VH Domain of the humanized anti-CEACAM5 / ANTI-CEACAM6 antibody 16C3 (EP 2585476) (**SEQ ID NO:305**) is shown below (CDR residues are shown underlined):

QVQLQQSGPE VVRPGVSVKI SCKGS**GYTFT DYAMH**WVKQS HAKSLEWIG**L**
ISTYSGDTKY NQNFKGKATM TVDKSASTAY MELSSLRSED TAVYYCAR**GD**
YSGSRYWFAY WGQGTLVTVS S

[0098] The amino acid sequence of the VL Domain of the humanized anti-CEACAM5 / CEACAM6 antibody hMN15 (WO 2011/034660) (**SEQ ID NO:306**) is shown below (CDR residues are shown underlined):

DIQLTQSPSS LSASVGDRVT MTC**SASSRVS YIH**WYQQKPG KAPKRWIY**GT**
STLASGVPAR FSGSGSGTDF TFTISSLQPE DIATYYC**QQW SYNPPT**FGQG
TKVEIKR

[0099] The amino acid sequence of the VH Domain of the humanized anti-CEACAM5 / CEACAM6 antibody hMN15 (WO 2011/034660) (**SEQ ID NO:307**) is shown below (CDR residues are shown underlined):

QVQLVESGGG VVQPGRSLRL SCSSSG**FALT DYYMS**WVRQA PGKGLEWLG**F**
IANKANGHTT DYSPSVKGRF TISRDNSKNT LFLQMDSLRP EDTGVYFCAR
DMGIRWNFDV WGQGTPVTVS S

4. DR5-Binding Domains

[00100] DR5 is a preferred Cancer Antigen of the present invention. The preferred anti-human DR5-binding molecules of the present invention possess the VL and/or VH Domains of murine anti-human DR5 monoclonal antibodies "**DR5 mAb 1**" and/or "**DR5 mAb 2**," and more preferably possess 1, 2 or all 3 of the CDRs of the VL Domain and/or 1, 2 or all 3 of the CDRs of the VH Domain of such anti-human DR5 monoclonal antibodies. Alternatively, any anti-human DR5 monoclonal antibody may be employed, particularly: **drozitumab** (designated herein as "**DR5 mAb 3**"), **conatumumab** (designated herein as "**DR5 mAb 4**"), **tigatumumab** (designated herein as "**DR5 mAb 5**"), **LBY135-1** (designated herein as "**DR5 mAb 6**"), **LBY135-2** (designated herein as "DR5 **mAb 7**") and **KMTR2** (designated herein as "**DR5 mAb 8**").

a. The Anti-Human DR5 Antibody DR5 mAb 1

[00101] DR5 has potential utility in the treatment of a wide range of cancers (*e.g.*, colorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer and rectal cancer. The amino acid sequence of human DR5 precursor (NCBI Sequence NP_003833.4) (**SEQ ID NO:2**) is:

MEQRGQNAPA ASGARKRHGP GPREARGARP GLRVPKTLVL VVAAVLLLVS
AESALITQQD LAPQQRVAPQ QKRSSPSEGL CPPGHHISED GRDCISCKYG
QDYSTHWNDL LFCLRCTRCD SGEVELSPCT TTRNTVCQCE EGTFREEDSP
EMCRKCRTGC PRGMVKVGDC TPWSDIECVH KESGTKHSGE APAVEETVTS
SPGTPASPCS LSGIIIGVTV AAVVLIVAVF VCKSLLWKKV LPYLKGICSG
GGGDPERVDR SSQRPGAEDN VLNEIVSILQ PTQVPEQEME VQEPAEPTGV
NMLSPGESEH LLEPAEAERS QRRRLLVPAN EGDPTETLRQ CFDDFADLVP
FDSWEPLMRK LGLMDNEIKV AKAEAAGHRD TLYTMLIKWV NKTGRDASVH
TLLDALETLG ERLAKQKIED HLLSSGKFMY LEGNADSAMS

[00102] The amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**) is shown below (CDR residues are shown underlined):

DIVLTQSPAS LAVSLGQRAT ISC**RASKSVS SSGYSYMH**WY QQKPGQPPKV LIF**LSSNLDS** GVPARFSGSG SGTDFTLNIH PVEDGDAATY YC**QHSRDLPP T**FGGGTKLEI K

CDR_L1 of DR5 mAb 1 (**SEQ ID NO:4**): **RASKSVSSSGYSYMH**

CDR_L2 of DR5 mAb 1 (**SEQ ID NO:5**): **LSSNLDS**

CDR_L3 of DR5 mAb 1 (**SEQ ID NO:6**): **QHSRDLPPT**

[00103] The VL Domain of DR5 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:7**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc atctcatgc**a gggccagcaa aagtgtcagt tcctctggct atagttatat gcac**tggtac caacagaaac caggacagcc acccaaagtc ctcatctttc**c tttcatccaa cctagattct** ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg atggggatgc tgcaacctat tactgt**cagc acagtaggga tcttcctccg acg**ttcggtg gaggcaccaa gctggaaatc aaa

[00104] The amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**) is shown below (CDR residues are shown underlined). The C-terminal amino acid may be substituted with alanine to facilitate subcloning of this VH Domain.

EVKFLESGGG LVQPGGSLKL SCVAS**GFDFS RYWMS**WVRQA PGKGLEWIG**E INPDSNTINY TPSLKD**KFII SRDNAKNTLY LQMTKVRSED TALYYCTR**RA YYGNPAWFAY** WGQGTLVTVSS

CDR_H1 of DR5 mAb 1 **(SEQ ID NO:9)**: **GFDFSRYWMS**

CDR_H2 of DR5 mAb 1 (**SEQ ID NO:10**): **EINPDSNTINYTPSLKD**

CDR_H3 of DR5 mAb 1 (**SEQ ID NO:11**): **RAYYGNPAWFAY**

[00105] The VH Domain of DR5 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:12**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc tcctgtgtag cctca**ggatt cgattttagt agatactgga tgagt**tgggt ccggcaggct ccagggaaag ggctagaatg gattgga**gaa attaatccag atagcaatac gataaactat acgccatctc taaaggat**aa

attcatcatc tccagagaca acgccaaaaa tacgctgtat ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aaga**agggcc tactatggta acccggcctg gtttgcttac** tggggccaag ggactctggt cactgtctct tcc

b. The Anti-Human DR5 Antibody DR5 mAb 2

(1) Murine Anti-Human Antibody DR5 mAb 2

[00106] The amino acid sequence of the VL Domain of DR5 mAb 2 (**SEQ ID NO:13**) is shown below (CDR residues are shown underlined):

DIVMTQSHKF MSTSVGDRVS ITC**KASQDVN TAVA**WYQQKP GQSPKLLIY**W ASTRHT**GVPD RFTGSGSGTD YTLTIKSVQA EDLTLYYC**QQ HYITPWT**FGG GTKLEIK

CDR$_L$1 of DR5 mAb 2 (**SEQ ID NO:14**): **KASQDVNTAVA**

CDR$_L$2 of DR5 mAb 2 (**SEQ ID NO:15**): **WASTRHT**

CDR$_L$3 of DR5 mAb 2 (**SEQ ID NO:16**): **QQHYITPWT**

[00107] The VL Domain of DR5 mAb 2 is preferably encoded by a polynucleotide (**SEQ ID NO:17**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga cagggtcagc atcacctgc**a aggccagtca ggatgtgaat actgctgtag cc**tggtatca acaaaaacca gggcaatctc ctaaactact gatttac**tgg gcatccaccc ggcacact**gg agtccctgat cgcttcacag gcagtggatc tgggacagat tatacactca ccatcaaaag tgtgcaggct gaagacctga cactttatta ctgt**cagcaa cactatatca ctccgtggac g**ttcggtgga ggcaccaagc tggaaatcaaa

[00108] The amino acid sequence of the VH Domain of DR5 mAb 2 (**SEQ ID NO:18**) is shown below (CDR residues are shown underlined):

KVQLQQSGAE LVKPGASVKL SCKAS**GYTFT EYILH**WVKQK SGQGLEWIG**W FYPGNNNIKY NEKFKD**KATL TADKSSSTVY MELSRLTSED SAVYFCAR**HE QGPGYFDY**WG QGTTLTVSS

CDR$_H$1 of DR5 mAb 2 (**SEQ ID NO:19**): **GYTFTEYILH**

CDR$_H$2 of DR5 mAb 2 (**SEQ ID NO:20**): **WFYPGNNNIKYNEKFKD**

CDR$_H$3 of DR5 mAb 2 (**SEQ ID NO:21**): **HEQGPGYFDY**

[00109] The VH Domain of DR5 mAb 2 is preferably encoded by a polynucleotide (**SEQ ID NO:22**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

aaggtccagc tgcagcagtc tggagctgaa ctggtgaaac ccggggcatc
agtgaagctg tcctgcaagg cttct**gggta caccttcact gagtatattt**
tacactgggt aaagcagaag tctggacagg gtcttgagtg gattggg**tgg**
ttttatcctg gaaataataa tataaagtac aatgagaaat tcaaggacaa
ggccacactg actgcggaca aatcctccag cacagtctat atggaactta
gtagattgac atctgaagac tctgcggtct atttctgtgc aaga**cacgaa**
caaggaccag gttactttga ctactggggc caaggcacca ctctcacagt
ctcctcc

(2) Humanized DR5 mAb 2 ("hDR5 mAb 2")

[00110] The above-described murine anti-human DR5 antibody DR5 mAb 2 was humanized in order to demonstrate the capability of humanizing an anti-human DR5 antibody so as to decrease its antigenicity upon administration to a human recipient. The humanization yielded four humanized VL Domains designated herein as "**hDR5 mAb 2 VL-2**," "**hDR5 mAb 2 VL-3**," "**hDR5 mAb 2 VL-4**," and "**hDR5 mAb 2 VL-5,**" and one humanized VH Domain, designated herein as "**hDR5 mAb 2 VH-2**." Any of the humanized VL Domains may be paired with the humanized VH Domain. Accordingly, any antibody comprising one of the humanized VL Domains paired with the humanized VH Domain is referred to generically as "**hDR5 mAb 2**," and particular combinations of humanized VL/VH Domains are referred to by reference to the VL domain.

[00111] The amino acid sequence of the VL Domain of **hDR5 mAb 2 VL-2** (**SEQ ID NO:23**) is shown below (CDR residues are shown underlined):

DIQMTQSPSF LSASVGDRVT ITC**KASQDVN TAVA**WYQQKP GKAPKLLIY**W**
ASTRHTGVPS RFSGSGSGTD FTLTISSLQP EDVATYYC**QQ HYITPWT**FGG
GTKLEIK

[00112] **hDR5 mAb 2 VL-2** is preferably encoded by a polynucleotide (**SEQ ID NO:24**) having the sequence shown below:

gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga
ccgcgtgact attacttgta aagcttctca ggatgtcaac accgccgtgg
cttggtacca gcagaagccc ggtaaagcac ctaagctgct gatctattgg
gccagcactc ggcacaccgg agtcccatct aggttctctg gcagtggatc
agggacagac tttaccctga caattagctc cctgcagccc gaggatgtgg

ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg
ggcacaaaac tggaaatcaa a

[00113] The amino acid sequence of the VL Domain of **hDR5 mAb 2 VL-3** (**SEQ ID NO:25**) is shown below (CDR residues are shown underlined):

DIQMTQSPSF LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYW
ASTRHTGVPD RFSGSGSGTD FTLTISSLQP EDVATYYCQQ HYITPWTFGG
GTKLEIK

[00114] **hDR5 mAb 2 VL-3** is preferably encoded by a polynucleotide (**SEQ ID NO:26**) having the sequence shown below:

gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga
ccgcgtgact attacttgtc gggcttctca ggatgtcaac accgccgtgg
cttggtacca gcagaagccc ggtaaagcac ctaagctgct gatctattgg
gccagcactc ggcacaccgg agtcccagat aggttctctg gcagtggatc
agggacagac tttaccctga caattagctc cctgcagccc gaggatgtgg
ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg
ggcacaaaac tggaaatcaa a

[00115] The amino acid sequence of the VL Domain of **hDR5 mAb 2 VL-4** (**SEQ ID NO:27**) is shown below (CDR residues are shown underlined):

DIQMTQSPSF LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYW
ASTRHTGVPS RFSGSGSGTD FTLTISSLQP EDIATYYCQQ HYITPWTFGG
GTKLEIK

[00116] **hDR5 mAb 2 VL-4** is preferably encoded by a polynucleotide (**SEQ ID NO:28**) having the sequence shown below:

gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga
ccgcgtgact attacttgtc gggcttctca ggatgtcaac accgccgtgg
cttggtacca gcagaagccc ggtaaagcac ctaagctgct gatctattgg
gccagcactc ggcacaccgg agtcccatct aggttctctg gcagtggatc
agggacagac tttaccctga caattagctc cctgcagcca gaggatatcg
ctacatacta ttgtcagcag cactacatca ctccttggac cttcggcggg
ggcacaaaac tggaaatcaa a

[00117] The amino acid sequence of the VL Domain of **hDR5 mAb 2 VL-5** (**SEQ ID NO:29**) is shown below (CDR residues are shown underlined):

DIQMTQSPSF LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYW
ASTRHTGVPD RFSGSGSGTD FTLTISSLQP EDIATYYCQQ HYITPWTFGG
GTKLEIK

[00118] **hDR5 mAb 2 VL-5** is preferably encoded by a polynucleotide (**SEQ ID NO:30**) having the sequence shown below:

gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga
ccgcgtgact attacttgtc gggcttctca ggatgtcaac accgccgtgg
cttggtacca gcagaagccc ggtaaagcac ctaagctgct gatctattgg
gccagcactc ggcacaccgg agtcccagat aggttctctg gcagtggatc
agggacagac tttaccctga caattagctc cctgcagccc gaggatatcg
ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg
ggcacaaaac tggaaatcaa a

[00119] The amino acid sequence of the VH Domain of **hDR5 mAb 2 VH-2** (**SEQ ID NO:31**) is shown below (CDR residues are shown underlined):

QVQLVQSGAE VKKPGASVKV SCKAS**GYTFT EYILH**WVRQA PGQGLEWMGW
FYPGNNNIKY NEKFKDRVTI TADKSTSTVY MELSSLRSED TAVYYCAR**HE**
QGPGYFDYWG QGTLVTVSS

[00120] **hDR5 mAb 2 VH-2** is preferably encoded by a polynucleotide (**SEQ ID NO:32**) having the sequence shown below:

caggtccagc tggtgcagag tggggcagag gtgaaaaagc caggggcatc
agtgaaagtg tcttgtaaag catcaggtta tacatttact gagtacatcc
tgcactgggt gcgacaggca ccaggacagg gactggaatg gatggggtgg
ttctaccctg gcaacaacaa cattaagtac aacgagaagt ttaaagaccg
ggtgaccatc acagcggata agtctaccag tacagtctat atggagctga
gctccctgag aagcgaagac accgccgtct actattgcgc tcgccacgaa
cagggtccag gttactttga ttattggggg cagggaactc tggtcacagt
cagctcc

[00121] The CDR1 of the VL Domain of hDR5 mAb 2 VL-3, hDR5 mAb 2 VL-4 and hDR5 mAb VL-5 has the amino acid sequence: **RASQDVNTAVA** (**SEQ ID NO:320**).

c. Drozitumab ("DR5 mAb 3")

[00122] The amino acid sequence of the VL Domain of **drozitumab** ("**DR5 mAb 3**") (**SEQ ID NO:54**) is shown below (CDR residues are shown underlined):

SELTQDPAVS VALGQTVRIT C**SGDSLRSYY AS**WYQQKPG QAPVLVIY**GA**
NNRPSGIPDR FSGSSSGNTA SLTITGAQAE DEADYYC**NSA DSSGNHVV**FG
GGTKLTVLG

CDR$_L$1 of DR5 mAb 3 (**SEQ ID NO:55**): **SGDSLRSYYAS**

CDR$_L$2 of DR5 mAb 3 (**SEQ ID NO:56**): **GANNRPS**

CDR$_L$3 of DR5 mAb 3 (**SEQ ID NO:57**): **NSADSSGNHVV**

[00123] The amino acid sequence of the VH Domain of **drozitumab** ("**DR5 mAb 3**") (**SEQ ID NO:58**) is shown below (CDR residues are shown underlined):

EVQLVQSGGG VERPGGSLRL SCAAS**GFTFD DYAMS**WVRQA PGKGLEWVSG **INWQGGSTGY ADSVKG**RVTI SRDNAKNSLY LQMNSLRAED TAVYYCAK**IL GAGRGWYFDY** WGKGTTVTVS S

CDR_H1 of DR5 mAb 3 (**SEQ ID NO:59**): **GFTFDDYAMS**

CDR_H2 of DR5 mAb 3 (**SEQ ID NO:60**): **INWQGGSTGYADSVKG**

CDR_H3 of DR5 mAb 3 (**SEQ ID NO:61**): **ILGAGRGWYFDY**

d. Conatumumab ("DR5 mAb 4")

[00124] The amino acid sequence of the VL Domain of **conatumumab** ("**DR5 mAb 4**") (**SEQ ID NO:62**) is shown below (CDR residues are shown underlined):

EIVLTQSPGT LSLSPGERAT LSC**RASQGIS RSYLA**WYQQK PGQAPSLLIY **GASSRAT**GIP DRFSGSGSGT DFTLTISRLE PEDFAVYYC**Q QFGSSPWT**FG QGTKVEIK

CDR_L1 of DR5 mAb 4 (**SEQ ID NO:63**): **RASQGISRSYLA**

CDR_L2 of DR5 mAb 4 (**SEQ ID NO:64**): **GASSRAT**

CDR_L3 of DR5 mAb 4 (**SEQ ID NO:65**): **QQFGSSPWT**

[00125] The amino acid sequence of the VH Domain of **conatumumab** ("**DR5 mAb 4**") (**SEQ ID NO:66**) is shown below (CDR residues are shown underlined):

QVQLQESGPG LVKPSQTLSL TCTVS**GGSIS SGDYFWS**WIR QLPGKGLEWI G**HIHNSGTTY YNPSLKS**RVT ISVDTSKKQF SLRLSSVTAA DTAVYYCAR**D RGGDYYYGMD V**WGQGTTVTV SS

CDR_H1 of DR5 mAb 4 (**SEQ ID NO:67**): **GGSISSGDYFWS**

CDR_H2 of DR5 mAb 4 (**SEQ ID NO:68**): **HIHNSGTTYYNPSLKS**

CDR_H3 of DR5 mAb 4 (**SEQ ID NO:69**): **DRGGDYYYGMDV**

e. Tigatumumab ("DR5 mAb 5")

[00126] The amino acid sequence of the VL Domain of **tigatumumab** ("**DR5 mAb 5**") (**SEQ ID NO:70**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITC**KASQDVG TAVA**WYQQKP GKAPKLLIY**W ASTRHT**GVPS RFSGSGSGTD FTLTISSLQP EDFATYYC**QQ YSSYRT**FGQG TKVEIK

CDR_L1 of DR5 mAb 5 (**SEQ ID NO:71**): **KASQDVGTAVA**

CDR_L2 of DR5 mAb 5 (**SEQ ID NO:72**): **WASTRHT**

CDR_L3 of DR5 mAb 5 (**SEQ ID NO:73**): **QQYSSYRT**

[00127] The amino acid sequence of the VH Domain of **tigatumumab** ("**DR5 mAb5**") (**SEQ ID NO:74**) is shown below (CDR residues are shown underlined):

EVQLVESGGG LVQPGGSLRL SCAAS**GFTFS SYVMS**WVRQA PGKGLEWVA**T ISSGGSYTYY PDSVKG**RFTI SRDNAKNTLY LQMNSLRAED TAVYYCAR**RG DSMITTDY**WG QGTLVTVSS

CDR_H1 of DR5 mAb 5 (**SEQ ID NO:75**): **GFTFSSYVMS**

CDR_H2 of DR5 mAb 5 (**SEQ ID NO:76**): **TISSGGSYTYYPDSVKG**

CDR_H3 of DR5 mAb 5 (**SEQ ID NO:77**): **RGDSMITTDY**

f. LBY135-1 ("DR5 mAb 6")

[00128] The amino acid sequence of the VL Domain of **LBY135-1** ("**DR5 mAb 6**") (**SEQ ID NO:78**) is shown below (CDR residues are shown underlined):

DIAMTQSHKF MSTLVGDRVS ITCKAS**QDVN TAIA**WYQQKP GQSPKLLIY**W ASTRHT**GVPD RFYGSGSGTD YTLTISSMEA EDAATYYC**QQ WSSNPLT**FGA GTKLELKRA

CDR_L1 of DR5 mAb 6 (**SEQ ID NO:79**): **QDVNTAIA**

CDR_L2 of DR5 mAb 6 (**SEQ ID NO:80**): **WASTRHT**

CDR_L3 of DR5 mAb 6 (**SEQ ID NO:81**): **QQWSSNPLT**

[00129] The amino acid sequence of the VH Domain of **LBY135-1** ("**DR5 mAb 6**") (**SEQ ID NO:82**) is shown below (CDR residues are shown underlined):

KVQLQQSGAE LVKPGASVKL SCKAS**GYTFT DYTIH**WVKQR SGQGLEWIG**W FYPGGGYIKY NEKFKD**RATL TADKSSNTVY MELSRLTSEG SAVYFCAR**HE EGIYFDY**WGQ GTTLTVSS

CDR_H1 of DR5 mAb 6 (**SEQ ID NO:83**): **GYTFTDYTIH**

CDR_H2 of DR5 mAb 6 (**SEQ ID NO:84**): **WFYPGGGYIKYNEKFKD**

CDR_H3 of DR5 mAb 6 (**SEQ ID NO:85**): **HEEGIYFDY**

g. LBY135-2 ("DR5 mAb 7")

[00130] The amino acid sequence of the VL Domain of **LBY135-2** ("**DR5 mAb 7**") (**SEQ ID NO:86**) is shown below (CDR residues are shown underlined):

DIVMTQSHKF MSTSVGDRVS ITC**KASQDVN TAIA**WYQQKP GQSPKLLIY**W ASTRHT**GVPD RFTGSGSGTD YTLTISSVQA EDLALYYC**QQ HYTTPFT**FGS GTKL

CDR$_L$1 of DR5 mAb 7 (**SEQ ID NO:87**): **KASQDVNTAIA**

CDR$_L$2 of DR5 mAb 7 (**SEQ ID NO:88**): **WASTRHT**

CDR$_L$3 of DR5 mAb 7 (**SEQ ID NO:89**): **QQHYTTPFT**

[00131] The amino acid sequence of the VH Domain of **LBY135-2** ("**DR5 mAb 7**") (**SEQ ID NO:90**) is shown below (CDR residues are shown underlined):

KVQLQQSGAE LVKPGASVKL SCKAS**GYTFT DYTIH**WVKQR SGQGLEWIG**W FYPGGGYIKY NEKFKD**RATL TADKSSNTVY MELSRLTSED SAVYFCAR**HE EGIYFDY**WGQ GTTLTVSS

CDR$_H$1 of DR5 mAb 7 (**SEQ ID NO:91**): **GYTFTDYTIH**

CDR$_H$2 of DR5 mAb 7 (**SEQ ID NO:92**): **WFYPGGGYIKYNEKFKD**

CDR$_H$3 of DR5 mAb 7 (**SEQ ID NO:93**): **HEEGIYFDY**

h. KMTR2 ("DR5 mAb 8")

[00132] The amino acid sequence of the VL Domain of **KMTR2** ("**DR5 mAb 8**") (**SEQ ID NO:94**) is shown below (CDR residues are shown underlined):

EIVLTQSPAT LSLSPGERAT LSC**RASQSVS SYLA**WYQQKP GQAPRLLIY**D ASNRAT**GIPA RFSGSGSGTD FTLTISSLEP EDFAVYYC**QQ RSNWPLT**FGG GTKVEIKR

CDR$_L$1 of DR5 mAb 8 (**SEQ ID NO:95**): **RASQSVSSYLA**

CDR$_L$2 of DR5 mAb 8 (**SEQ ID NO:96**): **DASNRAT**

CDR$_L$3 of DR5 mAb 8 (**SEQ ID NO:97**): **QQRSNWPLT**

[00133] The amino acid sequence of the VH Domain of **KMTR2** ("**DR5 mAb 8**") (**SEQ ID NO:98**) is shown below (CDR residues are shown underlined):

QVQLVQSGAE MKKPGASVKV SCKTS**GYTFT NYKIN**WVRQA PGQGLEWMG**W MNPDTDSTGY PQKFQG**RVTM TRNTSISTAY MELSSLRSED TAVYYCAR**SY GSGSYYRDYY YGMDV**WGQGT TVTVSS

CDR_H1 of DR5 mAb 8 (**SEQ ID NO:99**): **GYTFTNYKIN**

CDR_H2 of DR5 mAb 8 (**SEQ ID NO:100**): **WMNPDTDSTGYPQKFQG**

CDR_H3 of DR5 mAb 8 (**SEQ ID NO:101**): **SYGSGSYYRDYYYGMDV**

5. EphA2-Binding Domains

[00134] The receptor tyrosine kinase, ephrin type-A receptor 2 (**EphA2**) is a preferred cancer antigen of the present invention. EphA2 is normally expressed at sites of cell-to-cell contact in adult epithelial tissues, however, recent studies have shown that it is also overexpressed in various types of epithelial carcinomas, with the greatest level of EphA2 expression observed in metastatic lesions. High expression levels of EphA2 have been found in a wide range of cancers and in numerous tumor cell lines, including prostate cancer, breast cancer, non-small cell lung cancer and melanoma (Xu, J. *et al.* (2014) "*High Epha2 Protein Expression In Renal Cell Carcinoma Is Associated With A Poor Disease Outcome*," Oncol. Lett. Aug 2014; 8(2): 687-692; Miao, B. *et al.* (2014) "*EphA2 is a Mediator of Vemurafenib Resistance and a Novel Therapeutic Target in Melanoma*," Cancer Discov. pii: CD-14-0295. EphA2 does not appear to be merely a marker for cancer, but rather appears to be persistently overexpressed and functionally changed in numerous human cancers (Chen, P. *et al.* (2014) "*Epha2 Enhances The Proliferation And Invasion Ability Of Lncap Prostate Cancer Cells*," Oncol. Lett. 8(1):41-46).

[00135] The invention particularly contemplates the selection of EphA2 as a Cancer Antigen, and the use of anti-EphA2 antibodies to provide the Cancer Antigen-Binding Domain of the Tri-Specific Binding Molecules of the present invention. Exemplary anti-EphA2 antibodies include "**EphA2 mAb 1**," "**EphA2 mAb 2**" and "**EphA2 mAb 3**."

a. EphA2 mAb 1

[00136] The amino acid sequence of the VL Domain of a preferred anti-human EphA2 antibody ("**EphA2 mAb 1**") (**SEQ ID NO:153**) is shown below (CDR residues are shown underlined):

DIQMTQTTSS LSASLGDRIT ISC**RASQDIS NYLN**WYQQKP DGTVKLLIY**Y**
TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFC**QQ GYTLYT**FGGG
TKLEIK

CDR_L1 of EphA2 mAb 1 (**SEQ ID NO:154**): **RASQDISNYLN**

CDR_L2 of EphA2 mAb 1 (**SEQ ID NO:155**): **YTSRLHS**

CDR_L3 of EphA2 mAb 1 (**SEQ ID NO:156**): **QQGYTLYT**

[00137] The VL Domain of EphA2 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:157**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga
cagaatcacc atcagttgc**a gggcaagtca ggacattagc aattatttaa**
actggtatca gcagaaacca gatggaactg ttaaactcct gatctac**tac**
acatcaagat tacactcagg agtcccatca aggttcagtg gcagtgggtc
tggaacagat tattctctca ccattagcaa cctggagcaa gaagatattg
ccacttactt ttgc**caacag ggttatacgc tgtacacg**tt cggaggggg
accaagctgg aaataaaa

[00138] The amino acid sequence of the VH Domain of EphA2 mAb 1 (**SEQ ID NO:158**) is shown below (CDR residues are shown underlined):

QVQLKESGPG LVAPSQSLSI TCTVS**GFSLS RYSVH**WVRQP PGKGLEWLG**M**
IWGGGSTDYN SALKSRLSIS KDNSKSQVFL KMNSLQTDDT AMYYCAR**KHG**
NYYTMDYWGQ GTSVTVSS

CDR_H1 of EphA2 mAb 1 (**SEQ ID NO:159**): **GFSLSRYSVH**

CDR_H2 of EphA2 mAb 1 (**SEQ ID NO:160**): **MIWGGGSTDYNSALKS**

CDR_H3 of EphA2 mAb 1 (**SEQ ID NO:161**): **KHGNYYTMDY**

[00139] The VH Domain of EphA2 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:162**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

caggtgcagc tgaaggagtc aggacctggc ctggtggcac cctcacagag
cctgtccatc acatgcactg tctct**gggtt ctcattatcc agatatagtg**
tacactgggt tcgccagcct ccaggaaagg gtctggagtg gctggga**atg**

atatggggtg gtggaagcac agactataat tcagctctca aatccagact
gagtatcagc aaggacaact ccaagagcca agttttctta aaaatgaaca
gtctgcaaac tgatgacaca gccatgtact actgtgccag a**aaacatggt**
aactactata ctatggacta ctggggtcaa ggaacctcag tcaccgtctc
ctcc

b. EphA2 mAb 2

[00140] The amino acid sequence of the VL Domain of a second preferred anti-human EphA2 antibody ("**EphA2 mAb 2**") (**SEQ ID NO:163**) is shown below (CDR residues are shown underlined):

DVVMTQTPLS LPVSLGDQAS ISC**RSSQSLV HSSGNTYLH**W YLQKPGQSPK
LLIY**KVSNRF S**GVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFC**SQSTHVP**
TFGSGTKLEI K

CDR$_L$1 of EphA2 mAb 2 (**SEQ ID NO:164**): **RSSQSLVHSSGNTYLH**

CDR$_L$2 of EphA2 mAb 2 (**SEQ ID NO:165**): **KVSNRFS**

CDR$_L$3 of EphA2 mAb 2 (**SEQ ID NO:166**): **SQSTHVPT**

[00141] The VL Domain of EphA2 mAb 2 is preferably encoded by a polynucleotide (**SEQ ID NO:318**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga
tcaagcctcc atctcttgc**a gatctagtca gagccttgta cacagtagtg**
gaaacaccta tttacattgg tacctgcaga agccaggcca gtctccaaag
ctcctgatct ac**aaagtttc caaccgattt tct**ggggtcc cagacaggtt
cagtggcagt ggatcaggga cagatttcac actcaagatc agcagagtgg
aggctgagga tctgggagtt tatttctgc**t ctcaaagtac acatgttccc**
acgttcggct cggggacaaa gttggaaata aaa

[00142] The amino acid sequence of the VH Domain of EphA2 mAb 2 (**SEQ ID NO:167**) is shown below (CDR residues are shown underlined):

QIQLVQSGPE LKKPGETVKI SCKAS**GFTFT NYGMN**WVKQA PGKGLKWMG**W**
INTYIGEPTY ADDFKGRFVF SLETSASTAY LQINNLKNED MATYFCAR**EL**
GPYYFDYWGQ GTTLTVSS

CDR$_H$1 of EphA2 mAb 2 (**SEQ ID NO:168**): **GFTFTNYGMN**

CDR$_H$2 of EphA2 mAb 2 (**SEQ ID NO:169**): **WINTYIGEPTYADDFKG**

CDR$_H$3 of EphA2 mAb 2 (**SEQ ID NO:170**): **ELGPYYFDY**

[00143] The VH Domain of EphA2 mAb 2 is preferably encoded by a polynucleotide (**SEQ ID NO:171**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac
agtcaagatc tcctgcaagg cttct**gggtt taccttcaca aactatggaa**
tgaactgggt gaagcaggct ccaggaaagg gtttaaagtg gatgggc**tgg**
ataaacacct atattggaga gccgacatat gctgatgact tcaagggacg
gtttgtcttc tctttggaaa cctctgccag cactgcctat ttgcagatca
acaacctcaa aaatgaggac atggccacat atttctgtgc aaga**gaactg**
ggaccatact actttgacta ctggggccaa ggcaccactc tcacagtctc
ctcc

c. EphA2 mAb 3

[00144] The amino acid sequence of the VL Domain of a further preferred anti-human EphA2 antibody ("**EphA2 mAb 3**") (**SEQ ID NO:172**) is shown below (CDR residues are shown underlined):

DIVLTQSHRS MSTSVGDRVN ITC**KASQDVT TAVA**WYQQKP GQSPKLLIF**W**
ASTRHAGVPD RFTGSGSGTD FTLTISSVQA GDLALYYC**QQ HYSTPYT**FGG
GTKLEIK

CDR$_L$1 of EphA2 mAb 3 (**SEQ ID NO:173**): **KASQDVTTAVA**

CDR$_L$2 of EphA2 mAb 3 (**SEQ ID NO:174**): **WASTRHA**

CDR$_L$3 of EphA2 mAb 3 (**SEQ ID NO:175**): **QQHYSTPYT**

[00145] The VL Domain of EphA2 mAb 3 is preferably encoded by a polynucleotide (**SEQ ID NO:176**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga
cagggtcaac atcacctgc**a aggccagtca ggatgtgact actgctgtag**
cctggtatca acaaaaacca gggcaatctc ctaaattact gattttc**tgg**
gcatccaccc ggcacgctgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tttactctca ccatcagcag tgtgcaggct ggagacctgg
cactttatta ctgt**caacaa cattatagca caccgtacac a**ttcggaggg
gggaccaagc tggaaataaa a

[00146] The amino acid sequence of the VH Domain of EphA2 mAb 3 (**SEQ ID NO:177**) is shown below (CDR residues are shown underlined):

EVQLVESGGG SVKPGGSLKL SCAAS**GFTFT DHYMY**WVRQT PEKRLEWVA**T**
ISDGGSFTSY PDSVKGRFTI SRDIAKNNLY LQMSSLKSED TAMYYCTR**DE**
SDRPFPYWGQ GTLVTVSS

CDR_H1 of EphA2 mAb 3 (**SEQ ID NO:178**): **GFTFTDHYMY**

CDR_H2 of EphA2 mAb 3 (**SEQ ID NO:179**): **TISDGGSFTSYPDSVKG**

CDR_H3 of EphA2 mAb 3 (**SEQ ID NO:180**): **DESDRPFPY**

[00147] The VH Domain of EphA2 mAb 3 is preferably encoded by a polynucleotide (**SEQ ID NO:319**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gaagtgcagc tggtggagtc tgggggaggc tcagtgaagc ctggagggtc
cctgaaactc tcctgtgcag cctct**ggatt cactttcact gaccattaca**
tgtattgggt tcgccagact ccggaaaaga ggctggagtg ggtcgca**acc**
attagtgatg gcggtagttt cacctcctat ccagacagtg tgaaggggcg
attcaccatc tccagagaca ttgccaagaa caacctgtac ctccaaatga
gcagtctgaa gtctgaggac acagccatgt attactgtac aaga**gatgag**
agcgataggc cgtttcctta ctggggccaa gggactctgg tcactgtctc
ctcc

6. gpA33-Binding Domains

[00148] gpA33 is also a preferred cancer antigen of the present invention. Colorectal cancer is among the most common malignancies of the Western world and is a leading cause of cancer deaths (Silverberg, E. *et al.* (1989) "*Cancer Statistics, 1989*," CA Cancer J Clin. 39(1):3-20). One potentially useful target for colon cancer is the 43kD transmembrane glycoprotein A33 (**gpA33**), which is expressed in >95% of all colorectal carcinomas (Heath, J.K. *et al.* (1997) "*The Human A33 Antigen Is A Transmembrane Glycoprotein And A Novel Member Of The Immunoglobulin* Superfamily," Proc. Natl. Acad. Sci. (U.S.A.) 94(2):469-474; Ritter, G. *et al.* (1997) "*Characterization Of Posttranslational Modifications Of Human A33 Antigen, A Novel Palmitoylated Surface Glycoprotein Of Human Gastrointestinal* Epithelium," Biochem. Biophys. Res. Commun. 236(3):682-686; Wong, N.A. *et al.* (2006) "*EpCAM and gpA33 Are Markers Of Barrett's Metaplasia*," J. Clin. Pathol. 59(3):260-263). gpA33 was first discovered through raising monoclonal murine antibodies against the human pancreatic carcinoma derived cell line ASPC1.

[00149] The invention particularly contemplates the selection of gpA33 as a Cancer Antigen, and the use of anti-gpA33 antibodies to provide the Cancer Antigen-Binding Domain of the Tri-Specific Binding Molecules of the present invention. An exemplary anti-gpA33 antibody is "**gpA33 mAb 1**."

[00150] The amino acid sequence of the VL Domain of a preferred anti-human gpA33 antibody ("**gpA33 mAb 1**") (**SEQ ID NO:181**) is shown below (CDR residues are shown underlined):

DIQLTQSPSF LSASVGDRVT ITC**SARSSIS FMY**WYQQKPG KAPKLLIY**DT SNLAS**GVPSR FSGSGSGTEF TLTISSLEAE DAATYYC**QQW SSYPLT**FGQG TKLEIK

CDR_L1 of gpA33 mAb 1 (**SEQ ID NO:182**): **SARSSISFMY**

CDR_L2 of gpA33 mAb 1 (**SEQ ID NO:183**): **DTSNLAS**

CDR_L3 of gpA33 mAb 1 (**SEQ ID NO:184**): **QQWSSYPLT**

[00151] The VL Domain of gpA33 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:185**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact attacttgc**t ctgctaggtc ctcaatcagc ttcatgtac**t ggtatcagca gaagcccggc aaagcaccta agctgctgat ctac**gacaca agcaacctgg cctcc**ggggt gccatctcgg ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta cctactattg c**agcagtgg agcagctatc ctctgacc**tt cggacagggg actaaactgg aaatcaag

[00152] The amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**) is shown below (CDR residues are shown underlined):

QVQLVQSGAE VKKPGASVKV SCKAS**GYTFT GSWMN**WVRQA PGQGLEWIG**R IYPGDGETNY NGKFKD**RVTI TADKSTSTAY MELSSLRSED TAVYYCAR**IY GNNVYFDV**WG QGTTVTVSS

CDR_H1 of gpA33 mAb 1 (**SEQ ID NO:187**): **GYTFTGSWMN**

CDR_H2 of gpA33 mAb 1 (**SEQ ID NO:188**): **RIYPGDGETNYNGKFKD**

CDR_H3 of gpA33 mAb 1 (**SEQ ID NO:189**): **IYGNNVYFDV**

[00153] The VH Domain of gpA33 mAb 1 is preferably encoded by a polynucleotide (**SEQ ID NO:190**) having the sequence shown below (polynucleotides encoding the CDRs are shown in underline):

caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag cgtgaaggtc tcctgcaaag catca**ggcta tacatttaca ggcagctgga tgaac**tgggt gaggcaggct ccaggacagg gactggagtg gatcggg**cgc atctaccctg gagacggcga aactaactat aatggaaagt tcaaagac**cg

agtgaccatc acagccgata agtctactag taccgcctac atggagctga gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt ctcctcc

7. Her2-Binding Domains

[00154] The invention also particularly contemplates the selection of Her2 as a Cancer Antigen, and the use of anti-Her2 antibodies to provide the Cancer Antigen-Binding Domain of the Tri-Specific Binding Molecules of the present invention. Exemplary anti-Her2 antibodies include "**Her2 mAb 1**" and **Trastuzumab**.

a. Her2 mAb 1

[00155] The amino acid sequence of the VL Domain of anti-Her2 antibody "**Her2 mAb 1**" (**SEQ ID NO:191**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLESGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKRT

[00156] The amino acid sequence of the VH Domain of anti-Her2 antibody "**Her2 mAb 1**" (**SEQ ID NO:192**) is shown below (CDR residues are shown underlined):

QVQLQQSGPE LVKPGASLKL SCTASGFNIK DTYIHWVKQR PEQGLEWIGR IYPTNGYTRY DPKFQDKATI TADTSSNTAY LQVSRLTSED TAVYYCSRWG GDGFYAMDYW GQGASVTVSS

b. Trastusumab

[00157] The amino acid sequence of the VL Domain of the humanized anti-Her2 antibody "**Trastuzumab**" (**SEQ ID NO:193**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ GTKVEIKR

[00158] The amino acid sequence of the VH Domain of the humanized anti-Her2 antibody "**Trastuzumab**" (**SEQ ID NO:194**) is shown below (CDR residues are shown underlined):

EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG GDGFYAMDYW GQGTLVTVSS

8. B7-H3-Binding Domains

[00159] In addition to its expression on neuroblastoma cells, human B7-H3 is also known to be expressed on a variety of other cancer cells (*e.g.*, gastric, ovarian and non-small cell lung cancers). B7-H3 protein expression has been immunohistologically detected in tumor cell lines (Chapoval, A. *et al.* (2001) "*B7-H3: A Costimulatory Molecule For T Cell Activation and IFN-γ Production*," Nature Immunol. 2:269–274; Saatian, B. *et al.* (2004) "*Expression Of Genes For B7-H3 And Other T Cell Ligands By Nasal Epithelial Cells During Differentiation And Activation*," Amer. J. Physiol. Lung Cell. Mol. Physiol. 287:L217–L225; Castriconi *et al.* (2004) "*Identification Of 4Ig-B7-H3 As A Neuroblastoma-Associated Molecule That Exerts A Protective Role From An NK Cell-Mediated Lysis*," Proc. Natl. Acad. Sci. (U.S.A.) 101(34):12640-12645); Sun, M. *et al.* (2002) "*Characterization of Mouse and Human B7-H3 Genes*," J. Immunol. 168:6294-6297). mRNA expression has been found in heart, kidney, testes, lung, liver, pancreas, prostate, colon, and osteoblast cells (Collins, M. *et al.* (2005) "*The B7 Family Of Immune-Regulatory Ligands*," Genome Biol. 6:223.1-223.7). At the protein level, B7-H3 is found in human liver, lung, bladder, testis, prostate, breast, placenta, and lymphoid organs (Hofmeyer, K. *et al.* (2008) "*The Contrasting Role Of B7-H3*," Proc. Natl. Acad. Sci. (U.S.A.) 105(30):10277-10278).

[00160] The invention also particularly contemplates the selection of B7-H3 as a Cancer Antigen, and the use of anti-B7-H3 antibodies to provide the Cancer Antigen-Binding Domain of the Tri-Specific Binding Molecules of the present invention. Exemplary anti-B7-H3 antibodies include "**B7-H3 mAb 1**," "**B7-H3 mAb 2**," and "**B7-H3 mAb 3**."

a. B7-H3 mAb 1

[00161] The amino acid sequence of the VL Domain of anti-B7-H3 antibody "**B7-H3 mAb 1**" (**SEQ ID NO:195**) is shown below (CDR residues are shown underlined):

DIAMTQSQKF MSTSVGDRVS VTC**KASQNVD TNVA**WYQQKP GQSPKALIY**S**
ASYRYSGVPD RFTGSGSGTD FTLTINNVQS EDLAEYFC**QQ YNNYPFT**FGS
GTKLEIK

[00162] The amino acid sequence of the VH Domain of anti-B7-H3 antibody "**B7-H3 mAb 1**" (**SEQ ID NO:196**) is shown below (CDR residues are shown underlined):

DVQLVESGGG LVQPGGSRKL SCAAS**GFTFS SFGMH**WVRQA PEKGLEWVA**Y**
ISSDSSAIYY ADTVKGRFTI SRDNPKNTLF LQMTSLRSED TAMYYCGR**GR**
ENIYYGSRLD YWGQGTTLTV SS

b. B7-H3 mAb 2

[00163] The amino acid sequence of the VL Domain of anti-B7-H3 antibody "**B7-H3 mAb 2**" (**SEQ ID NO:197**) is shown below (CDR residues are shown underlined):

DIQMTQTTSS LSASLGDRVT ISC**RASQDIS NYLN**WYQQKP DGTVKLLIY**Y**
TSRLHSGVPS RFSGSGSGTD YSLTIDNLEQ EDIATYFC**QQ GNTLPPT**FGG
GTKLEIK

[00164] The amino acid sequence of the VH Domain of anti-B7-H3 antibody "**B7-H3 mAb 2**" (**SEQ ID NO:198**) is shown below (CDR residues are shown underlined):

QVQLQQSGAE LARPGASVKL SCKAS**GYTFT SYWMQ**WVKQR PGQGLEWIG**T**
IYPGDGDTRY TQKFKGKATL TADKSSSTAY MQLSSLASED SAVYYCAR**RG**
IPRLWYFDVW GAGTTVTVSS

c. B7-H3 mAb 3

[00165] The amino acid sequence of the VL Domain of anti-B7-H3 antibody "**B7-H3 mAb 3**" (**SEQ ID NO:199**) is shown below (CDR residues are shown underlined):

DIQMTQSPAS LSVSVGETVT ITC**RASESIY SYLA**WYQQKQ GKSPQLLVY**N**
TKTLPEGVPS RFSGSGSGTQ FSLKINSLQP EDFGRYYC**QH HYGTPPWT**FG
GGTNLEIK

[00166] The amino acid sequence of the VH Domain of anti-B7-H3 antibody "**B7-H3 mAb 3**" (**SEQ ID NO:200**) is shown below (CDR residues are shown underlined):

EVQQVESGGD LVKPGGSLKL SCAAS**GFTFS SYGMS**WVRQT PDKRLEWVA**T**
INSGGSNTYY PDSLKGRFTI SRDNAKNTLY LQMRSLKSED TAMYYCAR**HD**
GGAMDYWGQG TSVTVSS

9. EGF Receptor-Binding Domains (Cetuximab)

[00167] The amino acid sequence of the VL Domain of the chimeric anti-EGFR antibody "**Cetuximab**" (**SEQ ID NO:201**) is shown below (CDR residues are shown underlined):

DILLTQSPVI LSVSPGERVS FSC**RASQSIG TNIH**WYQQRT NGSPRLLIK**Y**
ASESISGIPS RFSGSGSGTD FTLSINSVES EDIADYYC**QQ NNNWPTT**FGA
GTKLELKR

[00168] The amino acid sequence of the VH Domain of the chimeric anti-EGFR antibody "**Cetuximab**" (**SEQ ID NO:202**) is shown below (CDR residues are shown underlined):

QVQLKQSGPG LVQPSQSLSI TCTVS**GFSLT NYGVH**WVRQS PGKGLEWLG**V**
IWSGGNTDYN TPFTSRLSIN KDNSKSQVFF KMNSLQSNDT AIYYCAR**ALT**
YYDYEFAYWG QGTLVTVSA

[00169] **Panitumumab** (e.g., Vectibix®, Amgen) is an alternative EGF receptor-binding antibody that may be used in accordance with the present invention.

10. VEGF-Binding Domains (Bevacizumab)

[00170] The amino acid sequence of the VL Domain of the humanized anti-VEGF antibody "**Bevacizumab**" (**SEQ ID NO:203**) is shown below (CDR residues are shown underlined):

DIQMTQSPSS LSASVGDRVT ITC**SASQDIS NYLN**WYQQKP GKAPKVLIY**F**
TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYC**QQ YSTVPWT**FGQ
GTKVEIKR

[00171] The amino acid sequence of the VH Domain of the humanized anti-VEGF antibody "**Bevacizumab**" (**SEQ ID NO:204**) is shown below (CDR residues are shown underlined):

EVQLVESGGG LVQPGGSLRL SCAAS**GYTFT NYGMN**WVRQA PGKGLEWVG**W**
INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCA**KYP**
HYYGSSHWYF DVWGQGTLVT VSS

11. 5T4-Binding Domains

[00172] The oncofetal protein, **5T4**, is a tumor-associated protein displayed on the cell membrane of many carcinomas, including kidney, colon, prostate, lung, carcinoma and in acute lymphoblastic leukemia (see, Boghaert, E.R. *et al.* (2008) "*The Oncofetal Protein, 5T4, Is A Suitable Target For Antibody-Guided Anti-Cancer*

Chemotherapy With Calicheamicin," Int. J. Oncol. 32(1):221-234; Eisen, T. *et al.* (2014) "*Naptumomab Estafenatox: Targeted Immunotherapy with a Novel Immunotoxin*," Curr. Oncol. Rep. 16:370, pp. 1-6). The amino acid sequence of the Light Chain Variable Domain of an exemplary anti-5T4 antibody ("**5T4 mAb 1**") is shown below (CDR residues are shown underlined): (**SEQ ID NO:308**):

DIQMTQSPSS LSASVGDRVT ITC**RASQGIS NYLA**WFQQKP GKAPKSLIY**R**
ANRLQSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYC**LQ YDDFPWT**FGQ
GTKLEIK

[00173] The amino acid sequence of the Heavy Chain Variable Domain of such exemplary anti-5T4 antibody is shown below (CDR residues are shown underlined): (**SEQ ID NO:309**):

QVQLVQSGAE VKKPGASVKV SCKAS**GYTFT SFWMH**WVRQA PGQGLEWMG**R**
IDPNRGGTEY NEKAKSRVTM TADKSTSTAY MELSSLRSED TAVYYCAG**GN**
PYYPMDYWGQ GTTVTVSS

[00174] The amino acid sequence of the Light Chain Variable Domain of a second exemplary anti-5T4 antibody ("**5T4 mAb 2**") is shown below (CDR residues are shown underlined): (**SEQ ID NO:310**):

DVLMTQTPLS LPVSLGDQAS ISC**RSSQSIV YSNGNTYLE**W YLQKPGQSPK
LLIY**KVSNRF S**GVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYC**FQGSHVP**
FTFGSGTKLE IK

[00175] The amino acid sequence of the Heavy Chain Variable Domain of such second exemplary anti-5T4 antibody is shown below (CDR residues are shown underlined) (**SEQ ID NO:311**):

QVQLQQPGAE LVKPGASVKM SCKAS**GYTFT SYWIT**WVKQR PGQGLEWIG**D**
IYPGSGRANY NEKFKSKATL TVDTSSSTAY MQLSSLTSED SAVYNCAR**YG**
PLFTTVVDPN SYAMDYWGQG TSVTVSS

12. IL13Rα2-Binding Domains

[00176] Interleukin-13 Receptor α2 (**IL13Rα2**) is overexpressed in a variety of cancers, including glioblastoma, colorectal cancer, cervical cancer, pancreatic cencer, multiple melanoma, osteosarcoma, leukemia, lymphoma, prostate cancer and lung cancer (PCT Pubmication No. WO 2008/146911;

[00177] Brown, C.E. *et al.* (2013) "Glioma IL13Rα2 Is Associated With Mesenchymal Signature Gene Expression And Poor Patient Prognosis," PLoS One.

18;8(10):e77769; Barderas, R. *et al.* (2012) "High Expression Of IL-13 Receptor A2 In Colorectal Cancer Is Associated With Invasion, Liver Metastasis, And Poor Prognosis," Cancer Res. 72(11):2780-2790; Kasaian, M.T. *et al.* (2011) "IL-13 Antibodies Influence IL-13 Clearance In Humans By Modulating Scavenger Activity Of IL-13Rα2," J. Immunol. 187(1):561-569; Bozinov, O. *et al.* (2010) "Decreasing Expression Of The Interleukin-13 Receptor IL-13Ralpha2 In Treated Recurrent Malignant Gliomas," Neurol. Med. Chir. (Tokyo) 50(8):617-621; Fujisawa, T. *et al.* (2009) "A novel role of interleukin-13 receptor alpha2 in pancreatic cancer invasion and metastasis," Cancer Res. 69(22):8678-8685). Antibodies that immunospecifically bind to IL13Rα2 are commercially available (Abnova Corporation, Biorbyt, LifeSpan BioSciences, United States Biologicals; see also PCT Publication No. WO 2008/146911). The amino acid sequence of the Light Chain Variable Domain of an exemplary anti-IL13Rα2 antibody ("**hu08**," PCT Publication No. WO 2014/072888) is shown below (CDR residues are shown underlined): (**SEQ ID NO:321**):

DIQMTQSPSS LSASVGDRVT ITC**KASQDVG TAVA**WYQQKP GKAPKLLIY**S**
ASYRSTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYC**QH HYSAPWT**FGG
GTKVEIK

[00178] The amino acid sequence of the Heavy Chain Variable Domain of such exemplary anti-IL13Rα2 antibody ("**hu08**," PCT Publication No. WO 2014/072888) is shown below (CDR residues are shown underlined): (**SEQ ID NO:322**):

EVQLVESGGG LVQPGGSLRL SCAAS**GFTFS RNGMS**WVRQA PGKGLEWVA**T**
VSSGGSYIYY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAR**QG**
TTALATRFFD VWGQGTLVTV SS

13. Integrin Beta6-Binding Domains

[00179] Integrinβ6 (**ITGB6**) is a subtype of integrin that is expressed exclusively on the surfaces of epithelial cells and is a receptor for extracellular matrix (ECM) proteins. ITGB6 expression is specifically expressed in tumor tissues (such as those of colon, prostate, kidney cancer), but is generally undetectable in healthy epithelial tissue (Liang, B. *et al.* (2014) "*Integrinβ6-targeted Immunoliposomes Mediate Tumor Specific Drug Delivery and Enhance Therapeutic Efficacy in Colon Carcinoma*," Clin. Cancer Res. Dec 30. pii: clincanres.1194.2014). Monoclonal antibodies that immunospecifically bind to ITGB6 are available commercially (e.g., MAB2075Z clone R6G9,EMD Millipore; see also, Weinacker, A. *et al.* (1994) "*Role Of The*

Integrin Alpha V Beta 6 In Cell Attachment To Fibronectin. Heterologous Expression Of Intact And Secreted Forms Of The Receptor," J. Biol. Chem. 269:6940-6948). Anti-ITGB6 monoclonal antibodies **3G9** and **8G6**, and variants thereof are disclosed in PCT Publication Nos. WO 03/100033 and WO 2007/008712.

[00180] The amino acid sequence of the Light Chain Variable Domain of an exemplary humanized anti-ITGB6 antibody (derived from antibody 3G9, PCT Publication No. WO 2007/008712) is shown below (CDR residues are shown underlined): (**SEQ ID NO:312**):

EIVLTQSPAT LSLSPGERAT LSC**SASSSVS SSYLY**WYQQK PGQAPRLLIY **STSNLAS**GIP ARFSGSGSGT GFTLTISSLE PEDFAVYYC**H QWSTYPPT**FG GGTKVEIK

[00181] The amino acid sequence of the Heavy Chain Variable Domain of such exemplary humanized anti-ITGB6 antibody (derived from antibody 3G9, PCT Publication No. WO 2007/008712) is shown below (CDR residues are shown underlined): (**SEQ ID NO:313**):

EVQLVESGGG LVQPGGSLRL SCAAS**GFTFS RYWMS**WVRQA PGKGLEWVA**S ISSGGRMYYP FTVKG**RFTIS RDNAKNSLYL QMNSLRAEDT AVYYCAR**GSI YDGYYVFPY**W GQGTLVTVSS

[00182] The amino acid sequence of the Light Chain Variable Domain of an exemplary anti-ITGB6 antibody (derived from antibody 8G6, PCT Publication No. WO 2007/008712) is shown below (CDR residues are shown underlined): (**SEQ ID NO:314**):

EIVLTQSPAT LSLSPGERAT LSC**RASQSVS TSSYSYMY**WY QQKPGQAPRL LIY**YASNLES** GIPARFSGSG SGTDFTLTIS SLEPEDFAVY YC**QHNWEIPF T**FGGGTKVEI K

[00183] The amino acid sequence of the Heavy Chain Variable Domain of such exemplary anti-ITGB6 antibody (derived from antibody 8G6, PCT Publication No. WO 2007/008712) is shown below (CDR residues are shown underlined): (**SEQ ID NO:315**):

QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDYAMH**WVRQAPGQGLEWMG**VISTYY GNTNYNQKFKG**RVTMTRDTSISTAYMELSRLRSDDTAVYYCAR**GGLRRGDRPSLQ YAMDY**WGQGTLVTVSS

14. Additional Anti-Cancer Antigen-Binding Domains

[00184] Additional anti-cancer antigen antibodies that may be used in accordance with the present invention include the following commercially available antibodies: **Brentuximab** (*e.g.*, Adcetris®), which binds to CD30; **Gemtuzumab** (*e.g.*, Mylotarg®, Wyeth), which binds to CD33; and **Ipilimumab** (*e.g.,* Yervoy®), which binds to CTLA-4.

C. Exemplary Effector Cell-Binding Domains

[00185] Antibodies that are capable of binding to immune system effector cells may be used to provide the Effector Cell-Binding Domains of the Tri-Specific Binding Molecules of the present invention. Particularly suitable are antibodies that bind to CD2, CD3, CD16, CD19, CD20, CD22, CD32B, CD64, the B cell Receptor (BCR), the T cell Receptor (TCR), and the NKG2D Receptor.

1. CD2-Binding Domains

[00186] CD2 is is a cell adhesion molecule found on the surface of T cells and natural killer (NK) cells. CD2 enhances NK cell cytotoxicity, possibly as a promoter of NK cell nanotube formation (Mace, E.M. *et al.* (2014) "*Cell Biological Steps And Checkpoints In Accessing NK Cell Cytotoxicity*," Immunol. Cell. Biol. 92(3):245-255; Comerci, C.J. *et al.* (2012) "*CD2 Promotes Human Natural Killer Cell Membrane Nanotube Formation*," PLoS One 7(10):e47664:1-12). The amino acid sequence of the VL Domain of anti-CD2 antibody (Lo-CD2a; ATCC Accession No: 11423) is (**SEQ ID NO:102**) (CDR residues are shown underlined):

DVVLTQTPPT LLATIGQSVS ISC**RSSQSLL** **HSSGNTYLN**W LLQRTGQSPQ PLIY**LVSKLE** **S**GVPNRFSGS GSGTDFTLKI SGVEAEDLGV YYC**MQFTHYP** **YT**FGAGTKLE LK

[00187] The amino acid sequence of the VH Domain of anti-CD2 antibody (Lo-CD2a; ATCC Accession No: 11423) is (**SEQ ID NO:103**) (CDR residues are shown underlined):

EVQLQQSGPE LQRPGASVKL SCKASGYIFT **EYYMY**WVKQR PKQGLELVG**R** **IDPEDGSIDY** **VEKFKK**KATL TADTSSNTAY MQLSSLTSED TATYFCAR**GK** **FNYRFAY**WGQ GTLVTVSS

2. CD3-Binding Domains

[00188] In a preferred embodiment, the second epitope that is bound by the Tri-Specific Binding Molecules of the present invention will be an epitope of CD3. CD3 is a T cell co-receptor composed of four distinct chains (Wucherpfennig, K.W. *et al.* (2010) "*Structural Biology Of The T-Cell Receptor: Insights Into Receptor Assembly, Ligand Recognition, And Initiation Of Signaling*," Cold Spring Harb. Perspect. Biol. 2(4):a005140; pages 1-14). In mammals, the complex contains a CD3γ chain, a CD3δ chain, and two CD3ε chains. These chains associate with a molecule known as the T cell receptor (TCR) in order to generate an activation signal in T lymphocytes. In the absence of CD3, TCRs do not assemble properly and are degraded (Thomas, S. *et al.* (2010) "*Molecular Immunology Lessons From Therapeutic T-Cell Receptor Gene Transfer*," Immunology 129(2):170–177). CD3 is found bound to the membranes of all mature T cells, and in virtually no other cell type (see, Janeway, C.A. *et al.* (2005) In: IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE," 6th ed. Garland Science Publishing, NY, pp. 214- 216; Sun, Z. J. *et al.* (2001) "*Mechanisms Contributing To T Cell Receptor Signaling And Assembly Revealed By The Solution Structure Of An Ectodomain Fragment Of The CD3ε:γ Heterodimer*," Cell 105(7):913-923; Kuhns, M.S. *et al.* (2006) "*Deconstructing The Form And Function Of The TCR/CD3 Complex*," Immunity. 2006 Feb;24(2):133-139).

[00189] As discussed below, in order to illustrate the present invention, bi-specific anti-human CD3 x anti-human DR5-binding molecules were produced. An anti-human CD3 antibody used for such constructs is designated herein as "**CD3 mAb 2**." The amino acid sequence of the VL Domain of **CD3 mAb 2** (**SEQ ID NO:104**) is shown below (CDR residues are shown underlined):

QAVVTQEPSL TVSPGGTVTL TC**RSSTGAVT TSNYAN**WVQQ KPGQAPRGLI G**GTNKRAP**WT PARFSGSLLG GKAALTITGA QAEDEADYYC **ALWYSNLWV**F GGGTKLTVLG

CDR$_L$1 of CD3 mAb 2 (**SEQ ID NO:105**): **RSSTGAVTTSNYAN**

CDR$_L$2 of CD3 mAb 2 (**SEQ ID NO:106**): **GTNKRAP**

CDR$_L$3 of CD3 mAb 2 (**SEQ ID NO:107**): **ALWYSNLWV**

[00190] The amino acid sequence of the VH Domain of **CD3 mAb 2** (**SEQ ID NO:108**) is shown below (CDR residues are shown underlined):

EVQLVESGGG LVQPGGSLRL SCAASGFTFS **TYAMN**WVRQA PGKGLEWVG**R**
IRSKYNNYAT YYADSVKDRF TISRDDSKNS LYLQMNSLKT EDTAVYYCVR
HGNFGNSYVS WFAYWGQGTL VTVSS

CDR_H1 of CD3 mAb 2 (**SEQ ID NO:109**): **TYAMN**

CDR_H2 of CD3 mAb 2 (**SEQ ID NO:110**): **RIRSKYNNYATYYADSVKD**

CDR_H3 of CD3 mAb 2 (**SEQ ID NO:111**): **HGNFGNSYVSWFAY**

[00191] In some of the CD3 constructs, a variant VH Domain was employed for **CD3 mAb 2**. The variant VH domainpossesses a D65G substitution, thus having the amino acid sequence shown below (**SEQ ID NO:112**) (CDR residues are shown underlined):

EVQLVESGGG LVQPGGSLRL SCAASGFTFS **TYAMN**WVRQA PGKGLEWVG**R**
IRSKYNNYAT YYADSVKGRF TISRDDSKNS LYLQMNSLKT EDTAVYYCVR
HGNFGNSYVS WFAYWGQGTL VTVSS

[00192] The substitution causes the CDR_H2 to have the amino acid sequence (**SEQ ID NO:113**) RIRSKYNNYATYYADSVKG. The substituted position (D65G) is shown in double underline.

[00193] A second anti-CD3 antibody used herein is antibody Muromonab-CD3 "**OKT3**" (Xu *et al.* (2000) *"In Vitro Characterization Of Five Humanized OKT3 Effector Function Variant Antibodies,"* Cell. Immunol. 200:16-26); Norman, D.J. (1995) "*Mechanisms Of Action And Overview Of OKT3*," Ther. Drug Monit. 17(6):615-620; Canafax, D.M. *et al.* (1987) "*Monoclonal Antilymphocyte Antibody (OKT3) Treatment Of Acute Renal Allograft Rejection*," Pharmacotherapy 7(4):121-124; Swinnen, L.J. *et al.* (1993) "*OKT3 Monoclonal Antibodies Induce Interleukin-6 And Interleukin-10: A Possible Cause Of Lymphoproliferative Disorders Associated With Transplantation*," Curr. Opin. Nephrol. Hypertens. 2(4):670-678). The amino acid sequence of the VL Domain of **OKT3** (**SEQ ID NO:114**) is shown below (CDR residues are shown underlined):

QIVLTQSPAI MSASPGEKVT MTC**SASSSVS YMN**WYQQKSG TSPKRWIY**DT**
SKLASGVPAH FRGSGSGTSY SLTISGMEAE DAATYYC**QQW SSNPFTF**GSG
TKLEINR

[00194] The amino acid sequence of the VH Domain of **OKT3** (**SEQ ID NO:115**) is shown below (CDR residues are shown underlined):

QVQLQQSGAE LARPGASVKM SCKASGYTFT **RYTMH**WVKQR PGQGLEWIG**Y**
INPSRGYTNY **NQKFKD**KATL TTDKSSSTAY MQLSSLTSED SAVYYCAR**YY**
DDHYCLDYWG QGTTLTVSS

3. CD16-Binding Domains

[00195] CD16 is the FcγRIIIA receptor. CD16 is expressed by neutrophils, eosinophils, natural killer (NK) cells, and tissue macrophages that bind aggregated but not monomeric human IgG (Peltz, G.A. *et al.* (1989) "*Human Fc Gamma RIII: Cloning, Expression, And Identification Of The Chromosomal Locus Of Two Fc Receptors For IgG*," Proc. Natl. Acad. Sci. (U.S.A.) 86(3):1013-1017; Bachanova, V. *et al.* (2014) "*NK Cells In Therapy Of Cancer*," Crit. Rev. Oncog. 19(1-2):133-141; Miller, J.S. (2013) "*Therapeutic Applications: Natural Killer Cells In The Clinic*," Hematology Am. Soc. Hematol. Educ. Program. 2013:247-253; Youinou, P. *et al.* (2002) "*Pathogenic Effects Of Anti-Fc Gamma Receptor IIIB (CD16) On Polymorphonuclear Neutrophils In Non-Organ-Specific Autoimmune Diseases*," Autoimmun Rev. 1(1-2):13-19; Peipp, M. *et al.* (2002) "*Bi-specific Antibodies Targeting Cancer Cells*," Biochem. Soc. Trans. 30(4):507-511).

[00196] The amino acid sequence of a Variable Light Chain Domain of anti-CD16 antibody 3G8 is (**SEQ ID NO:116**) (CDR residues are shown underlined):

DTVLTQSPAS LAVSLGQRAT ISC**KASQSVD** **FDGDSFMN**WY QQKPGQPPKL
LIY**TTSNLES** GIPARFSASG SGTDFTLNIH PVEEEDTATY YC**QQSNEDPY**
TFGGGTKLEI K

[00197] The amino acid sequence of the Variable Heavy Chain Domain of anti-CD16 antibody 3G8 is (**SEQ ID NO:117**) (CDR residues are shown underlined):

QVTLKESGPG ILQPSQTLSL TCSFSGFSLR **TSGMGVG**WIR QPSGKGLEWL
A**HIWWDDDKR** **YNPALKS**RLT ISKDTSSNQV FLKIASVDTA DTATYYCAQ**I**
NPAWFAYWGQ GTLVTVSA

[00198] The amino acid sequence of a Variable Light Chain Domain of anti-CD16 antibody A9 is (**SEQ ID NO:118**) (CDR residues are shown underlined):

DIQAVVTQES ALTTSPGETV TLTC**RSNTGT** **VTTSNYAN**WV QEKPDHLFTG
LIG**HTNNRAP** GVPARFSGSL IGDKAALTIT GAQTEDEAIY FC**ALWYNNHW**
VFGGGTKLTVL

[00199] The amino acid sequence of the Variable Heavy Chain Domain of anti-CD16 antibody A9 is (**SEQ ID NO:119**) (CDR residues are shown underlined):

QVQLQQSGAE LVRPGTSVKI SCKASGYTFT **NYWLG**WVKQR PGHGLEWIG**D**
IYPGGGYTNY **NEKFKG**KATV TADTSSRTAY VQVRSLTSED SAVYFCAR**SA**
SWYFDVWGAR TTVTVSS

4. CD19-Binding Domains

[00200] CD19 antigen is a type I transmembrane glycoprotein belonging to the immunoglobulin Ig superfamily. CD19 is expressed on follicular dendritic cells and B cells. It is considered a pan B cell marker expressed throughout B cell development but with threefold higher expression in mature cells as compared to immature B cells (Raufi A. *et al.* (2013) "*Targeting CD19 In B-Cell Lymphoma: Emerging Role Of SAR3419*," Cancer Manag. Res. 5:225-233). Many CD19 antibodies have been described (*e.g.*, MD1342, MEDI-551, *etc.*) (Mei, H.E. *et al.* (2012) "*Rationale Of Anti-CD19 Immunotherapy: An Option To Target Autoreactive Plasma Cells In Autoimmunity*," Arthritis Res. Ther. 14(Suppl 5):S1:1-16). The anti-CD19 binding molecule "blinatumomab" is disclosed in EP 2186527.

[00201] The amino acid sequence of the VL Domain of a preferred anti-CD19 antibody (HD37) is (**SEQ ID NO:120**) (CDR residues are shown underlined):

DILITQSPKS MSMSVGERVT LTC**KASENVV** **TYVS**WYQQKP EQSPKLLIY**G**
ASNRYTGVPD RFTGSGSATD FTLTISSVQA EDLADYHC**GQ** **GYSYPYT**FGG
GTKLEIKR

[00202] The amino acid sequence of the VH Domain of anti-CD19 antibody HD37 is (**SEQ ID NO:121**) (CDR residues are shown underlined):

QVQLQQSGAE LVRPGSSVKI SCKAS**GYAFS** **SYWMN**WVKQR PGQGLEWIG**Q**
IWPGDGDTNY **NGKFKG**KATL TADESSSTAY MQLSSLASED SAVYFCAR**RE**
TTTVGRYYYA **MDY**WGQGTSV TVSS

5. CD20-Binding Domains

[00203] CD20 is a B cell-specific differentiation antigen that is expressed on mature B cells and in most B cell non-Hodgkin's lymphomas but not on early B cell progenitors or later mature plasma cells (Maloney, D.G. (2012) "*Anti-CD20 Antibody Therapy for B-Cell Lymphomas*," N. Engl. J. Med. 366:2008-2016). Rituximab is an illustrative anti-human CD20 antibody. The amino acid sequence of the VL Domain

of a chimeric anti-CD20 antibody (rituximab) is (**SEQ ID NO:122**) (CDR residues are shown underlined):

QIVLSQSPAI LSASPGEKVT MTC**RASSSVS YIH**WFQQKPG SSPKPWIY**AT SNLAS**GVPVR FSGSGSGTSY SLTISRVEAE DAATYYC**QQW TSNPPT**FGGG TKLEIKR

[00204] The amino acid sequence of the VH Domain of anti-CD20 antibody (rituximab) is (**SEQ ID NO:123**) (CDR residues are shown underlined):

QVQLQQPGAE LVKPGASVKM SCKAS**GYTFT SYNMH**WVKQT PGRGLEWIG**A IYPGNGDTSY NQKFKG**KATL TADKSSSTAY MQLSSLTSED SAVYYCAR**ST YYGGDWYFNV** WGAGTTVTVS A

[00205] Alternative anti-CD20 antibodies that may be used in accordance with the present invention include the following commercially available antibodies: **Ibritumomab** (*e.g.*, Zevalin®, Spectrum Pharmaceuticals, Inc.), **Ofatumumab** (*e.g.*, Arzerra®, SmithKlineGlaxo) and **Tositumomab** (*e.g.*, Bexxar®,GlaxoSmithKline).

6. CD22-Binding Domains

[00206] CD22 is a sugar binding transmembrane protein found on the surface of mature B cells and to a lesser extent on some immature B cells (WO 2011/032633; Poe, J.C. *et al.* (2012) "*CD22 And Siglec-G In B Cell Function And Tolerance*," Trends Immunol. 33(8):413-420; Chen, W.C. *et al.* (2012) "*Targeting B Lymphoma With Nanoparticles Bearing Glycan Ligands Of CD22*," Leuk. Lymphoma 53(2):208-210; Walker, J.A. (2008) "*CD22: An Inhibitory Enigma*," Immunology 123(3):314-325; Coleman, M. *et al.* (2003) "*Epratuzumab: Targeting B-Cell Malignancies Through CD22*," Clin. Cancer Res. 9(10 Pt 2):3991S-3994S).

[00207] The amino acid sequence of the VL Domain of anti-CD22 antibody (epratuzumab) is (**SEQ ID NO:124**) (CDR residues are shown underlined):

DIQLTQSPSS LSASVGDRVT MSC**KSSQSVL YSANHKNYLA** WYQQKPGKAP KLLIY**WASTR ES**GVPSRFSG SGSGTDFTFT ISSLQPEDIA TYYC**HQYLSS WT**FGGGTKVQ IKR

[00208] The amino acid sequence of the VH Domain of anti-CD22 antibody (epratuzumab) is (**SEQ ID NO:125**) (CDR residues are shown underlined):

QVQLVQSGAE VKKPGSSVKV SCKAS**GYTFT SYWLH**WVRQA PGQGLEWIG**Y INPRNDYTEY NQNFKD**KATI TADESTNTAY MELSSLRSED TAFYFCAR**RD ITTFY**WGQGT TVTVSS

7. CD32B-Binding Domains

[00209] A preferred sequence for the VL domain of an antibody that binds to human CD32B is CD32B mAb 1 (**SEQ ID NO:126**) (CDR residues are shown underlined):

DIQMTQSPSS LLAALGERVS LTC**RASQEIS GYLS**WLQQKP DGTIKRLIY**A**
ASTLDSGVPK RFSGSESGSD YSLTISSLES EDFADYYC**LQ YFSYPLT**FGA
GTKLELK

[00210] A preferred sequence for the VH domain of the CD32B mAb 1 antibody that binds to human CD32B is (**SEQ ID NO:127**) (CDR residues are shown underlined):

EVKLEESGGG LVQPGGSMKL SCEAS**GFTFS DAWMD**WVRQS PEKGLEWVA**E**
IRNKAKNHAT YYAESVIGRF TISRDDSKSS VYLQMNSLRA EDTGIYYCGA
LGLDYWGQGT TLTVSS

8. CD64-Binding Domains

[00211] CD64 is the FcγRI receptor and is expressed on monocytes/macrophages, dendritic cells, and activated granulocytes. The expression can be upregulated by IFN-γ stimulation. CD64 binds IgG immune complex. CD64 plays a role in antigen capture, phagocytosis of IgG/antigen complexes, and antibody-dependent cellular cytotoxicity (WO 2006/002438).

[00212] A preferred sequence for the VL domain of an antibody that binds to human CD64 is CD64 mAb 1 (**SEQ ID NO:128**) (CDR residues are shown underlined):

EIVLTQSPAT LSLSPGERAT LSC**RASQSVS SYLA**WYQQKP GQAPRLLIY**D**
ASSRATGIPA RFGGSGSGGT DFTLTISSLE PEDFAVYYC**Q LRSNWPPYT**F
GQGTKLEIK

[00213] A preferred sequence for the VH domain of an antibody that binds to human CD64 is (**SEQ ID NO:129**) (CDR residues are shown underlined):

QVQLVESGGG VVQPGRSLRL SCAASGFIFS **GYGMH**WVRQA PGKGLEWVT**V**
IWYDGSNKYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAR**DT**
GDRFFDYWGQ GTLVTVSS

9. BCR/CD79-Binding Domains

[00214] The BCR is composed of a membrane immunoglobulin which, together with non-covalently associated α and β subunits of CD79 ("CD79a" and "CD79b,"

respectively), forms the BCR complex. CD79a and CD79b are signal transducing subunits that contain a conserved immunoreceptor tyrosine-based activation motif ("ITAM") required for signal transduction (Dylke, J. *et al.* (2007) "*Role Of The Extracellular And Transmembrane Domain Of Ig-Alpha/Beta In Assembly Of The B Cell Antigen Receptor (BCR)*," Immunol. Lett. 112(1):47-57; Cambier, J.C. (1995) "*New Nomenclature For The Reth Motif (or ARH1/TAM/ARAM/YXXL)*," Immunol. Today 16:110). Aggregation of the BCR complex by multivalent antigen initiates transphosphorylation of the CD79a and CD79b ITAMs and activation of receptor-associated kinases (DeFranco, A.L. (1997) "*The Complexity Of Signaling Pathways Activated By The BCR*," Curr. Opin. Immunol. 9:296-308; Kurosaki, T. (1997) "*Molecular Mechanisms In B Cell Antigen Receptor Signaling*," Curr. Opin. Immunol. 9:309-318; Kim, K.M. *et al.* (1993) "*Signalling Function Of The B-Cell Antigen Receptors*," Immun. Rev. 132:125-146). Phosphorylated ITAMs recruit additional effectors such as PI_3K, PLC-γ and members of the Ras/MAPK pathway. These signaling events are responsible for both the B cell proliferation and increased expression of activation markers (such as MHCII and CD86) that are required to prime B cells for their subsequent interactions with T helper ("T_h") cells.

[00215] A preferred sequence for the VL domain of an antibody that binds to the human B Cell Receptor (CD79) is CD79 mAb 1 (**SEQ ID NO:130**) (CDR residues are shown underlined):

DVVMTQTPLT LSVNIGQPAS ISC**KSSQSLL DTDGKTYLN**W LLQRPQGSPN
RLIY**LVSKLD S**GVPDRFTGS GSGTDFTLKI SRVEAEDLGI YYC**WQGTHFP**
LTFGAGTKLE LK

[00216] A preferred sequence for the VH domain of the CD79 mAb 1 antibody that binds to the human B Cell Receptor (CD79) is (**SEQ ID NO:131**) (CDR residues are shown underlined):

QVQLQQPGAE LVRPGASVKL SCKA**SGYTFT SYWMN**WVKQR PGQGLEWIG**M**
VDPSDSETHY NQMFKDKATL TVDKSSSTAY MQLSSLTSED SAVYYCARAM
GYWGQGTSVT VSS

10. T Cell Receptor-Binding Domains

[00217] In an alternate embodiment, the second epitope that is bound by the Tri-Specific Binding Molecules of the present invention will be an epitope of the T cell

Receptor (TCR). The T cell Receptor is natively expressed by CD4+ or CD8+ T cells, and permits such cells to recognize antigenic peptides that are bound and presented by class I or class II MHC proteins of antigen presenting cells. Recognition of a pMHC (peptide–MHC) complex by a TCR initiates the propagation of a cellular immune response that leads to the production of cytokines and the lysis of the antigen presenting cell (see, *e.g.*, Armstrong, K.M. *et al.* (2008) "*Conformational Changes And Flexibility In T-Cell Receptor Recognition Of Peptide–MHC Complexes*," Biochem. J. 415(Pt 2):183–196; Willemsen, R. (2008) "*Selection Of Human Antibody Fragments Directed Against Tumor T-Cell Epitopes For Adoptive T-Cell Therapy*," Cytometry A. 73(11):1093-1099; Beier, K.C. *et al.* (2007) "*Master Switches Of T-Cell Activation And Differentiation*," Eur. Respir. J. 29:804-812; Mallone, R. *et al.* (2005) "*Targeting T Lymphocytes For Immune Monitoring And Intervention In Autoimmune Diabetes*," Am. J. Ther. 12(6):534–550). CD3 is the receptor that binds to the TCR (Thomas, S. *et al.* (2010) "*Molecular Immunology Lessons From Therapeutic T-Cell Receptor Gene Transfer*," Immunology 129(2):170-177; Guy, C.S. *et al.* (2009) "*Organization Of Proximal Signal Initiation At The TCR:CD3 Complex*," Immunol. Rev. 232(1):7-21; St. Clair, E.W. (Epub 2009 Oct 12) "*Novel Targeted Therapies For Autoimmunity*," Curr. Opin. Immunol. 21(6):648-657; Baeuerle, P.A. *et al.* (Epub 2009 Jun 9) "*Bi-specific T-Cell Engaging Antibodies For Cancer Therapy*," Cancer Res. 69(12):4941-4944; Smith-Garvin, J.E. *et al.* (2009) "*T Cell Activation*," Annu. Rev. Immunol. 27:591-619; Renders, L. *et al.* (2003) "*Engineered CD3 Antibodies For Immunosuppression*," Clin. Exp. Immunol. 133(3):307-309).

[00218] Antibodies that specifically bind to the T cell Receptor include the anti-TCR antibody BMA 031 (EP 0403156; Kurrle, R. *et al.* (1989) "*BMA 031 – A TCR-Specific Monoclonal Antibody For Clinical Application*," Transplant Proc. 21(1 Pt 1):1017-1019; Nashan, B. *et al.* (1987) "Fine Specificity Of A Panel Of Antibodies Against The TCR/CD3 Complex," Transplant Proc. 19(5):4270-4272; Shearman, C.W. *et al.* (1991) "Construction, Expression, And Biologic Activity Of Murine/Human Chimeric Antibodies With Specificity For The Human α/β T Cell," J. Immunol. 146(3):928-935; Shearman, C.W. *et al.* (1991) "*Construction, Expression And Characterization of Humanized Antibodies Directed Against The Human α/β T Cell Receptor*," J. Immunol. 147(12):4366-4373).

[00219] The amino acid sequence of the VL Domain of anti-TCR antibody BMA 031 is (**SEQ ID NO:132**) (CDR residues are shown underlined):

EIVLTQSPAT LSLSPGERAT LSC**SATSSVS YMH**WYQQKPG KAPKRWIY**DT SKLAS**GVPSR FSGSGSGTEF TLTISSLQPE DFATYYC**QQW SSNPLT**FGQG TKLEIK

[00220] The amino acid sequence of a VH Domain of anti-TCR antibody BMA 031 is (**SEQ ID NO:133**) (CDR residues are shown underlined):

QVQLVQSGAE VKKPGASVKV SCKASGYKFT **SYVMH**WVRQA PGQGLEWIG**Y INPYNDVTKY NEKFKG**RVTI TADKSTSTAY LQMNSLRSED TAVHYCAR**GS YYDYDGFVY**W GQGTLVTVSS

11. NKG2D Receptor-Binding Domains

[00221] In an alternate embodiment, the second epitope that is bound by the Tri-Specific Binding Molecules of the present invention will be an epitope of the NKG2D receptor. The NKG2D receptor is expressed on all human (and other mammalian) Natural Killer cells (Bauer, S. *et al.* (1999) "*Activation Of NK Cells And T Cells By NKG2D, A Receptor For Stress-Inducible MICA*," Science 285(5428):727-729; Jamieson, A.M. *et al.* (2002) "*The Role Of The NKG2D Immunoreceptor In Immune Cell Activation And Natural Killing*," Immunity 17(1):19-29) as well as on all $CD8^+$ T cells (Groh, V. *et al.* (2001) "*Costimulation Of CD8αβ T Cells By NKG2D Via Engagement By MIC Induced On Virus-Infected Cells*," Nat. Immunol. 2(3):255-260; Jamieson, A.M. *et al.* (2002) "*The Role Of The NKG2D Immunoreceptor In Immune Cell Activation And Natural Killing*," Immunity 17(1):19-29). Such binding ligands, and particularly those which are not expressed on normal cells, include the histocompatibility 60 (H60) molecule, the product of the retinoic acid early inducible gene-1 (RAE-1), and the murine UL16-binding proteinlike transcript 1 (MULT1) (Raulet D.H. (2003) "*Roles Of The NKG2D Immunoreceptor And Its Ligands*," Nature Rev. Immunol. 3:781-790; Coudert, J.D. *et al.* (2005) "*Altered NKG2D Function In NK Cells Induced By Chronic Exposure To Altered NKG2D Ligand-Expressing Tumor Cells*," Blood 106:1711-1717). Antibodies that specifically bind to the NKG2D Receptor include KYK-2.0 (Kwong, KY *et al.* (2008) "*Generation, Affinity Maturation, And Characterization Of A Human Anti-Human NKG2D Monoclonal Antibody With Dual Antagonistic And Agonistic Activity*," J. Mol. Biol. 384:1143-1156; and PCT/US09/54911).

[00222] The amino acid sequence of the VL Domain of anti-NKG2D antibody KYK-1.0 is (**SEQ ID NO:134**) (CDR residues are shown underlined):

QPVLTQPSSV SVAPGETARI PC**GGDDIETK SVH**WYQQKPG QAPVLVIY**DD DDRPS**GIPER FFGSNSGNTA TLSISRVEAG DEADYYC**QVW DDNNDEWV**FG GGTQLTVL

[00223] The amino acid sequence of the VH Domain of anti-NKG2D antibody KYK-1.0 is (**SEQ ID NO:135**) (CDR residues are shown underlined):

EVQLVESGGG VVQPGGSLRL SCAASGFTFS **SYGMH**WVRQA PGKGLEWVA**F IRYDGSNKYY ADSVKG**RFTI SRDNSKNTKY LQMNSLRAED TAVYYCAK**DR FGYYLDY**WGQ GTLVTVSS

[00224] The amino acid sequence of a VL Domain of anti-NKG2D antibody KYK-2.0 is (**SEQ ID NO:136**) (CDR residues are shown underlined):

QSALTQPASV SGSPGQSITI SC**SGSSSNIG NNAVN**WYQQL PGKAPKLLIY **YDDLLPS**GVS DRFSGSKSGT SAFLAISGLQ SEDEADYYC**A AWDDSLNGPV** FGGGTKLTVL

[00225] The amino acid sequence of a VH Domain of anti-NKG2D antibody KYK-2.0 is (**SEQ ID NO:137**) (CDR residues are shown underlined):

QVQLVESGGG LVKPGGSLRL SCAASGFTFS **SYGMH**WVRQA PGKGLEWVA**F IRYDGSNKYY ADSVKG**RFTI SRDNSKNTLY LQMNSLRAED TAVYYCAK**DR GLGDGTYFDY** WGQGTTVTVS S

D. Preferred Trispecific Binding Molecules of the Present Invention

1. Preferred Fc Domains

[00226] The CH2 and CH3 Domains of the two heavy chains interact to form the **Fc Domain**, which is a domain that is recognized by cellular **Fc Receptors (FcγRs)**. As used herein, the term "Fc Domain" is used to define a C-terminal region of an IgG heavy chain. The amino acid sequence of the CH2-CH3 domain of an exemplary human IgG1 is (**SEQ ID NO:1**):

| CH2 →

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APELLGGPS  VFLFPPKPKD  TLMISRTPEV  TCVVVDVSHE  DPEVKFNWYV  DGVEVHNAKT
231        240         250         260         270         280

                                                ←CH2 | CH3→
KPREEQYNST  YRVVSVLTVL  HQDWLNGKEY  KCKVSNKALP  APIEKTISKA  K  GQPREPQVY
290         300         310         320         330         340

TLPPSREEMT  KNQVSLTCLV  KGFYPSDIAV  EWESNGQPEN  NYKTTPPVLD  SDGSFFLYSK
350         360         370         380         390         400

                                    ←CH3 |
LTVDKSRWQQ  GNVFSCSVMH  EALHNHYTQK  SLSLSPGK
410         420         430         440
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[00227] Throughout the present specification, the numbering of the residues in an IgG heavy chain is that of the EU index as in Kabat *et al.,* Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, NH1, MD (1991), expressly incorporated herein by references. The "EU index as in Kabat" refers to the numbering of the human IgG1 EU antibody. Amino acids from the variable regions of the mature heavy and light chains of immunoglobulins are designated by the position of an amino acid in the chain. Kabat described numerous amino acid sequences for antibodies, identified an amino acid consensus sequence for each subgroup, and assigned a residue number to each amino acid. Kabat's numbering scheme is extendible to antibodies not included in his compendium by aligning the antibody in question with one of the consensus sequences in Kabat by reference to conserved amino acids. This method for assigning residue numbers has become standard in the field and readily identifies amino acids at equivalent positions in different antibodies, including chimeric or humanized variants. For example, an amino acid at position 50 of a human antibody light chain occupies the equivalent position to an amino acid at position 50 of a mouse antibody light chain.

[00228] Although boundaries may vary slightly, the CH2 domain of a human IgG Fc Domain usually extends from amino acids 231 to amino acid 341 of a human IgG according to the numbering system of Kabat. The CH3 domain of a human IgG usually extends from amino acids 342 to 447 according to the numbering system of Kabat. The "hinge region" or "hinge domain" is generally defined as stretching from Glu216 to Pro230 of human IgG1.

[00229] Polymorphisms have been observed at a number of different positions within antibody constant regions (*e.g.*, Fc positions, including but not limited to positions 270, 272, 312, 315, 356, and 358 as numbered by the EU index as set forth in Kabat), and thus slight differences between the presented sequence and sequences in the prior art can exist. Polymorphic forms of human immunoglobulins have been well-characterized. At present, 18 Gm allotypes are known: G1m (1, 2, 3, 17) or G1m (a, x, f, z), G2m (23) or G2m (n), G3m (5, 6, 10, 11, 13, 14, 15, 16, 21, 24, 26, 27, 28) or G3m (b1, c3, b3, b0, b3, b4, s, t, g1, c5, u, v, g5) (Lefranc, *et al.*, The human IgG subclasses: molecular analysis of structure, function and regulation. Pergamon, Oxford, pp. 43-78 (1990); Lefranc, G. *et al.*, 1979, Hum. Genet.: 50, 199-211). It is specifically contemplated that the antibodies of the present invention may be incorporate any allotype, isoallotype, or haplotype of any immunoglobulin gene, and are not limited to the allotype, isoallotype or haplotype of the sequences provided herein.

[00230] Activating and inhibitory signals are transduced through the Fc Receptors (FcγRs) following their ligation to an Fc Domain. These diametrically opposing functions result from structural differences among the different receptor isoforms. Two distinct domains within the cytoplasmic signaling domains of the receptor called immunoreceptor tyrosine-based activation motifs (ITAMs) or immunoreceptor tyrosine-based inhibitory motifs (ITIMS) account for the different responses. The recruitment of different cytoplasmic enzymes to these structures dictates the outcome of the FcγR-mediated cellular responses. ITAM-containing FcγR complexes include FcγRI, FcγRIIA, FcγRIIIA, whereas ITIM-containing complexes only include FcγRIIB. Human neutrophils express the FcγRIIA gene. FcγRIIA clustering via immune complexes or specific antibody cross-linking serves to aggregate ITAMs along with receptor-associated kinases which facilitate ITAM phosphorylation. ITAM phosphorylation serves as a docking site for Syk kinase, activation of which results in activation of downstream substrates (*e.g.*, PI_3K). Cellular activation leads to release of proinflammatory mediators. The FcγRIIB gene is expressed on B lymphocytes; its extracellular domain is 96% identical to FcγRIIA and binds IgG complexes in an indistinguishable manner. The presence of an ITIM in the cytoplasmic domain of FcγRIIB defines this inhibitory subclass of FcγR. Recently

the molecular basis of this inhibition was established. When co-ligated along with an activating FcγR, the ITIM in FcγRIIB becomes phosphorylated and attracts the SH2 domain of the inositol polyphosphate 5'-phosphatase (SHIP), which hydrolyzes phosphoinositol messengers released as a consequence of ITAM-containing FcγR-mediated tyrosine kinase activation, consequently preventing the influx of intracellular Ca^{++}. Thus cross-linking of FcγRIIB dampens the activating response to FcγR ligation and inhibits cellular responsiveness. B cell activation, B cell proliferation and antibody secretion is thus aborted.

[00231] The Fc Domain of the binding molecules of the present invention may be either a complete Fc Domain (*e.g.*, a complete IgG Fc Domain) or only a fragment of a complete Fc Domain. Although the Fc Domain of the bi-specific monovalent Fc diabodies of the present invention may possess the ability to bind to one or more Fc receptors (*e.g.*, FcγR(s)), more preferably such Fc Domain will cause altered binding to FcγRIA (CD64), FcγRIIA (CD32A), FcγRIIB (CD32B), FcγRIIIA (CD16a) or FcγRIIIB (CD16b) (relative to the binding exhibited by a wild-type Fc Domain) or will substantially eliminate the ability of such Fc Domain to bind to inhibitory receptor(s). Thus, the Fc Domain of the Fc Domain-containing diabodies of the present invention may include some or all of the CH2 Domain and/or some or all of the CH3 Domain of a complete Fc Domain, or may comprise a variant CH2 and/or a variant CH3 sequence (that may include, for example, one or more insertions and/or one or more deletions with respect to the CH2 or CH3 domains of a complete Fc Domain). Such Fc Domains may comprise non-Fc polypeptide portions, or may comprise portions of non-naturally complete Fc Domains, or may comprise non-naturally occurring orientations of CH2 and/or CH3 domains (such as, for example, two CH2 domains or two CH3 Domains, or in the N-terminal to C-terminal direction, a CH3 Domain linked to a CH2 Domain, etc.).

[00232] Fc Domain modifications identified as altering effector function are known in the art, including modifications that increase binding to activating receptors (*e.g.*, FcγRIIA (CD16A) and reduce binding to inhibitory receptors (*e.g.*, FcγRIIB (CD32B) (see, *e.g.*, Stavenhagen, J.B. *et al.* (2007) "*Fc Optimization Of Therapeutic Antibodies Enhances Their Ability To Kill Tumor Cells In Vitro And Controls Tumor Expansion*

In Vivo Via Low-Affinity Activating Fcgamma Receptors," Cancer Res. 57(18):8882-8890).

[00233] In particular, it is preferred for the CH2-CH3 domains of the polypeptide chains of the Fc Domain-containing diabodies of the present invention to exhibit decreased (or substantially no) binding to FcγRIA (CD64), FcγRIIA (CD32A), FcγRIIB (CD32B), FcγRIIIA (CD16a) or FcγRIIIB (CD16b) (relative to the binding exhibited by the wild-type Fc Domain (**SEQ ID NO:1**). Fc variants and mutant forms capable of mediating such altered binding are described above. In a preferred embodiment the CH2-CH3 Domain of the first and/or third polypeptide chains of such diabodies include any 1, 2, 3, 4, 5, 6, or 7 of the substitutions: L234A, L235A, F243L, R292P, Y300L, V305I and P396L. Exemplary variants of human IgG1 Fc Domains with reduced binding to CD32B and/or increased binding to CD16A contain F243L, R292P, Y300L, V305I or P296L substitutions. These amino acid substitutions may be present in a human IgG1 Fc Domain in any combination. In one embodiment, the human IgG1 Fc Domain variant contains a F243L, R292P and Y300L substitution. In another embodiment, the human IgG1 Fc Domain variant contains a F243L, R292P, Y300L, V305I and P296L substitution. In one embodiment the CH2-CH3 Domain of the first and/or third polypeptide chains of such diabodies include any 1, 2, or 3, of the substitutions: L234A, L235A, N297G, N297Q. In another embodiment, the human IgG1 Fc Domain variant contains an N297Q substitution, L234A and L235A substitutions or a D265A substitution, as these mutations abolish FcR binding. Alternatively, a CH2-CH3 domain which inherently exhibits decreased (or substantially no) binding to FcγRIIIA (CD16a) and/or reduced effector function (relative to the binding exhibited by the wild-type IgG1 Fc Domain (**SEQ ID NO:1**)) is utilized. In a specific embodiment, the Fc Domain-containing diabodies of the present invention comprise an IgG2 Fc Domain or an IgG4 Fc Domain. Where an IgG4 Fc Domain in utilized the instant invention also encompasses the introduction of a stabilizing mutation such as S228P, as numbered by the EU index as set forth in Kabat (Lu *et al.*, (2008) "*The Effect Of A Point Mutation On The Stability Of Igg4 As Monitored By Analytical Ultracentrifugation*," J Pharmaceutical Sciences 97:960-969) to reduce the incidence of strand exchange. Other stabilizing mutations known in the art may be introduced into an IgG4 Fc Domain (Peters, P et al., (2012)

"*Engineering an Improved IgG4 Molecule with Reduced Disulfide Bond Heterogeneity and Increased Fab Domain Thermal Stability*," J. Biol. Chem., 287:24525-24533; PCT Patent Publication No: WO 2008/145142). Since the N297A, L234A, L235A and D265A substitutions abolish effector function, in circumstances in which effector function is desired, these substitutions would preferably not be employed.

[00234] The CH2 and/or CH3 Domains of such polypeptide chains need not be identical in sequence, and advantageously are modified to foster complexing between the two polypeptide chains. For example, an amino acid substitution (preferably a substitution with an amino acid comprising a bulky side group forming a "knob", *e.g.,* tryptophan) can be introduced into the CH2 or CH3 Domain such that steric interference will prevent interaction with a similarly mutated domain and will obligate the mutated domain to pair with a domain into which a complementary, or accommodating mutation has been engineered, *i.e.*, "the hole" (*e.g.*, a substitution with glycine). Such sets of mutations can be engineered into any two of the polypeptides of the Tri-Specific Binding Molecule. Methods of protein engineering to favor heterodimerization over homodimerization are well-known in the art, in particular with respect to the engineering of immunoglobulin-like molecules, and are encompassed herein (see *e.g.,* Ridgway *et al.* (1996) *"'Knobs-Into-Holes' Engineering Of Antibody CH3 Domains For Heavy Chain Heterodimerization,"* Protein Engr. 9:617-621, Atwell *et al.* (1997) *"Stable Heterodimers From Remodeling The Domain Interface Of A Homodimer Using A Phage Display Library,"* J. Mol. Biol. 270: 26-35, and Xie *et al.* (2005) *"A New Format Of Bi-specific Antibody: Highly Efficient Heterodimerization, Expression And Tumor Cell Lysis,"* J. Immunol. Methods 296:95-101; each of which is hereby incorporated herein by reference in its entirety). Preferably the "knob" is engineered into the CH2-CH3 Domains of the first polypeptide chain and the "hole" is engineered into the CH2-CH3 Domains of the other CH2-CH3-containing polypeptide chain. Thus, the "knob" will help in preventing the first polypeptide chain from homodimerizing via its CH2 and/or CH3 Domains. The CH2-CH3 "hole-bearing" polypeptide chain will heterodimerize with the CH2-CH3 "knob-bearing" polypeptide chain, and will also homodimerize with itself. A preferred knob is created by modifying a native IgG Fc

Domain to contain the modification T366W. A preferred hole is created by modifying a native IgG Fc Domain to contain the modification T366S, L368A and Y407V. To aid in purifying the "hole-bearing" polypeptide chain homodimer from the final Tri-Specific Binding Molecule, the protein A binding site of the CH2 and CH3 Domains of the "hole-bearing" Fc Domain is preferably mutated by amino acid substitution at position 435 (H435R). Thus, the "hole-bearing" Fc Domain homodimer will not bind to protein A, whereas the desired Tri-Specific Binding Molecule will retain its ability to bind protein A via the protein A binding site on the first polypeptide chain.

[00235] A preferred sequence for the CH2 and CH3 Domains of the first polypeptide chain of an Fc Domain-containing diabody of the present invention will have the "**knob-bearing**" sequence (**SEQ ID NO:52**):

APE**AA**GGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSL**W**C**L**VK GFYPSDIAVE
WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE
ALHN**H**YTQKS LSLSPGK

[00236] A preferred sequence for the CH2 and CH3 Domains of the second polypeptide chain of an Fc Domain-containing diabody of the present invention having two polypeptide chains (or the third polypeptide chain of an Fc Domain-containing diabody having three polypeptide chains) will have the "**hole-bearing**" sequence (**SEQ ID NO:53**):

APE**AA**GGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSL**S**C**A**VK GFYPSDIAVE
WESNGQPENN YKTTPPVLDS DGSFFL**V**SKL TVDKSRWQQG NVFSCSVMHE
ALHN**R**YTQKS LSLSPGK

[00237] As will be noted, the CH2-CH3 Domains of **SEQ ID NO:52** and **SEQ ID NO:53** include a substitution at position 234 with alanine and 235 with alanine, and thus form an Fc Domain exhibit decreased (or substantially no) binding to FcγRIA (CD64), FcγRIIA (CD32A), FcγRIIB (CD32B), FcγRIIIA (CD16a) or FcγRIIIB (CD16b) (relative to the binding exhibited by the wild-type Fc Domain (**SEQ ID NO:1**).

[00238] It is preferred that the first polypeptide chain will have a "knob-bearing" CH2-CH3 sequence, such as that of **SEQ ID NO:52**. However, as will be recognized, a "hole-bearing" CH2-CH3 Domain (*e.g.*, **SEQ ID NO:53**) could be employed in the first polypeptide chain, in which case, a "knob-bearing" CH2-CH3 Domain (*e.g.*, **SEQ ID NO:52**) would be employed in the second polypeptide chain of an Fc Domain-containing diabody of the present invention having two polypeptide chains (or the third polypeptide chain of an Fc Domain-containing diabody having three polypeptide chains).

2. Preferred First Polypeptide Chain

[00239] A first polypeptide chain of a preferred binding molecule of the present invention will comprise a Variable Light Chain Domain capable of binding to Epitope I (**VL_I**), a Variable Heavy Chain Domain capable of binding to Epitope II (**VH_{II}**), a Heterodimer-Promoting Domain and a CH2-CH3 Domain.

[00240] Since the Variable Light Chain and Variable Heavy Chain Domains of the first polypeptide are directed toward different epitopes, they cannot associate together to form a Binding Domain that is able to bind either Epitope I or Epitope II. The Variable Light Chain and Variable Heavy Chain Domains of the first polypeptide are spaced apart from one another by an intervening linker peptide that is sufficiently short as to substantially prevent the association of these Domains. An exemplary linker, termed "**Linker 1**," has the sequence (**SEQ ID NO:33**): GGGSGGGG.

[00241] The Variable Heavy Chain Domain of the first polypeptide and the Heterodimer-Promoting Domain of that polypeptide are preferably spaced apart from one another by an intervening linker peptide that contains 1, 2, 3 or more cysteine residues. A preferred cysteine-containing spacer peptide ("Linker 2") has the sequence is **SEQ ID NO:34**: GGCGGG.

[00242] Linkers that may be employed to link a CH2-CH3 Domain to a polypeptide chain of the molecules of the present invention include: ASTKG (**SEQ ID NO:47**), DKTHTCPPCP (**SEQ ID NO:48**), LEPKSS (**SEQ ID NO:49**), and APSSSPME (**SEQ ID NO:50**), APSSS (**SEQ ID NO:152**) and GGG or GCG. **SEQ**

ID NO:49 may be used in lieu of GGG or GCG for ease of cloning. Additionally, **SEQ ID NO:49** may be immediately followed by **SEQ ID NO:47** to form an alternate linker (LEPKSSDKTHTCPPCP; **SEQ ID NO:51)**.

[00243] The Heterodimer-Promoting Domain of the first polypeptide and the Heterodimer-Promoting Domain of the second polypeptide are coordinately selected. The Domains differ from one another and are designed to associate with one another so as to promote the association of the first and second polypeptide chains. For example, one of the Heterodimer-Promoting Domains will be engineered to have a negative charge at pH 7, while the other of the two polypeptide chains will be engineered to have a positive charge at pH 7. The presence of such charged Domains promotes association between the first and second polypeptides, and thus fosters heterodimerization. It is immaterial which Heterodimer-Promoting Domains is provided to which chain, as long as the Domains employed on the first and second polypeptide chains differ so as to foster heterodimerization between such chains.

[00244] The Heterodimer-Promoting Domains may be the IgG CL and CH1 domains or may be a peptide having the amino acid sequence GVEPKSC **(SEQ ID NO:35)** or VEPKSC **(SEQ ID NO:36)**, derived from the hinge domain of a human IgG, and in lieu of the CL domain, one may employ the C-terminal 6 amino acids of the human kappa light chain, GFNRGEC **(SEQ ID NO:37)** or FNRGEC **(SEQ ID NO:38)**.

[00245] More preferably, however, the Heterodimer-Promoting Domains of such diabodies are formed from one, two, three or four tandemly repeated coil domains of opposing charge that comprise a sequence of at least six, at least seven or at least eight charged amino acid residues (Apostolovic, B. *et al.* (2008) "*pH-Sensitivity of the E3/K3 Heterodimeric Coiled Coil*," Biomacromolecules 9:3173–3180; Arndt, K.M. *et al.* (2001) "*Helix-stabilized Fv (hsFv) Antibody Fragments: Substituting the Constant Domains of a Fab Fragment for a Heterodimeric Coiled-coil Domain*," J. Molec. Biol. 312:221-228; Arndt, K.M. *et al.* (2002) "*Comparison of In Vivo Selection and Rational Design of Heterodimeric Coiled Coils*," Structure 10:1235-1248; Boucher, C. *et al.* (2010) "*Protein Detection By Western Blot Via Coiled–Coil Interactions*,"

Analytical Biochemistry 399:138-140; Cachia, P.J. *et al.* (2004) "*Synthetic Peptide Vaccine Development: Measurement Of Polyclonal Antibody Affinity And Cross-Reactivity Using A New Peptide Capture And Release System For Surface Plasmon Resonance Spectroscopy*," J. Mol. Recognit. 17:540-557; De Crescenzo, G.D. *et al.* (2003) "*Real-Time Monitoring of the Interactions of Two-Stranded de novo Designed Coiled-Coils: Effect of Chain Length on the Kinetic and Thermodynamic Constants of Binding*," Biochemistry 42:1754-1763; Fernandez-Rodriquez, J. *et al.* (2012) "*Induced Heterodimerization And Purification Of Two Target Proteins By A Synthetic Coiled-Coil Tag*," Protein Science 21:511-519; Ghosh, T.S. *et al.* (2009) "*End-To-End And End-To-Middle Interhelical Interactions: New Classes Of Interacting Helix Pairs In Protein Structures*," Acta Crystallographica D65:1032-1041; Grigoryan, G. *et al.* (2008) "*Structural Specificity In Coiled-Coil Interactions*," Curr. Opin. Struc. Biol. 18:477-483; Litowski, J.R. *et al.* (2002) "*Designing Heterodimeric Two-Stranded α-Helical Coiled-Coils: The Effects Of Hydrophobicity And α-Helical Propensity On Protein Folding, Stability, And Specificity*," J. Biol. Chem. 277:37272-37279; Steinkruger, J.D. *et al.* (2012) "*The d'--d--d' Vertical Triad is Less Discriminating Than the a'--a--a' Vertical Triad in the Antiparallel Coiled-coil Dimer Motif*," J. Amer. Chem. Soc. 134(5):2626–2633; Straussman, R. *et al.* (2007) "*Kinking the Coiled Coil – Negatively Charged Residues at the Coiled-coil Interface*," J. Molec. Biol. 366:1232-1242; Tripet, B. *et al.* (2002) "*Kinetic Analysis of the Interactions between Troponin C and the C-terminal Troponin I Regulatory Region and Validation of a New Peptide Delivery/Capture System used for Surface Plasmon Resonance*," J. Molec. Biol. 323:345–362; Woolfson, D.N. (2005) "*The Design Of Coiled-Coil Structures And Assemblies*," Adv. Prot. Chem. 70:79-112; Zeng, Y. *et al.* (2008) "*A Ligand-Pseudoreceptor System Based On de novo Designed Peptides For The Generation Of Adenoviral Vectors With Altered Tropism*," J. Gene Med. 10:355-367).

[00246] Such repeated coil domains may be exact repeats or may have substitutions. For example, the Heterodimer-Promoting Domain of the first polypeptide chain may comprise a sequence of eight negatively charged amino acid residues and the Heterodimer-Promoting Domain of the second polypeptide chain may comprise a sequence of eight negatively charged amino acid residues. It is

immaterial which coil is provided to the first or second polypeptide chains, provided that a coil of opposite charge is used for the other polypeptide chain. The positively charged amino acid may be lysine, arginine, histidine, *etc.* and/or the negatively charged amino acid may be glutamic acid, aspartic acid, *etc.* The positively charged amino acid is preferably lysine and/or the negatively charged amino acid is preferably glutamic acid. It is possible for only a single Heterodimer-Promoting Domain to be employed (since such domain will inhibit homodimerization and thereby promote heterodimerization), however, it is preferred for both the first and second polypeptide chains of the diabodies of the present invention to contain Heterodimer-Promoting Domains.

[00247] In a preferred embodiment, one of the Heterodimer-Promoting Domains will comprise four tandem "E-coil" helical domains (**SEQ ID NO:39**: EVAALEK-EVAALEK-EVAALEK-EVAALEK), whose glutamate residues will form a negative charge at pH 7, while the other of the Heterodimer-Promoting Domains will comprise four tandem "K-coil" domains (**SEQ ID NO:40**: KVAALKE-KVAALKE-KVAALKE-KVAALKE), whose lysine residues will form a positive charge at pH 7. The presence of such charged domains promotes association between the first and second polypeptides, and thus fosters heterodimerization. Especially preferred is a Heterodimer-Promoting Domain in which one of the four tandem "E-coil" helical domains of **SEQ ID NO:39** has been modified to contain a cysteine residue: EVAACEK-EVAALEK-EVAALEK-EVAALEK (**SEQ ID NO:41**). Likewise, especially preferred is a Heterodimer-Promoting Domain in which one of the four tandem "K-coil" helical domains of **SEQ ID NO:40** has been modified to contain a cysteine residue: KVAACKE-KVAALKE-KVAALKE-KVAALKE (**SEQ ID NO:42**).

[00248] As disclosed in WO 2012/018687, in order to improve the *in vivo* pharmacokinetic properties of diabodies, a diabody may be modified to contain a polypeptide portion of a serum-binding protein at one or more of the termini of the diabody. Most preferably, such polypeptide portion of a serum-binding protein will be installed at the C-terminus of the diabody. Albumin is the most abundant protein in plasma and has a half-life of 19 days in humans. Albumin possesses several small molecule binding sites that permit it to non-covalently bind to other proteins and

thereby extend their serum half-lives. The Albumin-Binding Domain 3 (ABD3) of protein G of Streptococcus strain G148 consists of 46 amino acid residues forming a stable three-helix bundle and has broad albumin-binding specificity (Johansson, M.U. *et al.* (2002) "*Structure, Specificity, And Mode Of Interaction For Bacterial Albumin-Binding Module*s," J. Biol. Chem. 277(10):8114-8120. Thus, a particularly preferred polypeptide portion of a serum-binding protein for improving the *in vivo* pharmacokinetic properties of a diabody is the Albumin-Binding Domain (ABD) from streptococcal protein G, and more preferably, the Albumin-Binding Domain 3 (ABD3) of protein G of Streptococcus strain G148 (**SEQ ID NO:43**): LAEAKVLANR ELDKYGVSDY YKNLIDNAKS AEGVKALIDE ILAALP.

[00249] As disclosed in WO 2012/162068 (herein incorporated by reference), "**deimmunized**" variants of **SEQ ID NO:43** have the ability to attenuate or eliminate MHC class II binding. Based on combinational mutation results, the following combinations of substitutions are considered to be preferred substitutions for forming such a deimmunized albumin-binding domain: 66S/70S +71A; 66S/70S +79A; 64A/65A/71A+66S; 64A/65A/71A+66D; 64A/65A/71A+66E; 64A/65A/79A+66S; 64A/65A/79A+66D; 64A/65A/79A+66E. Variant ABDs having the modifications L64A, I65A and D79A or the modifications N66S, T70S and D79A. Variant deimmunized ABD having the amino acid sequence:

LAEAKVLANR ELDKYGVSDY YKN**A**$_{64}$**A**$_{65}$NNAKT VEGVKALI**A**$_{79}$E ILAALP (**SEQ ID NO: 44**),

or the amino acid sequence:

LAEAKVLANR ELDKYGVSDY YKNLI**S**$_{66}$NAK**S**$_{70}$ VEGVKALI**A**$_{79}$E ILAALP (**SEQ ID NO: 45**),

are particularly preferred as such deimmunized Albumin-Binding Domains exhibit substantially wild-type binding while providing attenuated MHC class II binding. Thus, the first polypeptide chain of such a diabody having an Albumin-Binding Domain contains a third linker (Linker 3) preferably positioned C-terminally to the E-coil (or K-coil) Domain of such polypeptide chain so as to intervene between the E-coil (or K-coil) Domain and the Albumin-Binding Domain (which is preferably a

deimmunized Albumin-Binding Domain). A preferred sequence for such Linker 3 is **SEQ ID NO:46**: GGGS.

[00250] Thus, in sum, a preferred first polypeptide chain of a preferred Tri-Specific Binding Molecule of the present invention will comprise the Domains and linkers: **(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(E-coil Heterodimer-Promoting Domain)—(Linker 3)—(Knob-Bearing CH2-CH3 Domain)**.

3. Alternative First Polypeptide Chain

[00251] In one embodiment, the orientations of the above-described Domains will be in the N-terminal to C-terminal direction. The present invention, however, also contemplates a variation thereof, wherein the orientations of the Domains of the first polypeptide chain are: **NH_2-(Knob-Bearing CH3-CH2 Domain)-(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(E-coil Heterodimer-Promoting Domain)**. Preferably, a cysteine-containing peptide is present, N-terminal to such CH2-CH3 Domain. The sequence of an exemplary peptide is sequence (**SEQ ID NO:48**): DKTHTCPPCP. Preferably in this embodiment, the CH3 Domain is spaced apart from the VL_I Domain by an intervening peptide linker (Linker 4), such as one having the amino acid sequence of (**SEQ ID NO:152**): APSSS, and more preferably, the amino acid sequence (**SEQ ID NO:50**): APSSSPME.

4. Preferred Second Polypeptide Chain

[00252] A second polypeptide chain of such preferred Tri-Specific Binding Molecules will comprise, in the N-terminal to C-terminal direction, a Variable Light Chain Domain capable of binding to Epitope II (**VL_{II}**), a Variable Heavy Chain Domain capable of binding to Epitope I (**VH_I**), and a Heterodimer-Promoting Domain.

[00253] Since the Variable Light Chain and Variable Heavy Chain Domains of the second polypeptide are directed toward different epitopes, they cannot associate together to form a Binding Domain that is able to bind either Epitope I or Epitope II. The Variable Light Chain and Variable Heavy Chain Domains of the second polypeptide are spaced apart from one another by an intervening linker peptide that is

sufficiently short as to substantially prevent the association of these Domains. "**Linker 1**," having the sequence (**SEQ ID NO:33**): GGGSGGGG is an exemplary linker for this purpose.

[00254] As in the case of the first polypeptide chain, the Variable Heavy Chain Domain of the second polypeptide and the Heterodimer-Promoting Domain of that polypeptide are preferably spaced apart from one another by an intervening linker peptide that contains 1, 2, 3 or more cysteine residues. "Linker 2," having the sequence (**SEQ ID NO:34**) GGCGGG is an exemplary linker for this purpose. Such cysteine residues can form disulfide bonds with cysteine residues in the cysteine-containing spacer peptide that separates the Variable Heavy Chain Domain of the first polypeptide and the Heterodimer-Promoting Domain of that polypeptide. Thus, the first and second polypeptides of the Binding Molecules of the present invention are covalently bonded to one another.

[00255] As discussed above, the Heterodimer-Promoting Domain of the second polypeptide chain is selected so as coordinate with the Heterodimer-Promoting Domain of the first polypeptide chain. Thus, in a preferred embodiment, the Heterodimer-Promoting Domain of the first polypeptide chain is either a "**K-coil**" Domain (**SEQ ID NO:40**) or an "**E-coil**" Domain (**SEQ ID NO:39**). If the cysteine-containing E-coil (**SEQ ID NO:41**) is employed in the first polypeptide chain, then the cysteine-containing K-coil (**SEQ ID NO:42**) is preferably employed in the second polypeptide chain. Conversely, if the cysteine-containing K-coil (**SEQ ID NO:42**) is employed in the first polypeptide chain, then the cysteine-containing E-coil (**SEQ ID NO:41**) is preferably employed in the second polypeptide chain. Since the first polypeptide chain will preferably possess an "**E-coil**" Domain, the second polypeptide chain will preferably contain a "**K-coil**" Domain.

[00256] As the first and second polypeptide chains are polypeptide chains of a diabody, they are able to associate together to form a Domain I Binding Domain (VL_A/VH_A) that recognizes and immunospecifically binds to Epitope I, and a Domain II Binding Domain (VL_B/VH_B) that recognizes and immunospecifically binds to Epitope II.

[00257] Thus, in sum, a preferred second polypeptide chain of a preferred Binding Molecule of the present invention will comprise the Domains and linkers: **(VL_{II} Domain)—(Linker 1)—(VH_{I} Domain)—(Linker 2)—(K-coil Heterodimer-Promoting Domain)**.

5. Preferred Third Polypeptide Chain

[00258] A third polypeptide chain of a preferred Binding Molecule of the present invention is a polypeptide that comprises, in the N-terminal to C-terminal direction, a Binding Domain, an optional CH1-Hinge Domain, and a CH2-CH3 Domain. The Binding Domain of the third polypeptide chain of a preferred Binding Molecule of the present invention may be a Variable Heavy Chain Domain capable of binding to Epitope III (**VH_{III}**), in which case, the fourth polypeptide chain of the preferred Binding Molecules of the present invention (discussed below) is a polypeptide that comprises a Variable Light Chain Domain capable of binding to Epitope III (**VL_{III}**), such that the Binding Domain is capable of immunospecific binding to an antigen possessing Epitope III. Alternatively, the Binding Domain of the third polypeptide chain of the preferred Binding Molecules of the present invention may comprise an Effector Cell Receptor-Type Binding Domain, in which case, the fourth polypeptide chain of the preferred Binding Molecules of the present invention (discussed below) is a polypeptide that comprises a complementary Effector Cell Receptor-Type Binding Domain, such that the interaction of two polypeptide chains forms a Binding Domain that is capable of physiospecific binding to molecule present on the surface of the effector cell. The third polypeptide chain may be isolated from naturally occurring antibodies. Alternatively, it may be constructed recombinantly. An exemplary CH1 Domain is a human IgG1 CH1 Domain having the amino acid sequence (**SEQ ID NO:207**):

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV
HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKV

[00259] A variant of the human IgG1 CH1 Domain of SEQ ID NO:207 is (**SEQ ID NO:208**):

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV
HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRV

[00260] An exemplary Hinge Domain is a human IgG1 Hinge Domain having the amino acid sequence (**SEQ ID NO:209**): EPKSCDKTHTCPPCP. As will be recognized, the exemplary Hinge Domain comprises multiple cysteine residues (Elkabetz *et al.* (2005) "*Cysteines In CH1 Underlie Retention Of Unassembled Ig Heavy Chains*," J. Biol. Chem. 280:14402-14412) that may participate in interchain covalent bonding.

[00261] Although a wild-type CH2-CH3 Domain may be employed, it is preferred, as described above, to employ a modified CH2-CH3 Domain that promotes heterodimerization with the CH2-CH3 Domain of the first polypeptide chain.

[00262] Preferably, therefore the CH2-CH3 Domain of the third polypeptide chain will be a "hole-bearing" CH2-CH3 Domain whose amino acid sequence is complementary to the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**) employed in the first polypeptide. As discussed above, the "hole-bearing" CH2-CH3 domain preferably should comprise a substitution at position 435 (H435R) to remove the Protein A binding site. An exemplary "hole-bearing" CH2-CH3 Domain with the H435R substitution for the third polypeptide is **SEQ ID NO:53**.

[00263] As will be recognized, a "knob-bearing" CH2-CH3 Domain (*e.g.*, **SEQ ID NO:52**) could be employed in the third polypeptide chain, in which case, a "hole-bearing" CH2-CH3 Domain (*e.g.*, **SEQ ID NO:53**) would be employed in the first polypeptide chain.

[00264] In the embodiment in which the third (and fourth) polypeptide chains of the preferred Tri-Specific Binding Molecules of the present invention each comprise a polypeptide chain of an Effector Cell Receptor-Type Binding Domain, methods for producing such Effector Cell Receptor-Type Binding Domains are well-known (*e.g.*, US2012/0294874A1).

[00265] Thus, in sum, a third polypeptide chain of the preferred Binding Molecules of the present invention will comprise the Domains and linkers: **(VH_{III} Domain)—(Optional CH1 Domain)—(Optional Hinge Domain)—("Hole-Bearing" CH2-CH3 Domain)**, or **(T Cell Receptor-Type Binding Domain; first or**

second polypeptide thereof)—(Optional CH1 Domain)—(Optional Hinge Domain)—("Hole-Bearing" CH2-CH3 Domain).

6. Preferred Fourth Polypeptide Chain

[00266] A fourth polypeptide chain of the preferred Tri-Specific Binding Molecules of the present invention is either a polypeptide of an Effector Cell Receptor-Type Binding Domain (wherein the third and fourth polypeptides form a ligand for a receptor found on the surface of an effector cell, or more preferably, a light chain of the above-indicated antibody that immunospecifically binds to Epitope III or which are complementary to the binding domain of the third polypeptide chain.

[00267] Thus, wherein the third and fourth polypeptides form a Fab-Type Binding Domain such fourth polypeptide chain comprises, in the N-terminal to C-terminal direction, a Variable Light Chain Domain capable of binding to Epitope III ($\mathbf{VL_{III}}$), and a Domain for promoting covalent bonding to the third polypeptide chain or a Binding Domain and such Domain for promoting covalent bonding to the third polypeptide chain. Such Domain may be a CL Domain, or a cysteine-containing portion thereof, such as **(SEQ ID NO:38)** FNRGEC or a linker such as Linker 2 (having the sequence **(SEQ ID NO:34)** GGCGGG. An exemplary a cysteine-containing peptide that forms disulfide bonds with such Linker 2 comprises the amino acid sequence VEPKSC **(SEQ ID NO:36)** or a Hinge Domain.

[00268] The fourth polypeptide chain may be isolated from naturally occurring antibodies. Alternatively, it may be constructed recombinantly. A preferred CL Domain is a human IgG1 CL Kappa Domain having the amino acid sequence (**SEQ ID NO:210**):

RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG
NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK
SFNRGEC

[00269] Alternatively, an exemplary CL Domain is a human IgG1 CL Lambda2 Domain having the amino acid sequence (**SEQ ID NO:211**):

QPKAAPSVTL FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA
GVETTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP
TECS

[00270] As will be noticed, the CL Domain, or other Cysteine-Containing Domain, of the fourth polypeptide chain comprises cysteine residues. Such cysteine residues are able to covalently bond to cysteine residues of the CH1 Domain of the third polypeptide chain to thereby covalently complex the third and fourth polypeptide chains of the binding molecules of the present invention to one another. Thus the third and fourth polypeptide chains are covalently bonded to one another.

[00271] Additionally, cysteine residues of the CH2-CH3 Domain of the first polypeptide chain can form disulfide bonds with cysteine residues of the CH2-CH3 Domain of the third polypeptide chain. Thus the first and third polypeptide chains are covalently bonded to one another.

E. Variant Fc Domains

[00272] In traditional immune function, the interaction of antibody-antigen complexes with cells of the immune system results in a wide array of responses, ranging from effector functions such as antibody-dependent cytotoxicity, mast cell degranulation, and phagocytosis to immunomodulatory signals such as regulating lymphocyte proliferation and antibody secretion. All of these interactions are initiated through the binding of the Fc Domain of antibodies or immune complexes to specialized cell surface receptors on hematopoietic cells. The diversity of cellular responses triggered by antibodies and immune complexes results from the structural heterogeneity of the three Fc receptors: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). FcγRI (CD64), FcγRIIA (CD32A) and FcγRIII (CD16) are activating (*i.e.*, immune system enhancing) receptors; FcγRIIB (CD32B) is an inhibiting (*i.e.*, immune system dampening) receptor. The amino acid sequence of an exemplary IgG1 Fc Domain (**SEQ ID NO:1**) is presented above.

[00273] Modification of the Fc Domain normally leads to an altered phenotype, for example altered serum half-life, altered stability, altered susceptibility to cellular enzymes or altered effector function. It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance the effectiveness of the antibody in treating cancer, for example. Reduction or elimination of effector function is desirable in certain cases, for example in the case of antibodies whose

mechanism of action involves blocking or antagonism, but not killing of the cells bearing a target antigen. Increased effector function is generally desirable when directed to undesirable cells, such as tumor and foreign cells, where the FcγRs are expressed at low levels, for example, tumor-specific B cells with low levels of FcγRIIB (*e.g.*, non-Hodgkins lymphoma, CLL, and Burkitt's lymphoma). In said embodiments, molecules of the invention with conferred or altered effector function activity are useful for the treatment and/or prevention of a disease, disorder or infection where an enhanced efficacy of effector function activity is desired.

[00274] In certain embodiments, the Tri-Specific Binding Molecules of the present invention comprise an Fc Domain that possesses one or more modifications (*e.g.*, substitutions, deletions, or insertions) to the sequence of amino acids of a wild-type Fc Domain (**SEQ ID NO:1**), which reduce the affinity and avidity of the Fc Domain and, thus, the molecule of the invention, for one or more FcγR receptors. In other embodiments, the molecules of the invention comprise an Fc Domain that possesses one or more modifications to the amino acids of the wild-type Fc Domain, which increase the affinity and avidity of the Fc Domain and, thus, the molecule of the invention, for one or more FcγR receptors. In other embodiments, the molecules comprise a variant Fc Domain wherein said variant confers or mediates increased ADCC activity and/or an increased binding to FcγRIIA, relative to a molecule comprising no Fc Domain or comprising a wild-type Fc Domain. In alternate embodiments, the molecules comprise a variant Fc Domain wherein said variant confers or mediates decreased ADCC activity (or other effector function) and/or an increased binding to FcγRIIB, relative to a molecule comprising no Fc Domain or comprising a wild-type Fc Domain. In some embodiments, the invention encompasses Tri-Specific Binding Molecules comprising a variant Fc Domain, which variant Fc Domain does not show a detectable binding to any FcγR, relative to a comparable molecule comprising the wild-type Fc Domain. In other embodiments, the invention encompasses Tri-Specific Binding Molecules comprising a variant Fc Domain, which variant Fc Domain only binds a single FcγR, preferably one of FcγRIIA, FcγRIIB, or FcγRIIIA. Any such increased affinity and/or avidity is preferably assessed by measuring *in vitro* the extent of detectable binding to the FcγR or FcγR-related activity in cells that express low levels of the FcγR when binding

activity of the parent molecule (without the modified Fc Domain) cannot be detected in the cells, or in cells which express non-FcγR receptor target antigens at a density of 30,000 to 20,000 molecules/cell, at a density of 20,000 to 10,000 molecules/cell, at a density of 10,000 to 5,000 molecules/cell, at a density of 5,000 to 1,000 molecules/cell, at a density of 1,000 to 200 molecules/cell or at a density of 200 molecules/cell or less (but at least 10, 50, 100 or 150 molecules/cell).

[00275] The Tri-Specific Binding Molecules of the present invention may comprise altered affinities for an activating and/or inhibitory Fcγ receptor. In one embodiment, the Tri-Specific Binding Molecule comprises a variant Fc Domain that has increased affinity for FcγRIIB and decreased affinity for FcγRIIIA and/or FcγRIIA, relative to a comparable molecule with a wild-type Fc Domain. In another embodiment, the Tri-Specific Binding Molecule of the present invention comprise a variant Fc Domain, which has decreased affinity for FcγRIIB and increased affinity for FcγRIIIA and/or FcγRIIA, relative to a comparable molecule with a wild-type Fc Domain. In yet another embodiment, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain that has decreased affinity for FcγRIIB and decreased affinity for FcγRIIIA and/or FcγRIIA, relative to a comparable molecule with a wild-type Fc Domain. In still another embodiment, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain, which has unchanged affinity for FcγRIIB and decreased (or increased) affinity for FcγRIIIA and/or FcγRIIA, relative to a comparable molecule with a wild-type Fc Domain.

[00276] In certain embodiments, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain having an altered affinity for FcγRIIIA and/or FcγRIIA such that the immunoglobulin has an enhanced effector function, e.g., antibody-dependent cell-mediated cytotoxicity. Non-limiting examples of effector cell functions include antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent phagocytosis, phagocytosis, opsonization, opsonophagocytosis, cell binding, rosetting, C1q binding, and complement dependent cell-mediated cytotoxicity.

[00277] In a preferred embodiment, the alteration in affinity or effector function is at least 2-fold, preferably at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 50-fold, or at least 100-fold, relative to a comparable molecule comprising a wild-type Fc Domain. In other embodiments of the invention, the variant Fc Domain immunospecifically binds one or more FcRs with at least 65%, preferably at least 70%, 75%, 80%, 85%, 90%, 95%, 100%, 125%, 150%, 175%, 200%, 225%, or 250% greater affinity relative to a molecule comprising a wild-type Fc Domain. Such measurements can be in vivo or in vitro assays, and in a preferred embodiment are in vitro assays such as ELISA or surface plasmon resonance assays.

[00278] In different embodiments, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain wherein said variant agonizes at least one activity of an FcγR receptor, or antagonizes at least one activity of an FcγR receptor. In a preferred embodiment, the molecules comprise a variant that antagonizes one or more activities of FcγRIIB, for example, B cell receptor-mediated signaling, activation of B cells, B cell proliferation, antibody production, intracellular calcium influx of B cells, cell cycle progression, FcγRIIB-mediated inhibition of FcεRI signaling, phosphorylation of FcγRIIB, SHIP recruitment, SHIP phosphorylation and association with Shc, or activity of one or more downstream molecules (e.g., MAP kinase, JNK, p38, or Akt) in the FcγRIIB signal transduction pathway. In another embodiment, the Tri-Specific Binding Molecules of the present invention comprise a variant that agonizes one or more activities of FcεRI, for example, mast cell activation, calcium mobilization, degranulation, cytokine production, or serotonin release.

[00279] In certain embodiments, the molecules comprise an Fc Domain comprising regions from two or more IgG isotypes (*e.g.*, IgG1, IgG2, IgG3 and IgG4). The various IgG isotypes exhibit differing physical and functional properties including serum half-life, complement fixation, FcγR binding affinities and effector function activities (e.g., ADCC, CDC, *etc.*) due to differences in the amino acid sequences of their hinge and/or Fc Domains, for example as described in Flesch and Neppert (1999) J. Clin. Lab. Anal. 14:141-156; Chappel *et al.* (1993) J. Biol. Chem. 33:25124-

25131; Chappel *et al.* (1991) Proc. Natl. Acad. Sci. (U.S.A.) 88:9036-9040; or Brüggemann *et al.* (1987) J. Exp. Med 166:1351-1361. This type of variant Fc Domain may be used alone, or in combination with an amino acid modification, to affect Fc-mediated effector function and/or binding activity. In combination, the amino acid modification and IgG hinge/Fc Domain may display similar functionality (e.g., increased affinity for FcγRIIA) and may act additively or, more preferably, synergistically to modify the effector functionality in the molecule of the invention, relative to a molecule of the invention comprising a wild-type Fc Domain. In other embodiments, the amino acid modification and IgG Fc Domain may display opposite functionality (e.g., increased and decreased affinity for FcγRIIA, respectively) and may act to selectively temper or reduce a specific functionality in the molecule of the invention, relative to a molecule of the invention not comprising an Fc Domain or comprising a wild-type Fc Domain of the same isotype.

[00280] In a preferred specific embodiment, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain, wherein said variant Fc Domain comprises at least one amino acid modification relative to a wild-type Fc Domain, such that said molecule has an altered affinity for an FcR, provided that said variant Fc Domain does not have a substitution at positions that make a direct contact with FcγR based on crystallographic and structural analysis of Fc-FcR interactions such as those disclosed by Sondermann *et al.* (2000) Nature 406:267-73. Examples of positions within the Fc Domain that make a direct contact with FcγR are amino acid residues 234-239 (hinge region), amino acid residues 265-269 (B/C loop), amino acid residues 297-299 (C'/E loop), and amino acid residues 327-332 (F/G loop). In some embodiments, the molecules of the invention comprise variant Fc Domains comprise modification of at least one residue that does not make a direct contact with an FcγR based on structural and crystallographic analysis, e.g., is not within the Fc-FcγR binding site.

[00281] Variant Fc Domains are well-known in the art, and any known Fc variant may be used in the present invention to confer or modify the effector function exhibited by a molecule of the invention comprising an Fc Domain (or portion thereof) as functionally assayed, e.g., in an NK dependent or macrophage dependent

assay. For example, Fc Domain variants identified as altering effector function are disclosed in the Antibody Engineering Technology Art, and any suitable variant disclosed therein may be used in the present molecules.

[00282] In certain embodiments, the Tri-Specific Binding Molecules of the present invention comprise a variant Fc Domain, having one or more amino acid modifications in one or more sites, which modification(s) alter (relative to a wild-type Fc Domain) the **Ratio of Affinities** of the variant Fc Domain to an activating FcγR (such as FcγRIIA or FcγRIIIA) relative to an inhibiting FcγR (such as FcγRIIB):

$$\text{Ratio of Affinities} = \frac{\text{Wild-Type to Variant Change in Affinity to Fc}\gamma\text{R}_{\text{Activating}}}{\text{Wild-Type to Variant Change in Affinity to Fc}\gamma\text{R}_{\text{Inhibiting}}}$$

[00283] Particularly preferred are Tri-Specific Binding Molecules of the present invention that possess a variant Fc Domain (relative to the wild-type Fc Domain) in which the Fc variant has a Ratio of Affinities greater than 1. Such molecules have particular use in providing a therapeutic or prophylactic treatment of a disease, disorder, or infection, or the amelioration of a symptom thereof, where an enhanced efficacy of effector cell function (e.g., ADCC) mediated by FcγR is desired, e.g., cancer or infectious disease. In contrast, an Fc variant having a Ratio of Affinities less than 1 mediates decreased efficacy of effector cell function. **Table 1** lists exemplary single, double, triple, quadruple and quintuple mutations by whether their Ratio of Affinities is greater than or less than 1.

Table 1
Exemplary Single and Multiple Mutations Listed by Ratio of Affinities

Single	Double	Triple	Quadruple	Quintuple
Ratio of Affinities > 1				
F243L D270E R292G R292P	F243L & R292P F243L & Y300L F243L & P396L D270E & P396L R292P & Y300L	F243L, P247L & N421K F243L, R292P & Y300L F243L, R292P & V305I F243L, R292P & P396L F243L, Y300L & P396L	L234F, F243L, R292P & Y300L L235I, F243L, R292P & Y300L L235Q, F243L, R292P & Y300L F243L, P247L, D270E & N421K F243L, R255L, D270E & P396L	L235V, F243L, R292P, Y300L & P396L L235P, F243L, R292P, Y300L & P396L F243L, R292P, V305I, Y300L & P396L

Table 1
Exemplary Single and Multiple Mutations Listed by Ratio of Affinities

Single	Double	Triple	Quadruple	Quintuple
Ratio of Affinities > 1				
	R292P & V305I	P247L, D270E & N421K	F243L, D270E, G316D & R416G	
	R292P & P396L	R255L, D270E & P396L	F243L, D270E, K392T & P396L	
	Y300L & P396L	D270E, G316D & R416G	F243L, D270E, P396L & Q419H	
	P396L & Q419H	D270E, K392T & P396L	F243L, R292P, Y300L, & P396L	
		D270E, P396L & Q419H	F243L, R292P, V305I & P396L	
		V284M, R292L & K370N	P247L, D270E, Y300L & N421K	
		R292P, Y300L & P396L	R255L, D270E, R292G & P396L	
			R255L, D270E, Y300L & P396L	
			D270E, G316D, P396L & R416G	
Ratio of Affinities < 1				
Y300L P396L	F243L & P396L	F243L, R292P & V305I		
	P247L & N421K			
	R255L & P396L			
	R292P & V305I			
	K392T & P396L			
	P396L & Q419H			

[00284] In a specific embodiment, in variant Fc Domains, any amino acid modifications (e.g., substitutions) at any of positions 235, 240, 241, 243, 244, 247, 262, 263, 269, 298, 328, or 330 and preferably one or more of the following residues: A240, I240, L241, L243, H244, N298, I328 or V330. In a different specific embodiment, in variant Fc Domains, any amino acid modifications (e.g., substitutions) at any of positions 268, 269, 270, 272, 276, 278, 283, 285, 286, 289, 292, 293, 301, 303, 305, 307, 309, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376,

416, 419, 430, 434, 435, 437, 438 or 439 and preferably one or more of the following residues: H280, Q280, Y280, G290, S290, T290, Y290, N294, K295, P296, D298, N298, P298, V298, I300 or L300.

[00285] In a preferred embodiment, in variant Fc Domains that bind an FcγR with an altered affinity, any amino acid modifications (e.g., substitutions) at any of positions 255, 256, 258, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 300, 301, 303, 305, 307, 309, 312, 320, 322, 326, 329, 330, 332, 331, 333, 334, 335, 337, 338, 339, 340, 359, 360, 373, 376, 416, 419, 430, 434, 435, 437, 438 or 439. Preferably, the variant Fc Domain has any of the following residues: A256, N268, Q272, D286, Q286, S286, A290, S290, A298, M301, A312, E320, M320, Q320, R320, E322, A326, D326, E326, N326, S326, K330, T339, A333, A334, E334, H334, L334, M334, Q334, V334, K335, Q335, A359, A360 or A430.

[00286] In a different embodiment, in variant Fc Domains that bind an FcγR (via its Fc Domain) with a reduced affinity, any amino acid modifications (e.g., substitutions) at any of positions 252, 254, 265, 268, 269, 270, 278, 289, 292, 293, 294, 295, 296, 298, 300, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438 or 439.

[00287] In a different embodiment, in variant Fc Domains that bind an FcγR (via its Fc Domain) with an enhanced affinity, any amino acid modifications (e.g., substitutions) at any of positions 280, 283, 285, 286, 290, 294, 295, 298, 300, 301, 305, 307, 309, 312, 315, 331, 333, 334, 337, 340, 360, 378, 398 or 430. In a different embodiment, in variant Fc Domains that binds FcγRIIA with an enhanced affinity, any of the following residues: A255, A256, A258, A267, A268, N268, A272, Q272, A276, A280, A283, A285, A286, D286, Q286, S286, A290, S290, M301, E320, M320, Q320, R320, E322, A326, D326, E326, S326, K330, A331, Q335, A337 or A430.

[00288] Preferred variants include one or more modifications at any of positions: 228, 230, 231, 232, 233, 234, 235, 239, 240, 241, 243, 244, 245, 247, 262, 263, 264,

265, 266, 271, 273, 275, 281, 284, 291, 296, 297, 298, 299, 302, 304, 305, 313, 323, 325, 326, 328, 330 or 332.

[00289] Particularly preferred variants include one or more modifications selected from groups A-AI:

A	228E, 228K, 228Y or 228G;
B	230A, 230E, 230Y or 230G;
C	231E, 231K, 231Y, 231P or 231G;
D	232E, 232K, 232Y, 232G;
E	233D;
F	234I or 234F;
G	235D, 235Q, 235P, 235I or 235V;
H	239D, 239E, 239N or 239Q;
I	240A, 240I, 240M or 240T;
J	243R, 243, 243Y, 243L, 243Q, 243W, 243H or 243I;
K	244H;
L	245A;
M	247G, 247V or 247L;
N	262A, 262E, 262I, 262T, 262E or 262F;
O	263A, 263I, 263M or 263T;
P	264F, 264E, 264R, 264I, 264A, 264T or 264W;
Q	265F, 265Y, 265H, 265I, 265L, 265T, 265V, 265N or 265Q;
R	266A, 266I, 266M or 266T;
S	271D, 271E, 271N, 271Q, 271K, 271R, 271S, 271T, 271H, 271A, 271V, 271L, 271I, 271F, 271M, 271Y, 271W or 271G;
T	273I;
U	275L or 275W;
V	281D, 281K, 281Y or 281P;
W	284E, 284N, 284T, 284L, 284Y or284M;
X	291D, 291E, 291Q, 291T, 291H, 291I or 291G;
Y	299A, 299D, 299E, 299F, 299G, 299H, 299I, 299K, 299L, 299M, 299N, 299P, 299Q, 299R, 299S, 299V, 299W or 299Y;
Z	302I;
AA	304D, 304N, 304T, 304H or 304L
AB	305I;
AC	313F;
AD	323I;
AE	325A, 325D, 325E, 325G, 325H, 325I, 325L, 325K, 325R, 325S, 325F, 325M, 325T, 325V, 325Y, 325W or 325P;
AF	328D, 328Q, 328K, 328R, 328S, 328T, 328V, 328I, 328Y, 328W, 328P, 328G, 328A, 328E, 328F, 328H, 328M or 328N;
AG	330L, 330Y, 330I or 330V;
AH	332A, 332D, 332E, 332H, 332N, 332Q, 332T, 332K, 332R, 332S, 332V, 332L, 332F, 332M, 332W, 332P, 332G or 332Y; and
AI	336E, 336K or 336Y

[00290] Still more particularly preferred variants include one or more modifications selected from Groups 1-105:

Group	Variant	Group	Variant
1	A330L / I332E	54	S239D / D265L / N297D / I332E
2	D265F / N297E / I332E	55	S239D / D265T / N297D / I332E

3	D265Y / N297D / I332E	56	S239D / D265V / N297D / I332E
4	D265Y / N297D / T299L / I332E	57	S239D / D265Y / N297D / I332E
5	F241E / F243Q / V262T / V264F	58	S239D / I332D
6	F241E / F243Q / V262T / V264E / I332E	59	S239D / I332E
7	F241E / F243R / V262E / V264R	60	S239D / I332E / A330I
8	F241E / F243R / V262E / V264R / I332E	61	S239D / I332N
9	F241E / F243Y / V262T / V264R	62	S239D / I332Q
10	F241E / F243Y / V262T / V264R / I332E	63	S239D / N297D / I332E
11	F241L / F243L / V262I / V264I	64	S239D / N297D / I332E / A330Y
12	F241L / V262I	65	S239D / N297D / I332E / A330Y / F241S / F243H / V262T / V264T
13	F241R / F243Q / V262T / V264R	66	S239D / N297D / I332E / K326E
14	F241R / F243Q / V262T / V264R / I332E	67	S239D / N297D / I332E / L235D
15	F241W / F243W / V262A / V264A	68	S239D / S298A / I332E
16	F241Y / F243Y / V262T / V264T	69	S239D / V264I / A330L / I332E
17	F241Y / F243Y / V262T / V264T / N297D / I332E	70	S239D / V264I / I332E
18	F243L / V262I / V264W	71	S239D / V264I / S298A / I332E
19	P243L / V264I	72	S239E / D265N
20	L328D / I332E	73	S239E / D265Q
21	L328E / I332E	74	S239E / I332D
22	L328H / I332E	75	S239E / I332E
23	L328I / I332E	76	S239E / I332N
24	L328M / I332E	77	S239E / I332Q
25	L328N / I332E	78	S239E / N297D / I332E
26	L328Q / I332E	79	S239E / V264I / A330Y / I332 E
27	L328T / I332E	80	S239E / V264I / I332 E
28	L328V / I332E	81	S239E / V264I / S298A / A330Y / I332E
29	N297D / A330Y / I332E	82	S239N / A330L / I332E
30	N297D / I332E	83	S239N / A330Y / I332E
31	N297D / I332E / S239D / A330L	84	S239N / I332D
32	N297D / S298A / A330Y / I 332E	85	S239N / I332E
33	N297D / T299L / I332E	86	S239N / I332N
34	N297D / T299F / I332E / N297D / T299H / I332E	87	S239N / I332Q
35	N297D / T299I / I332E	88	S239N1S298A / I332E
36	N297D / T299L / I332E	89	S239Q / I332D
37	N297D / T299V / I332E	90	S239Q / I332E
38	N297E / I332E	91	S239Q / I332N
39	N297S / I332E	92	S239Q / I332Q
40	P230A / E233D / I332E	93	S239Q / V264I / I332E
41	P244H / P245A / P247V	94	S298A / I332E
42	S239D / A330L / I332E	95	V264E / N297D / I332E

43	S239D / A330Y / I332E	96	V264I / A330L / I332E
44	S239D / A330Y / I332E / K326E	97	V264I / A330Y / I332E
45	S239D / A330Y / I332E / K326T	98	V264I / I332E
46	S239D / A330Y / I332E / L234I	99	V264I / S298A / I332E
47	S239D / A330Y / I332E / L235D	100	Y296D / N297D / I332E
48	S239D / A330Y / I332E / V240I	101	Y296E / N297D / I332 E
49	S239D / A330Y / I332E / V264T	102	Y296H / N297D / I332E
50	S239D / A330Y / I332E / V266I	103	Y296N / N297D / I332E
51	S239D / D265F / N297D / I332E	104	Y296Q / N297I / I332E
52	S239D / D265H / N297D / I332E	105	Y296T / N297D / I332E.
53	S239D / D265I / N297D / I332E		

[00291] In one embodiment, a multivalent DR5 binding molecule of the invention will comprise a variant Fc Domain having at least one modification in the Fc Domain. In certain embodiments, the variant Fc Domain comprises at least one substitution selected from the group consisting of L235V, F243L, R292P, Y300L, V305I, and P396L, wherein said numbering is that of the EU index as in Kabat.

[00292] In a specific embodiment, the variant Fc Domain comprises:

(A) at least one substitution selected from the group consisting of F243L, R292P, Y300L, V305I, and P396L;

(B) at least two substitutions selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P; and

(3) R292P and V305I;

(C) at least three substitutions selected from the group consisting of:

(1) F243L, R292P and Y300L;

(2) F243L, R292P and V305I;

(3) F243L, R292P and P396L; and

(4) R292P, V305I and P396L;

(D) at least four substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L and P396L; and

(2) F243L, R292P, V305I and P396L; or

(E) at least the five substitutions selected from the group consisting of:

(1) F243L, R292P, Y300L, V305I and P396L; and

(2) L235V, F243L, R292P, Y300L and P396L.

[00293] In another specific embodiment, the variant Fc Domain comprises substitutions of:

(A) F243L, R292P, and Y300L;

(B) L235V, F243L, R292P, Y300L, and P396L; or

(C) F243L, R292P, Y300L, V305I, and P396L.

[00294] In other embodiments, the invention encompasses the use of any Fc variant known in the art, such as those disclosed in Jefferis, B.J. *et al.* (2002) "*Interaction Sites On Human IgG-*Fc *For FcgammaR: Current Models*," Immunol. Lett. 82:57-65; Presta, L.G. *et al.* (2002) "*Engineering Therapeutic Antibodies For Improved Function*," Biochem. Soc. Trans. 30:487-90; Idusogie, E.E. *et al.* (2001) "*Engineered Antibodies With Increased Activity To Recruit Complement*," J. Immunol. 166:2571-75; Shields, R.L. *et al.* (2001) "*High Resolution Mapping Of The Binding Site On Human IgG1 For Fc Gamma RI, Fc Gamma RII, Fc Gamma RIII, And FcRn And Design Of IgG1 Variants With Improved Binding To The Fc gamma R*," J. Biol. Chem. 276:6591-6604; Idusogie, E.E. *et al.* (2000) "*Mapping Of The C1q Binding Site On Rituxan, A Chimeric Antibody With A Human IgG Fc*," J. Immunol. 164:4178-84; Reddy, M.P. *et al.* (2000) "*Elimination Of Fc Receptor-Dependent Effector Functions Of A Modified IgG4 Monoclonal Antibody To Human CD4*," J. Immunol. 164:1925-1933; Xu, D. *et al.* (2000) "*In Vitro Characterization of Five Humanized OKT3 Effector Function Variant Antibodies*," Cell. Immunol. 200:16-26; Armour, K.L. *et al.* (1999) "*Recombinant human IgG Molecules Lacking Fcgamma Receptor I Binding And Monocyte Triggering Activities*," Eur. J. Immunol. 29:2613-24; Jefferis, R. *et al.* (1996) "*Modulation Of Fc(Gamma)R And Human Complement Activation By IgG3-Core Oligosaccharide Interactions*," Immunol. Lett. 54:101-04; Lund, J. *et al.* (1996) "*Multiple Interactions Of IgG With Its Core Oligosaccharide Can Modulate Recognition By Complement And Human Fc Gamma Receptor I And Influence The Synthesis Of Its Oligosaccharide Chains*," J. Immunol. 157:4963-4969; Hutchins *et al.* (1995) "*Improved Biodistribution, Tumor Targeting, And Reduced Immunogenicity In Mice With A Gamma 4 Variant Of Campath-1H*," Proc. Natl. Acad. Sci. (U.S.A.) 92:11980-84; Jefferis, R. *et al.* (1995) "*Recognition Sites On Human IgG For Fc Gamma Receptors: The Role Of Glycosylation*," Immunol. Lett. 44:111-17; Lund, J. *et al.* (1995) "*Oligosaccharide-Protein Interactions In IgG Can*

Modulate Recognition By Fc Gamma Receptors," FASEB J. 9:115-19; Alegre, M.L. *et al.* (1994) "*A Non-Activating "Humanized" Anti-CD3 Monoclonal Antibody Retains Immunosuppressive Properties In Vivo*," Transplantation 57:1537-1543; Lund *et al.* (1992) "*Multiple Binding Sites On The CH2 Domain Of IgG For Mouse Fc Gamma R11*," Mol. Immunol. 29:53-59; Lund *et al.* (1991) "*Human Fc Gamma RI And Fc Gamma RII Interact With Distinct But Overlapping Sites On Human IgG*," J. Immunol. 147:2657-2662; Duncan, A.R. *et al.* (1988) "*Localization Of The Binding Site For The Human High-Affinity Fc Receptor On IgG*," Nature 332:563-564; US Patent Nos. 5,624,821; 5,885,573; 6,194,551; 7,276,586; and 7,317,091; and PCT Publications WO 00/42072 and PCT WO 99/58572.

[00295] In some embodiments, the molecules of the invention further comprise one or more glycosylation sites, so that one or more carbohydrate moieties are covalently attached to the molecule. Preferably, the molecules of the invention with one or more glycosylation sites and/or one or more modifications in the Fc Domain confer or have an enhanced antibody-mediated effector function, *e.g.*, enhanced ADCC activity, compared to a parent antibody. In some embodiments, the invention further comprises molecules comprising one or more modifications of amino acids that are directly or indirectly known to interact with a carbohydrate moiety of the antibody, including but not limited to amino acids at positions 241, 243, 244, 245, 245, 249, 256, 258, 260, 262, 264, 265, 296, 299, and 301. Amino acids that directly or indirectly interact with a carbohydrate moiety of an antibody are known in the art, *see, e.g.*, Jefferis *et al.*, 1995 *Immunology Letters*, 44: 111-7, which is incorporated herein by reference in its entirety.

[00296] In another embodiment, the invention encompasses molecules that have been modified by introducing one or more glycosylation sites into one or more sites of the molecules, preferably without altering the functionality of the molecules, *e.g.*, binding activity to target antigen or FcγR. Glycosylation sites may be introduced into the variable and/or constant region of the molecules of the invention. As used herein, "glycosylation sites" include any specific amino acid sequence in an antibody to which an oligosaccharide (*i.e.*, carbohydrates containing two or more simple sugars linked together) will specifically and covalently attach. Oligosaccharide side chains

are typically linked to the backbone of an antibody via either N-or O-linkages. N-linked glycosylation refers to the attachment of an oligosaccharide moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of an oligosaccharide moiety to a hydroxyamino acid, *e.g.*, serine, threonine. The molecules of the invention may comprise one or more glycosylation sites, including N-linked and O-linked glycosylation sites. Any glycosylation site for N-linked or O-linked glycosylation known in the art may be used in accordance with the instant invention. An exemplary N-linked glycosylation site that is useful in accordance with the methods of the present invention is the amino acid sequence: Asn-X-Thr/Ser, wherein X may be any amino acid and Thr/Ser indicates a threonine or a serine. Such a site or sites may be introduced into a molecule of the invention using methods well-known in the art to which this invention pertains (see for example, *IN VITRO* MUTAGENESIS, RECOMBINANT DNA: A SHORT COURSE, J. D. Watson, *et al.* W.H. Freeman and Company, New York, 1983, chapter 8, pp. 106-116, which is incorporated herein by reference in its entirety. An exemplary method for introducing a glycosylation site into a molecule of the invention may comprise: modifying or mutating an amino acid sequence of the molecule so that the desired Asn-X-Thr/Ser sequence is obtained.

[00297] In some embodiments, the invention encompasses methods of modifying the carbohydrate content of a molecule of the invention by adding or deleting a glycosylation site. Methods for modifying the carbohydrate content of antibodies (and molecules comprising antibody domains) are well-known in the art and encompassed within the invention, *see*, *e.g.*, U.S. Patent No. 6,218,149; EP 0 359 096 B1; U.S. Publication No. US 2002/0028486; WO 03/035835; U.S. Publication No. 2003/0115614; U.S. Patent No. 6,218,149; U.S. Patent No. 6,472,511; all of which are incorporated herein by reference in their entirety. In other embodiments, the invention encompasses methods of modifying the carbohydrate content of a molecule of the invention by deleting one or more endogenous carbohydrate moieties of the molecule. In a specific embodiment, the invention encompasses shifting the glycosylation site of the Fc Domain of an antibody, by modifying positions adjacent to 297. In a specific embodiment, the invention encompasses modifying position 296 so that position 296 and not position 297 is glycosylated.

[00298] Effector function can also be modified by techniques such as by introducing one or more cysteine residues into the Fc Domain, thereby allowing interchain disulfide bond formation in this region to occur, resulting in the generation of a homodimeric antibody that may have improved internalization capability and/or increased complement-mediated cell killing and ADCC (Caron, P.C. *et al.* (1992) "*Engineered Humanized Dimeric Forms Of IgG Are More Effective Antibodies*," J. Exp. Med. 176:1191-1195; Shopes, B. (1992) "*A Genetically Engineered Human IgG Mutant With Enhanced Cytolytic Activity*," J. Immunol. 148(9):2918-2922. Homodimeric antibodies with enhanced antitumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff, E.A. *et al.* (1993) "*Monoclonal Antibody Homodimers: Enhanced Antitumor Activity In Nude Mice*," Cancer Research 53:2560-2565. Alternatively, an antibody can be engineered which has dual Fc Domains and may thereby have enhanced complement lysis and ADCC capabilities (Stevenson, G.T. *et al.* (1989) "*A Chimeric Antibody With Dual Fc Domains (bisFabFc) Prepared By Manipulations At The IgG Hinge*," Anti-Cancer Drug Design 3:219-230).

III. Exemplary Trispecific Binding Molecules

F. gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1

[00299] An exemplary Tri-Specific Binding Molecule composed of four polypeptide chains was constructed. The Tri-Specific Binding Molecule comprises the VL and VH domains of gpA33 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of DR5 mAb 1, and was accordingly designated "**gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:212**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL
EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT

PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK

[00300] In **SEQ ID NO:212**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00301] A polynucleotide that encodes **SEQ ID NO:212** is **SEQ ID NO:213**:

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga

tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct ccgggtaaa

[00302] The amino acid sequence of the second polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:214**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KASGYTFTGS WMNWVRQAPG QGLEWIGRIY PGDGETNYNG KFKDRVTITA DKSTSTAYME LSSLRSEDTA VYYCARIYGN NVYFDVWGQG TTVTVSSGGC GGGKVAALKE KVAALKEKVA ALKEKVAALK E

[00303] In **SEQ ID NO:214**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-243 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 244-271 are a K-coil Domain (**SEQ ID NO:40**).

[00304] A polynucleotide that encodes **SEQ ID NO:214** is (**SEQ ID NO:215**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc gcacttaagg aaaaggtcgc agccctgaaa gag

[00305] The amino acid sequence of the third polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:216**):

EVKFLESGGG LVQPGGSLKL SCVASGFDFS RYWMSWVRQA PGKGLEWIGE INPDSNTINY TPSLKDKFII SRDNAKNTLY LQMTKVRSED TALYYCTRRA

YYGNPAWFAY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEAAG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLS CAVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL VSKLTVDKSR WQQGNVFSCS VMHEALHNRY TQKSLSLSPG
K

[00306] In **SEQ ID NO:216**, amino acid residues 1-121 correspond to the amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**), residues 122-219 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 220-234 correspond to a linker (**SEQ ID NO:209**), and residues 235-451 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00307] A polynucleotide that encodes **SEQ ID NO:216** is (**SEQ ID NO:217**):

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc
cctgaaactc tcctgtgtag cctcaggatt cgattttagt agatactgga
tgagttgggt ccggcaggct ccagggaaag ggctagaatg gattggagaa
attaatccag atagcaatac gataaactat acgccatctc taaaggataa
attcatcatc tccagagaca acgccaaaaa tacgctgtat ctgcaaatga
ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc
tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt
cactgtctct tccgcctcca ccaagggccc atcggtcttc cccctggcac
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct
gaccagcggc gtgcacacct tcccggctgt cctacagtcc tcaggactct
actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa
gagagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc
cagcacctga agccgcgggg ggaccgtcag tcttcctctt cccccaaaa
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt
ggtggacgtg agccacgaag accctgaggt caagttcaac tggtacgtgg
acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg
gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag
cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt
cagcctgagt tgcgcagtca aaggcttcta tcccagcgac atcgccgtgg
agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga
caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg
aggctctgca caaccgctac acgcagaaga gcctctccct gtctccgggt
aaa

[00308] The amino acid sequence of the fourth polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:218**):

DIVLTQSPAS LAVSLGQRAT ISCRASKSVS SSGYSYMHWY QQKPGQPPKV
LIFLSSNLDS GVPARFSGSG SGTDFTLNIH PVEDGDAATY YCQHSRDLPP
TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV
THQGLSSPVT KSFNRGEC

[00309] In **SEQ ID NO:218**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**), and residues 112-218 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00310] A polynucleotide that encodes **SEQ ID NO:218** is (**SEQ ID NO:219**):

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca
gagggccacc atctcatgca gggccagcaa aagtgtcagt tcctctggct
atagttatat gcactggtac caacagaaac caggacagcc acccaaagtc
ctcatctttc tttcatccaa cctagattct ggggtccctg ccaggttcag
tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg
atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg
acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc
atcggtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg
cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta
cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt
cacagagcag gacagcaagg acagcaccta cagcctcagc agcaccctga
cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc
acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga
gtgt

G. gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2

[00311] A second exemplary Tri-Specific Binding Molecule composed of four polypeptide chains was constructed. The Tri-Specific Binding Molecule comprises the VL and VH domains of gpA33 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of DR5 mAb 2, and was accordingly designated "**gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:220**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL
EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP

PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

[00312] In **SEQ ID NO:220**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00313] A polynucleotide that encodes **SEQ ID NO:220** is (**SEQ ID NO:221**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gccccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg

ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaaa

[00314] The amino acid sequence of the second polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2 is (**SEQ ID NO:222**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KASGYTFTGS
WMNWVRQAPG QGLEWIGRIY PGDGETNYNG KFKDRVTITA DKSTSTAYME
LSSLRSEDTA VYYCARIYGN NVYFDVWGQG TTVTVSSGGC GGGKVAALKE
KVAALKEKVA ALKEKVAALK E

[00315] In **SEQ ID NO:222**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-243 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 244-271 are a K-coil Domain (**SEQ ID NO:40**).

[00316] A polynucleotide that encodes **SEQ ID NO:222** is (**SEQ ID NO:223**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtc cagctggtcc agagcggggc cgaagtcaaa aaacccggag
caagcgtgaa ggtctcctgc aaagcatcag gctatacatt tacaggcagc
tggatgaact gggtgaggca ggctccagga cagggactgg agtggatcgg
gcgcatctac cctggagacg gcgaaactaa ctataatgga aagttcaaag
accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat
ttacggaaac aatgtctatt ttgacgtgtg ggggcaggga acaactgtga
ctgtctcctc cggaggatgt ggcggtggaa aagtggccgc actgaaggag
aaagttgctg ctttgaaaga gaaggtcgcc gcacttaagg aaaaggtcgc
agccctgaaa gag

[00317] The amino acid sequence of the third polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2 is (**SEQ ID NO:224**):

KVQLQQSGAE LVKPGASVKL SCKASGYTFT EYILHWVKQK SGQGLEWIGW
FYPGNNNIKY NEKFKDKATL TADKSSSTVY MELSRLTSED SAVYFCARHE
QGPGYFDYWG QGTTLTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPEAAGGP SVFLFPPKPK
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV
YTLPPSREEM TKNQVSLSCA VKGFYPSDIA VEWESNGQPE NNYKTTPPVL
DSDGSFFLVS KLTVDKSRWQ QGNVFSCSVM HEALHNRYTQ KSLSLSPGK

[00318] In **SEQ ID NO:224**, amino acid residues 1-119 correspond to the amino acid sequence of the VH Domain of DR5 mAb 2 (**SEQ ID NO:18**), residues 120-217 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 218-232 correspond to a linker (**SEQ ID NO:209**), and residues 233-449 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00319] A polynucleotide that encodes **SEQ ID NO:224** is (**SEQ ID NO:225**):

aaggtccagc tgcagcagtc tggagctgaa ctggtgaaac ccggggcatc
agtgaagctg tcctgcaagg cttctgggta caccttcact gagtatattt
tacactgggt aaagcagaag tctggacagg gtcttgagtg gattgggtgg
ttttatcctg gaaataataa tataaagtac aatgagaaat tcaaggacaa
ggccacactg actgcggaca aatcctccag cacagtctat atggaactta
gtagattgac atctgaagac tctgcggtct atttctgtgc aagacacgaa
caaggaccag gttactttga ctactggggc caaggcacca ctctcacagt
ctcctccgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag
cggcgtgcac accttcccgg ctgtcctaca gtcctcagga ctctactccc
tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt
tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac
ctgaagccgc gggggggaccg tcagtcttcc tcttcccccc aaaacccaag
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga
cgtgagccac gaagaccctg aggtcaagtt caactggtac gtggacggcg
tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa
tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct
gagttgcgca gtcaaaggct tctatcccag cgacatcgcc gtggagtggg
agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag

caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc
tgcacaaccg ctacacgcag aagagcctct ccctgtctcc gggtaaa

[00320] The amino acid sequence of the fourth polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2 is (**SEQ ID NO:226**):

DIVMTQSHKF MSTSVGDRVS ITCKASQDVN TAVAWYQQKP GQSPKLLIYW
ASTRHTGVPD RFTGSGSGTD YTLTIKSVQA EDLTLYYCQQ HYITPWTFGG
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

[00321] In **SEQ ID NO:226**, amino acid residues 1-107 correspond to the amino acid sequence of the VL Domain of DR5 mAb 2 (**SEQ ID NO:13**), and residues 108-214 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00322] A polynucleotide that encodes **SEQ ID NO:226** is (**SEQ ID NO:227**):

gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga
cagggtcagc atcacctgca aggccagtca ggatgtgaat actgctgtag
cctggtatca acaaaaacca gggcaatctc ctaaactact gatttactgg
gcatccaccc ggcacactgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tatacactca ccatcaaaag tgtgcaggct gaagacctga
cactttatta ctgtcagcaa cactatatca ctccgtggac gttcggtgga
ggcaccaagc tggaaatcaa acgtacggtg gctgcaccat cggtcttcat
cttcccgcca tctgatgagc agttgaaatc tggaactgcc tctgttgtgt
gcctgctgaa taacttctat cccagagagg ccaaagtaca gtggaaggtg
gataacgccc tccaatcggg taactcccag gagagtgtca cagagcagga
cagcaaggac agcacctaca gcctcagcag caccctgacg ctgagcaaag
cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt

H. EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1

[00323] A further exemplary Tri-Specific Binding Molecule composed of four polypeptide chains was constructed. The Tri-Specific Binding Molecule comprises the VL and VH domains of EphA2 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of DR5 mAb 1, and was accordingly designated "**EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:228**):

DIQMTQTTSS LSASLGDRIT ISCRASQDIS NYLNWYQQKP DGTVKLLIYY
TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GYTLYTFGGG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL

EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

[00324] In **SEQ ID NO:228**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 1 (**SEQ ID NO:153**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00325] A polynucleotide that encodes **SEQ ID NO:228** is (**SEQ ID NO:229**):

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga
cagaatcacc atcagttgca gggcaagtca ggacattagc aattatttaa
actggtatca gcagaaacca gatggaactg ttaaactcct gatctactac
acatcaagat tacactcagg agtcccatca aggttcagtg gcagtgggtc
tggaacagat tattctctca ccattagcaa cctggagcaa gaagatattg
ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
accaagctgg aaataaaagg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa

ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaa

[00326] The amino acid sequence of the second polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:230**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLKESGPGLV APSQSLSITC TVSGFSLSRY
SVHWVRQPPG KGLEWLGMIW GGGSTDYNSA LKSRLSISKD NSKSQVFLKM
NSLQTDDTAM YYCARKHGNY YTMDYWGQGT SVTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00327] In **SEQ ID NO:230**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 1 (**SEQ ID NO:158**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00328] A polynucleotide that encodes **SEQ ID NO:230** is (**SEQ ID NO:231**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtg cagctgaagg agtcaggacc tggcctggtg gcaccctcac
agagcctgtc catcacatgc actgtctctg ggttctcatt atccagatat
agtgtacact gggttcgcca gcctccagga aagggtctgg agtggctggg
aatgatatgg ggtggtggaa gcacagacta taattcagct ctcaaatcca
gactgagtat cagcaaggac aactccaaga gccaagtttt cttaaaaatg
aacagtctgc aaactgatga cacagccatg tactactgtg ccagaaaaca
tggtaactac tatactatgg actactgggg tcaaggaacc tcagtcaccg
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00329] The amino acid sequence of the third polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:232**):

EVKFLESGGG LVQPGGSLKL SCVASGFDFS RYWMSWVRQA PGKGLEWIGE
INPDSNTINY TPSLKDKFII SRDNAKNTLY LQMTKVRSED TALYYCTRRA
YYGNPAWFAY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEAAG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLS CAVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL VSKLTVDKSR WQQGNVFSCS VMHEALHNRY TQKSLSLSPG
K

[00330] In **SEQ ID NO:232**, amino acid residues 1-121 correspond to the amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**), residues 122-219 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 220-234 correspond to a linker (**SEQ ID NO:209**), and residues 235-451 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00331] A polynucleotide that encodes **SEQ ID NO:232** is (**SEQ ID NO:233)**:

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc
cctgaaactc tcctgtgtag cctcaggatt cgattttagt agatactgga
tgagttgggt ccggcaggct ccagggaaag ggctagaatg gattggagaa
attaatccag atagcaatac gataaactat acgccatctc taaaggataa
attcatcatc tccagagaca acgccaaaaa tacgctgtat ctgcaaatga
ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc
tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt
cactgtctct tccgcctcca ccaagggccc atcggtcttc cccctggcac
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct
gaccagcggc gtgcacacct tcccggctgt cctacagtcc tcaggactct
actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa
gagagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc
cagcacctga agccgcgggg ggaccgtcag tcttcctctt ccccccaaaa
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt
ggtggacgtg agccacgaag accctgaggt caagttcaac tggtacgtgg
acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg
gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag
ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt
cagcctgagt tgcgcagtca aaggcttcta tcccagcgac atcgccgtgg
agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga

caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg
aggctctgca caaccgctac acgcagaaga gcctctccct gtctccgggt
aaa

[00332] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:234**):

DIVLTQSPAS LAVSLGQRAT ISCRASKSVS SSGYSYMHWY QQKPGQPPKV
LIFLSSNLDS GVPARFSGSG SGTDFTLNIH PVEDGDAATY YCQHSRDLPP
TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV
THQGLSSPVT KSFNRGEC

[00333] In **SEQ ID NO:234**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**), and residues 112-218 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00334] A polynucleotide that encodes **SEQ ID NO:234** is (**SEQ ID NO:235**):

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca
gagggccacc atctcatgca gggccagcaa aagtgtcagt tcctctggct
atagttatat gcactggtac caacagaaac caggacagcc acccaaagtc
ctcatctttc tttcatccaa cctagattct ggggtccctg ccaggttcag
tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg
atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg
acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc
atcggtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg
cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta
cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt
cacagagcag gacagcaagg acagcaccta cagcctcagc agcaccctga
cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc
acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga
gtgt

I. EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1

[00335] A further exemplary Tri-Specific Binding Molecule composed of four polypeptide chains was constructed. The Tri-Specific Binding Molecule comprises the VL and VH domains of EphA2 mAb 2, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of DR5 mAb 1, and was accordingly designated "**EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:236**):

DVVMTQTPLS LPVSLGDQAS ISCRSSQSLV HSSGNTYLHW YLQKPGQSPK
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVP
TFGSGTKLEI KGGGSGGGGE VQLVESGGGL VQPGGSLRLS CAASGFTFST

YAMNWVRQAP GKGLEWVGRI RSKYNNYATY YADSVKGRFT ISRDDSKNSL
YLQMNSLKTE DTAVYYCVRH GNFGNSYVSW FAYWGQGTLV TVSSGGCGGG
EVAALEKEVA ALEKEVAALE KEVAALEKGG GDKTHTCPPC PAPEAAGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT
KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA
KGQPREPQVY TLPPSREEMT KNQVSLWCLV KGFYPSDIAV EWESNGQPEN
NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK
SLSLSPGK

[00336] In **SEQ ID NO:236**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 2 (**SEQ ID NO:163**), residues 112-119 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 120-244 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 245-250 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 251-278 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 279-281 are the linker GGG, residues 282-291 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 292-508 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00337] A polynucleotide that encodes **SEQ ID NO:236** is (**SEQ ID NO:237**):

gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga
tcaagcctcc atctcttgca gatctagtca gagccttgta cacagtagtg
gaaacaccta tttacattgg tacctgcaga agccaggcca gtctccaaag
ctcctgatct acaaagtttc caaccgattt tctggggtcc cagacaggtt
cagtggcagt ggatcaggga cagatttcac actcaagatc agcagagtgg
aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc
acgttcggct cggggacaaa gttggaaata aaaggtggag gatccggcgg
cggaggcgag gtgcagctgg tggagtctgg gggaggcttg gtccagcctg
gagggtccct gagactctcc tgtgcagcct ctggattcac cttcagcaca
tacgctatga attgggtccg ccaggctcca gggaaggggc tggagtgggt
tggaaggatc aggtccaagt acaacaatta tgcaacctac tatgccgact
ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg
tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg
tgtgagacac ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt
ggggacaggg gacactggtg actgtgtctt ccggaggatg tggcggtgga
gaagtggccg cactggagaa agaggttgct gctttggaga aggaggtcgc
tgcacttgaa aaggaggtcg cagccctgga gaaaggcggc ggggacaaaa
ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac
ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct
caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg

tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc
aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga
ggagatgacc aagaaccagg tcagcctgtg gtgcctggtc aaaggcttct
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct
ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
agcctctccc tgtctccggg taaa

[00338] The amino acid sequence of the second polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:238**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQI QLVQSGPELK KPGETVKISC KASGFTFTNY
GMNWVKQAPG KGLKWMGWIN TYIGEPTYAD DFKGRFVFSL ETSASTAYLQ
INNLKNEDMA TYFCARELGP YYFDYWGQGT TLTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00339] In **SEQ ID NO:238**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 2 (**SEQ ID NO:167**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00340] A polynucleotide that encodes **SEQ ID NO:238** is (**SEQ ID NO:239**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacagatc cagttggtgc agtctggacc tgagctgaag aagcctggag
agacagtcaa gatctcctgc aaggcttctg ggtttacctt cacaaactat
ggaatgaact gggtgaagca ggctccagga aagggtttaa agtggatggg
ctggataaac acctatattg gagagccgac atatgctgat gacttcaagg
gacggtttgt cttctctttg gaaacctctg ccagcactgc ctatttgcag
atcaacaacc tcaaaaatga ggacatggcc acatatttct gtgcaagaga
actgggacca tactactttg actactgggg ccaaggcacc actctcacag
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00341] The amino acid sequence of the third polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:240**):

EVKFLESGGG LVQPGGSLKL SCVASGFDFS RYWMSWVRQA PGKGLEWIGE
INPDSNTINY TPSLKDKFII SRDNAKNTLY LQMTKVRSED TALYYCTRRA
YYGNPAWFAY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEAAG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLS CAVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL VSKLTVDKSR WQQGNVFSCS VMHEALHNRY TQKSLSLSPG
K

[00342] In **SEQ ID NO:240**, amino acid residues 1-121 correspond to the amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**), residues 122-219 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 220-234 correspond to a linker (**SEQ ID NO:209**), and residues 235-451 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00343] A polynucleotide that encodes **SEQ ID NO:240** is (**SEQ ID NO:241**):

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc
cctgaaactc tcctgtgtag cctcaggatt cgattttagt agatactgga
tgagttgggt ccggcaggct ccagggaaag ggctagaatg gattggagaa
attaatccag atagcaatac gataaactat acgccatctc taaaggataa
attcatcatc tccagagaca acgccaaaaa tacgctgtat ctgcaaatga
ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc
tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt
cactgtctct tccgcctcca ccaagggccc atcggtcttc cccctggcac
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct
gaccagcggc gtgcacacct tcccggctgt cctacagtcc tcaggactct
actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa
gagagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc
cagcacctga agccgcgggg ggaccgtcag tcttcctctt ccccccaaaa
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt
ggtggacgtg agccacgaag accctgaggt caagttcaac tggtacgtgg
acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg
gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag
cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt
cagcctgagt tgcgcagtca aaggcttcta tcccagcgac atcgccgtgg
agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga

caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac acgcagaaga gcctctccct gtctccgggt aaa

[00344] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:242**):

DIVLTQSPAS LAVSLGQRAT ISCRASKSVS SSGYSYMHWY QQKPGQPPKV LIFLSSNLDS GVPARFSGSG SGTDFTLNIH PVEDGDAATY YCQHSRDLPP TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

[00345] In **SEQ ID NO:242**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**), and residues 112-218 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00346] A polynucleotide that encodes **SEQ ID NO:242** is (**SEQ ID NO:243**):

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt

J. EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1

[00347] A further exemplary Tri-Specific Binding Molecule composed of four polypeptide chains was constructed. The Tri-Specific Binding Molecule comprises the VL and VH domains of EphA2 mAb 3, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of DR5 mAb 1, and was accordingly designated "**EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:244**):

DIVLTQSHRS MSTSVGDRVN ITCKASQDVT TAVAWYQQKP GQSPKLLIFW ASTRHAGVPD RFTGSGSGTD FTLTISSVQA GDLALYYCQQ HYSTPYTFGG GTKLEIKGGG SGGGGEVQLV ESGGGLVQPG GSLRLSCAAS GFTFSTYAMN

WVRQAPGKGL EWVGRIRSKY NNYATYYADS VKGRFTISRD DSKNSLYLQM
NSLKTEDTAV YYCVRHGNFG NSYVSWFAYW GQGTLVTVSS GGCGGGEVAA
LEKEVAALEK EVAALEKEVA ALEKGGGDKT HTCPPCPAPE AAGGPSVFLF
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP
REPQVYTLPP SREEMTKNQV SLWCLVKGFY PSDIAVEWES NGQPENNYKT
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
SPGK

[00348] In **SEQ ID NO:244**, amino acid residues 1-107 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 3 (**SEQ ID NO:172**), residues 108-115 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 116-240 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 241-246 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 247-274 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 275-277 are the linker GGG, residues 278-287 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 288-504 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00349] A polynucleotide that encodes **SEQ ID NO:244** is (**SEQ ID NO:245**):

gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga
cagggtcaac atcacctgca aggccagtca ggatgtgact actgctgtag
cctggtatca acaaaaacca gggcaatctc ctaaattact gattttctgg
gcatccaccc ggcacgctgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tttactctca ccatcagcag tgtgcaggct ggagacctgg
cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg
gggaccaagc tggaaataaa aggtggagga tccggcggcg gaggcgaggt
gcagctggtg gagtctgggg gaggcttggt ccagcctgga gggtccctga
gactctcctg tgcagcctct ggattcacct tcagcacata cgctatgaat
tgggtccgcc aggctccagg gaaggggctg gagtgggttg gaaggatcag
gtccaagtac aacaattatg caacctacta tgccgactct gtgaagggta
gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg
aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg
taacttcggc aattcttacg tgtcttggtt tgcttattgg ggacagggga
cactggtgac tgtgtcttcc ggaggatgtg gcggtggaga agtggccgca
ctggagaaag aggttgctgc tttggagaag gaggtcgctg cacttgaaaa
ggaggtcgca gccctggaga aaggcggcgg ggacaaaact cacacatgcc
caccgtgccc agcacctgaa gccgcggggg gaccgtcagt cttcctcttc
cccccaaaac ccaaggacac cctcatgatc tcccggaccc ctgaggtcac
atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc aagttcaact
ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag
gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag

ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc
cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa
gaaccaggtc agcctgtggt gcctggtcaa aggcttctat cccagcgaca
tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct
caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg
tctccgggta aa

[00350] The amino acid sequence of the second polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:246**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGEV QLVESGGGSV KPGGSLKLSC AASGFTFTDH
YMYWVRQTPE KRLEWVATIS DGGSFTSYPD SVKGRFTISR DIAKNNLYLQ
MSSLKSEDTA MYYCTRDESD RPFPYWGQGT LVTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00351] In **SEQ ID NO:246**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 3 (**SEQ ID NO:177**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00352] A polynucleotide that encodes **SEQ ID NO:246** is (**SEQ ID NO:247**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggagaagtg cagctggtgg agtctggggg aggctcagtg aagcctggag
ggtccctgaa actctcctgt gcagcctctg gattcacttt cactgaccat
tacatgtatt gggttcgcca gactccggaa aagaggctgg agtgggtcgc
aaccattagt gatggcggta gtttcacctc ctatccagac agtgtgaagg
ggcgattcac catctccaga gacattgcca agaacaacct gtacctccaa
atgagcagtc tgaagtctga ggacacagcc atgtattact gtacaagaga
tgagagcgat aggccgtttc cttactgggg ccaagggact ctggtcactg
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00353] The amino acid sequence of the third polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:248**):

EVKFLESGGG LVQPGGSLKL SCVASGFDFS RYWMSWVRQA PGKGLEWIGE
INPDSNTINY TPSLKDKFII SRDNAKNTLY LQMTKVRSED TALYYCTRRA
YYGNPAWFAY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEAAG GPSVFLFPPK
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP
QVYTLPPSRE EMTKNQVSLS CAVKGFYPSD IAVEWESNGQ PENNYKTTPP
VLDSDGSFFL VSKLTVDKSR WQQGNVFSCS VMHEALHNRY TQKSLSLSPG
K

[00354] In **SEQ ID NO:248**, amino acid residues 1-121 correspond to the amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**), residues 122-219 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 220-234 correspond to a linker (**SEQ ID NO:209**), and residues 235-451 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00355] A polynucleotide that encodes **SEQ ID NO:248** is (**SEQ ID NO:249**):

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc
cctgaaactc tcctgtgtag cctcaggatt cgattttagt agatactgga
tgagttgggt ccggcaggct ccagggaaag ggctagaatg gattggagaa
attaatccag atagcaatac gataaactat acgccatctc taaaggataa
attcatcatc tccagagaca acgccaaaaa tacgctgtat ctgcaaatga
ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc
tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt
cactgtctct tccgcctcca ccaagggccc atcggtcttc cccctggcac
cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggtc
aaggactact tccccgaacc ggtgacggtg tcgtggaact caggcgccct
gaccagcggc gtgcacacct tcccggctgt cctacagtcc tcaggactct
actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa
gagagttgag cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc
cagcacctga agccgcgggg ggaccgtcag tcttcctctt ccccccaaaa
cccaaggaca ccctcatgat ctcccggacc cctgaggtca catgcgtggt
ggtggacgtg agccacgaag accctgaggt caagttcaac tggtacgtgg
acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg
gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa gccctcccag
ccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca
caggtgtaca ccctgccccc atcccgggag gagatgacca agaaccaggt
cagcctgagt tgcgcagtca aaggcttcta tcccagcgac atcgccgtgg
agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga

caagagcagg tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac acgcagaaga gcctctccct gtctccgggt aaa

[00356] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1 is (**SEQ ID NO:250**):

DIVLTQSPAS LAVSLGQRAT ISCRASKSVS SSGYSYMHWY QQKPGQPPKV LIFLSSNLDS GVPARFSGSG SGTDFTLNIH PVEDGDAATY YCQHSRDLPP TFGGGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

[00357] In **SEQ ID NO:250**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**), and residues 112-218 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00358] A polynucleotide that encodes **SEQ ID NO:250** is (**SEQ ID NO:251**):

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt

[00359] Although the exemplary Tri-Specific Binding Molecules described above comprise three Light Chain (VL) CDRs and three Heavy Chain (VH) CDRs for each binding domain, it will be recognized that the invention also includes Tri-Specific Binding Molecules that possess:

(1) at least one of the CDRs of the VL Domain of any such binding domain;

(2) at least two of the CDRs of the VL Domain of any such binding domain;

(3) the three CDRs of the VL Domain of any such binding domain;

(4) at least one of the CDRs of the VH Domain of any such binding domain;

(5) at least two of the CDRs of the VH Domain of any such binding domain;

(6) the three CDRs of the VH Domain of any such binding domain;

(7) at least one of the CDRs of the VL Domain of any such binding domain and at least one of the CDRs of the VH Domain of that binding domain;

(8) at least two of the CDRs of the VL Domain of any such binding domain and at least two of the CDRs of the VH Domain of that binding domain;

(9) the three CDRs of the VL Domain of any such binding domain and the three CDRs of the VH Domain of that binding domain;

(10) the VL Domain of any such binding domain;

(11) the VH Domain of any such binding domain; or

(12) the VL and VH Domains of any such binding domain.

K. gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 1

[00360] A Tri-Specific Binding Molecule composed of four polypeptide chains was constructed that comprises the VL and VH domains of gpA33 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of EphA2 mAb 1. The Tri-Specific Binding Molecule was accordingly designated "**gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:252**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL
EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

[00361] In **SEQ ID NO:252**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00362] A polynucleotide that encodes **SEQ ID NO:252** is (**SEQ ID NO:253**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaaa

[00363] The amino acid sequence of the second polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 1 is (**SEQ ID NO:254**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KASGYTFTGS
WMNWVRQAPG QGLEWIGRIY PGDGETNYNG KFKDRVTITA DKSTSTAYME
LSSLRSEDTA VYYCARIYGN NVYFDVWGQG TTVTVSSGGC GGGKVAALKE
KVAALKEKVA ALKEKVAALK E

[00364] In **SEQ ID NO:254**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-243 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 244-271 are a K-coil Domain (**SEQ ID NO:40**).

[00365] A polynucleotide that encodes **SEQ ID NO:254** is (**SEQ ID NO:255**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtc cagctggtcc agagcggggc cgaagtcaaa aaacccggag
caagcgtgaa ggtctcctgc aaagcatcag gctatacatt tacaggcagc
tggatgaact gggtgaggca ggctccagga cagggactgg agtggatcgg
gcgcatctac cctggagacg gcgaaactaa ctataatgga aagttcaaag
accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat
ttacggaaac aatgtctatt ttgacgtgtg ggggcaggga acaactgtga
ctgtctcctc cggaggatgt ggcggtggaa aagtggccgc actgaaggag
aaagttgctg ctttgaaaga gaaggtcgcc gcacttaagg aaaaggtcgc
agccctgaaa gag

[00366] The amino acid sequence of the third polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 1 is (**SEQ ID NO:256**):

QVQLKESGPG LVAPSQSLSI TCTVSGFSLS RYSVHWVRQP PGKGLEWLGM
IWGGGSTDYN SALKSRLSIS KDNSKSQVFL KMNSLQTDDT AMYYCARKHG
NYYTMDYWGQ GTSVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPEAAGGPS VFLFPPKPKD

TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY
TLPPSREEMT KNQVSLSCAV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNRYTQK SLSLSPGK

[00367] In **SEQ ID NO:256**, amino acid residues 1-118 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 1 (**SEQ ID NO:158**), residues 119-216 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 217-231 correspond to a linker (**SEQ ID NO:209**), and residues 232-448 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00368] A polynucleotide that encodes **SEQ ID NO:256** is (**SEQ ID NO:257**):

caggtgcagc tgaaggagtc aggacctggc ctggtggcac cctcacagag
cctgtccatc acatgcactg tctctgggtt ctcattatcc agatatagtg
tacactgggt tcgccagcct ccaggaaagg gtctggagtg gctgggaatg
atatggggtg gtggaagcac agactataat tcagctctca aatccagact
gagtatcagc aaggacaact ccaagagcca agttttctta aaaatgaaca
gtctgcaaac tgatgacaca gccatgtact actgtgccag aaaacatggt
aactactata ctatggacta ctggggtcaa ggaacctcag tcaccgtctc
ctccgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac
ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg
cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc
tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga
gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg
aagccgcggg gggaccgtca gtcttcctct tccccccaaa acccaaggac
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt
gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg
caaggagtac aagtgcaagg tctccaacaa agccctccca gccccccatcg
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac
accctgcccc catcccggga ggagatgacc aagaaccagg tcagcctgag
ttgcgcagtc aaaggcttct atcccagcga catcgccgtg gagtgggaga
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag
gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc
acaaccgcta cacgcagaag agcctctccc tgtctccggg taaa

[00369] The amino acid sequence of the fourth polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 1 is (**SEQ ID NO:258**):

DIQMTQTTSS LSASLGDRIT ISCRASQDIS NYLNWYQQKP DGTVKLLIYY
TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GYTLYTFGGG
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD

NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
SSPVTKSFNR GEC

[00370] In **SEQ ID NO:258**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 1 (**SEQ ID NO:153**), and residues 107-213 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00371] A polynucleotide that encodes **SEQ ID NO:258** is (**SEQ ID NO:259**):

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga
cagaatcacc atcagttgca gggcaagtca ggacattagc aattatttaa
actggtatca gcagaaacca gatggaactg ttaaactcct gatctactac
acatcaagat tacactcagg agtcccatca aggttcagtg gcagtgggtc
tggaacagat tattctctca ccattagcaa cctggagcaa gaagatattg
ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
accaagctgg aaataaaacg tacggtggct gcaccatcgg tcttcatctt
cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat
aacgccctcc aatcgggtaa ctcccaggag agtgtcacag agcaggacag
caaggacagc acctacagcc tcagcagcac cctgacgctg agcaaagcag
actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg
agctcgcccg tcacaaagag cttcaacagg ggagagtgt

L. gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2

[00372] A Tri-Specific Binding Molecule composed of four polypeptide chains was constructed that comprises the VL and VH domains of gpA33 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of EphA2 mAb 2. The Tri-Specific Binding Molecule was accordingly designated "**gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:260**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL
EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

[00373] In **SEQ ID NO:260**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00374] A polynucleotide that encodes **SEQ ID NO:260** is (**SEQ ID NO:261**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaaa

[00375] The amino acid sequence of the second polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2 is (**SEQ ID NO:262**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KASGYTFTGS
WMNWVRQAPG QGLEWIGRIY PGDGETNYNG KFKDRVTITA DKSTSTAYME
LSSLRSEDTA VYYCARIYGN NVYFDVWGQG TTVTVSSGGC GGGKVAALKE
KVAALKEKVA ALKEKVAALK E

[00376] In **SEQ ID NO:262**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-243 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 244-271 are a K-coil Domain (**SEQ ID NO:40**).

[00377] A polynucleotide that encodes **SEQ ID NO:262** is (**SEQ ID NO:263)**:

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtc cagctggtcc agagcggggc cgaagtcaaa aaacccggag
caagcgtgaa ggtctcctgc aaagcatcag gctatacatt tacaggcagc
tggatgaact gggtgaggca ggctccagga cagggactgg agtggatcgg
gcgcatctac cctggagacg gcgaaactaa ctataatgga aagttcaaag
accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat
ttacggaaac aatgtctatt ttgacgtgtg ggggcaggga acaactgtga
ctgtctcctc cggaggatgt ggcggtggaa aagtggccgc actgaaggag
aaagttgctg ctttgaaaga gaaggtcgcc gcacttaagg aaaaggtcgc
agccctgaaa gag

[00378] The amino acid sequence of the third polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2 is (**SEQ ID NO:264**):

QIQLVQSGPE LKKPGETVKI SCKASGFTFT NYGMNWVKQA PGKGLKWMGW
INTYIGEPTY ADDFKGRFVF SLETSASTAY LQINNLKNED MATYFCAREL
GPYYFDYWGQ GTTLTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPEAAGGPS VFLFPPKPKD

TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY
TLPPSREEMT KNQVSLSCAV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNRYTQK SLSLSPGK

[00379] In **SEQ ID NO:264**, amino acid residues 1-118 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 2 (**SEQ ID NO:167**), residues 119-216 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 217-231 correspond to a linker (**SEQ ID NO:209**), and residues 232-448 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00380] A polynucleotide that encodes **SEQ ID NO:264** is (**SEQ ID NO:265**):

cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac
agtcaagatc tcctgcaagg cttctgggtt taccttcaca aactatggaa
tgaactgggt gaagcaggct ccaggaaagg gtttaaagtg gatgggctgg
ataaacacct atattggaga gccgacatat gctgatgact tcaagggacg
gtttgtcttc tctttggaaa cctctgccag cactgcctat ttgcagatca
acaacctcaa aaatgaggac atggccacat atttctgtgc aagagaactg
ggaccatact actttgacta ctggggccaa ggcaccactc tcacagtctc
ctccgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac
ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg
cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc
tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga
gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg
aagccgcggg gggaccgtca gtcttcctct tccccccaaa acccaaggac
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt
gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg
caaggagtac aagtgcaagg tctccaacaa agccctccca gccccccatcg
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac
accctgcccc catcccggga ggagatgacc aagaaccagg tcagcctgag
ttgcgcagtc aaaggcttct atcccagcga catcgccgtg gagtgggaga
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag
gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc
acaaccgcta cacgcagaag agcctctccc tgtctccggg taaa

[00381] The amino acid sequence of the fourth polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2 is (**SEQ ID NO:266**):

DVVMTQTPLS LPVSLGDQAS ISCRSSQSLV HSSGNTYLHW YLQKPGQSPK
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVP
TFGSGTKLEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV

QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC

[00382] In **SEQ ID NO:266**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 1 (**SEQ ID NO:163**), and residues 112-218 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00383] A polynucleotide that encodes **SEQ ID NO:266** is (**SEQ ID NO:267**):

gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc atctcttgca gatctagtca gagccttgta cacagtagtg gaaacaccta tttacattgg tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc acgttcggct cggggacaaa gttggaaata aaacgtacgg tggctgcacc atcggtcttc atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt

M. gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 3

[00384] A Tri-Specific Binding Molecule composed of four polypeptide chains was constructed that comprises the VL and VH domains of gpA33 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of EphA2 mAb 3. The Tri-Specific Binding Molecule was accordingly designated "**gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 3**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:268**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK

[00385] In **SEQ ID NO:268**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00386] A polynucleotide that encodes **SEQ ID NO:268** is (**SEQ ID NO:269**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaaa

[00387] The amino acid sequence of the second polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 3 is (**SEQ ID NO:270**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KASGYTFTGS
WMNWVRQAPG QGLEWIGRIY PGDGETNYNG KFKDRVTITA DKSTSTAYME
LSSLRSEDTA VYYCARIYGN NVYFDVWGQG TTVTVSSGGC GGGKVAALKE
KVAALKEKVA ALKEKVAALK E

[00388] In **SEQ ID NO:270**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-243 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 244-271 are a K-coil Domain (**SEQ ID NO:40**).

[00389] A polynucleotide that encodes **SEQ ID NO:270** is (**SEQ ID NO:271**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtc cagctggtcc agagcggggc cgaagtcaaa aaacccggag
caagcgtgaa ggtctcctgc aaagcatcag gctatacatt tacaggcagc
tggatgaact gggtgaggca ggctccagga cagggactgg agtggatcgg
gcgcatctac cctggagacg gcgaaactaa ctataatgga aagttcaaag
accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat
ttacggaaac aatgtctatt ttgacgtgtg ggggcaggga acaactgtga
ctgtctcctc cggaggatgt ggcggtggaa aagtggccgc actgaaggag
aaagttgctg ctttgaaaga gaaggtcgcc gcacttaagg aaaaggtcgc
agccctgaaa gag

[00390] The amino acid sequence of the third polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 3 is (**SEQ ID NO:272**):

EVQLVESGGG SVKPGGSLKL SCAASGFTFT DHYMYWVRQT PEKRLEWVAT
ISDGGSFTSY PDSVKGRFTI SRDIAKNNLY LQMSSLKSED TAMYYCTRDE
SDRPFPYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPEAAGGPS VFLFPPKPKD

TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY
TLPPSREEMT KNQVSLSCAV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNRYTQK SLSLSPGK

[00391] In **SEQ ID NO:272**, amino acid residues 1-118 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 3 (**SEQ ID NO:177**), residues 119-216 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 217-231 correspond to a linker (**SEQ ID NO:209**), and residues 232-448 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00392] A polynucleotide that encodes **SEQ ID NO:272** is (**SEQ ID NO:273**):

gaagtgcagc tggtggagtc tgggggaggc tcagtgaagc ctggagggtc
cctgaaactc tcctgtgcag cctctggatt cactttcact gaccattaca
tgtattgggt tcgccagact ccggaaaaga ggctggagtg ggtcgcaacc
attagtgatg gcggtagttt cacctcctat ccagacagtg tgaaggggcg
attcaccatc tccagagaca ttgccaagaa caacctgtac ctccaaatga
gcagtctgaa gtctgaggac acagccatgt attactgtac aagagatgag
agcgataggc cgtttcctta ctggggccaa gggactctgg tcactgtctc
ctccgcctcc accaagggcc catcggtctt ccccctggca ccctcctcca
agagcacctc tgggggcaca gcggccctgg gctgcctggt caaggactac
ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg
cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca
gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc
tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga
gcccaaatct tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg
aagccgcggg gggaccgtca gtcttcctct tccccccaaa acccaaggac
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt
gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg
aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg
caaggagtac aagtgcaagg tctccaacaa agccctccca gcccccatcg
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac
accctgcccc catcccggga ggagatgacc aagaaccagg tcagcctgag
ttgcgcagtc aaaggcttct atcccagcga catcgccgtg gagtgggaga
gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag
gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc
acaaccgcta cacgcagaag agcctctccc tgtctccggg taaa

[00393] The amino acid sequence of the fourth polypeptide chain of gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 3 is (**SEQ ID NO:274**):

DIVLTQSHRS MSTSVGDRVN ITCKASQDVT TAVAWYQQKP GQSPKLLIFW
ASTRHAGVPD RFTGSGSGTD FTLTISSVQA GDLALYYCQQ HYSTPYTFGG
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

[00394] In **SEQ ID NO:274**, amino acid residues 1-107 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 3 (**SEQ ID NO:172**), and residues 108-214 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00395] A polynucleotide that encodes **SEQ ID NO:274** is (**SEQ ID NO:275**):

gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga
cagggtcaac atcacctgca aggccagtca ggatgtgact actgctgtag
cctggtatca acaaaaacca gggcaatctc ctaaattact gattttctgg
gcatccaccc ggcacgctgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tttactctca ccatcagcag tgtgcaggct ggagacctgg
cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg
gggaccaagc tggaaataaa acgtacggtg gctgcaccat cggtcttcat
cttcccgcca tctgatgagc agttgaaatc tggaactgcc tctgttgtgt
gcctgctgaa taacttctat cccagagagg ccaaagtaca gtggaaggtg
gataacgccc tccaatcggg taactcccag gagagtgtca cagagcagga
cagcaaggac agcacctaca gcctcagcag caccctgacg ctgagcaaag
cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc
ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt

N. EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1

[00396] An alternative EphA2 / CD3 / gpA33 Tri-Specific Binding Molecule was constructed. The molecule was composed of four polypeptide chains and comprises the VL and VH domains of EphA2 mAb 1, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of gpA33 mAb 1. The molecule was designated "**EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:276**):

DIQMTQTTSS LSASLGDRIT ISCRASQDIS NYLNWYQQKP DGTVKLLIYY
TSRLHSGVPS RFSGSGSGTD YSLTISNLEQ EDIATYFCQQ GYTLYTFGGG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSG GCGGGEVAAL
EKEVAALEKE VAALEKEVAA LEKGGGDKTH TCPPCPAPEA AGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS REEMTKNQVS LWCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

[00397] In **SEQ ID NO:276**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 1 (**SEQ ID NO:153**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-245 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 246-273 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 274-276 are the linker GGG, residues 277-286 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 287-503 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00398] A polynucleotide that encodes **SEQ ID NO:276** is (**SEQ ID NO:277**):

gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga
cagaatcacc atcagttgca gggcaagtca ggacattagc aattatttaa
actggtatca gcagaaacca gatggaactg ttaaactcct gatctactac
acatcaagat tacactcagg agtcccatca aggttcagtg gcagtgggtc
tggaacagat tattctctca ccattagcaa cctggagcaa gaagatattg
ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
accaagctgg aaataaaagg tggaggatcc ggcggcggag gcgaggtgca
gctggtggag tctgggggag gcttggtcca gcctggaggg tccctgagac
tctcctgtgc agcctctgga ttcaccttca gcacatacgc tatgaattgg
gtccgccagg ctccagggaa ggggctggag tgggttggaa ggatcaggtc
caagtacaac aattatgcaa cctactatgc cgactctgtg aagggtagat
tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa
cttcggcaat tcttacgtgt cttggtttgc ttattgggga caggggacac
tggtgactgt gtcttccgga ggatgtggcg gtggagaagt ggccgcactg
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaag gcggcgggga caaaactcac acatgcccac
cgtgcccagc acctgaagcc gcgggggac cgtcagtctt cctcttcccc
ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg
cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt
acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag
cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca
ggactggctg aatggcaagg agtacaagtg caaggtctcc aacaaagccc
tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa
ccaggtcagc ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg
ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg
cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac
cgtggacaag agcaggtggc agcaggggaa cgtcttctca tgctccgtga
tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
ccgggtaaa

[00399] The amino acid sequence of the second polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:278**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQV QLKESGPGLV APSQSLSITC TVSGFSLSRY
SVHWVRQPPG KGLEWLGMIW GGGSTDYNSA LKSRLSISKD NSKSQVFLKM
NSLQTDDTAM YYCARKHGNY YTMDYWGQGT SVTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00400] In **SEQ ID NO:278**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 1 (**SEQ ID NO:158**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00401] A polynucleotide that encodes **SEQ ID NO:278** is (**SEQ ID NO:279**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacaggtg cagctgaagg agtcaggacc tggcctggtg gcaccctcac
agagcctgtc catcacatgc actgtctctg ggttctcatt atccagatat
agtgtacact gggttcgcca gcctccagga aagggtctgg agtggctggg
aatgatatgg ggtggtggaa gcacagacta taattcagct ctcaaatcca
gactgagtat cagcaaggac aactccaaga gccaagtttt cttaaaaatg
aacagtctgc aaactgatga cacagccatg tactactgtg ccagaaaaca
tggtaactac tatactatgg actactgggg tcaaggaacc tcagtcaccg
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00402] The amino acid sequence of the third polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:280**):

QVQLVQSGAE VKKPGASVKV SCKASGYTFT GSWMNWVRQA PGQGLEWIGR
IYPGDGETNY NGKFKDRVTI TADKSTSTAY MELSSLRSED TAVYYCARIY
GNNVYFDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPEAAGGP SVFLFPPKPK

DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV
YTLPPSREEM TKNQVSLSCA VKGFYPSDIA VEWESNGQPE NNYKTTPPVL
DSDGSFFLVS KLTVDKSRWQ QGNVFSCSVM HEALHNRYTQ KSLSLSPGK

[00403] In **SEQ ID NO:280**, amino acid residues 1-119 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 120-217 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 218-232 correspond to a linker (**SEQ ID NO:209**), and residues 233-449 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00404] A polynucleotide that encodes **SEQ ID NO:280** is (**SEQ ID NO:281**):

caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag
cgtgaaggtc tcctgcaaag catcaggcta tacatttaca ggcagctgga
tgaactgggt gaggcaggct ccaggacagg gactggagtg gatcgggcgc
atctaccctg gagacggcga aactaactat aatggaaagt tcaaagaccg
agtgaccatc acagccgata agtctactag taccgcctac atggagctga
gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac
ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt
ctcctccgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag
cggcgtgcac accttcccgg ctgtcctaca gtcctcagga ctctactccc
tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt
tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac
ctgaagccgc ggggggaccg tcagtcttcc tcttcccccc aaaacccaag
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga
cgtgagccac gaagaccctg aggtcaagtt caactggtac gtggacggcg
tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa
tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct
gagttgcgca gtcaaaggct tctatcccag cgacatcgcc gtggagtggg
agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag
caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc
tgcacaaccg ctacacgcag aagagcctct ccctgtctcc gggtaaa

[00405] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:282**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD

NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

[00406] In **SEQ ID NO:282**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), and residues 107-213 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00407] A polynucleotide that encodes **SEQ ID NO:282** is (**SEQ ID NO:283**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg agctcgcccg tcacaaagag cttcaacagg ggagagtgt

O. EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb 1

[00408] A second alternative EphA2 / CD3 / gpA33 Tri-Specific Binding Molecule was constructed. The molecule was composed of four polypeptide chains and comprises the VL and VH domains of EphA2 mAb 2, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of gpA33 mAb 1. The molecule was designated "**EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:284**):

DVVMTQTPLS LPVSLGDQAS ISCRSSQSLV HSSGNTYLHW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVP TFGSGTKLEI KGGGSGGGGE VQLVESGGGL VQPGGSLRLS CAASGFTFST YAMNWVRQAP GKGLEWVGRI RSKYNNYATY YADSVKGRFT ISRDDSKNSL YLQMNSLKTE DTAVYYCVRH GNFGNSYVSW FAYWGQGTLV TVSSGGCGGG EVAALEKEVA ALEKEVAALE KEVAALEKGG GDKTHTCPPC PAPEAAGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT KNQVSLWCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK

[00409] In **SEQ ID NO:284**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 2 (**SEQ ID NO:163**), residues 112-119 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 120-244 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 245-250 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 251-278 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 279-281 are the linker GGG, residues 282-291 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 292-508 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00410] A polynucleotide that encodes **SEQ ID NO:284** is (**SEQ ID NO:285**):

gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga
tcaagcctcc atctcttgca gatctagtca gagccttgta cacagtagtg
gaaacaccta tttacattgg tacctgcaga agccaggcca gtctccaaag
ctcctgatct acaaagtttc caaccgattt tctggggtcc cagacaggtt
cagtggcagt ggatcaggga cagatttcac actcaagatc agcagagtgg
aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc
acgttcggct cggggacaaa gttggaaata aaaggtggag gatccggcgg
cggaggcgag gtgcagctgg tggagtctgg gggaggcttg gtccagcctg
gagggtccct gagactctcc tgtgcagcct ctggattcac cttcagcaca
tacgctatga attgggtccg ccaggctcca gggaaggggc tggagtgggt
tggaaggatc aggtccaagt acaacaatta tgcaacctac tatgccgact
ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg
tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg
tgtgagacac ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt
ggggacaggg gacactggtg actgtgtctt ccggaggatg tggcggtgga
gaagtggccg cactggagaa agaggttgct gctttggaga aggaggtcgc
tgcacttgaa aaggaggtcg cagccctgga gaaaggcggc ggggacaaaa
ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac
ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa gaccctgagg
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca
aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct
caccgtcctg caccaggact ggctgaatgg caaggagtac aagtgcaagg
tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc
aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga
ggagatgacc aagaaccagg tcagcctgtg gtgcctggtc aaaggcttct
atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac
aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct
ctacagcaag ctcaccgtgg acaagagcag gtggcagcag gggaacgtct
tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
agcctctccc tgtctccggg taaa

[00411] The amino acid sequence of the second polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:286**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGQI QLVQSGPELK KPGETVKISC KASGFTFTNY
GMNWVKQAPG KGLKWMGWIN TYIGEPTYAD DFKGRFVFSL ETSASTAYLQ
INNLKNEDMA TYFCARELGP YYFDYWGQGT TLTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00412] In **SEQ ID NO:286**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 2 (**SEQ ID NO:167**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00413] A polynucleotide that encodes **SEQ ID NO:286** is (**SEQ ID NO:287**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggacagatc cagttggtgc agtctggacc tgagctgaag aagcctggag
agacagtcaa gatctcctgc aaggcttctg ggtttacctt cacaaactat
ggaatgaact gggtgaagca ggctccagga aagggtttaa agtggatggg
ctggataaac acctatattg gagagccgac atatgctgat gacttcaagg
gacggtttgt cttctctttg gaaacctctg ccagcactgc ctatttgcag
atcaacaacc tcaaaaatga ggacatggcc acatatttct gtgcaagaga
actgggacca tactactttg actactgggg ccaaggcacc actctcacag
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00414] The amino acid sequence of the third polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:288**):

QVQLVQSGAE VKKPGASVKV SCKASGYTFT GSWMNWVRQA PGQGLEWIGR
IYPGDGETNY NGKFKDRVTI TADKSTSTAY MELSSLRSED TAVYYCARIY
GNNVYFDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPEAAGGP SVFLFPPKPK

DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV
YTLPPSREEM TKNQVSLSCA VKGFYPSDIA VEWESNGQPE NNYKTTPPVL
DSDGSFFLVS KLTVDKSRWQ QGNVFSCSVM HEALHNRYTQ KSLSLSPGK

[00415] In **SEQ ID NO:288**, amino acid residues 1-119 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 120-217 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 218-232 correspond to a linker (**SEQ ID NO:209**), and residues 233-449 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00416] A polynucleotide that encodes **SEQ ID NO:288** is (**SEQ ID NO:289**):

caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag
cgtgaaggtc tcctgcaaag catcaggcta tacatttaca ggcagctgga
tgaactgggt gaggcaggct ccaggacagg gactggagtg gatcgggcgc
atctaccctg gagacggcga aactaactat aatggaaagt tcaaagaccg
agtgaccatc acagccgata agtctactag taccgcctac atggagctga
gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac
ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt
ctcctccgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag
cggcgtgcac accttcccgg ctgtcctaca gtcctcagga ctctactccc
tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt
tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac
ctgaagccgc ggggggaccg tcagtcttcc tcttcccccc aaaacccaag
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga
cgtgagccac gaagaccctg aggtcaagtt caactggtac gtggacggcg
tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa
tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct
gagttgcgca gtcaaaggct tctatcccag cgacatcgcc gtggagtggg
agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag
caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc
tgcacaaccg ctacacgcag aagagcctct ccctgtctcc gggtaaa

[00417] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:290**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD

NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
SSPVTKSFNR GEC

[00418] In **SEQ ID NO:290**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), and residues 107-213 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00419] A polynucleotide that encodes **SEQ ID NO:290** is (**SEQ ID NO:291**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt
cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat
aacgccctcc aatcgggtaa ctcccaggag agtgtcacag agcaggacag
caaggacagc acctacagcc tcagcagcac cctgacgctg agcaaagcag
actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg
agctcgcccg tcacaaagag cttcaacagg ggagagtgt

P. EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb 1

[00420] A third alternative EphA2 / CD3 / gpA33 Tri-Specific Binding Molecule was constructed. The molecule was composed of four polypeptide chains and comprises the VL and VH domains of EphA2 mAb 3, the VL and VH domains of antibody CD3 mAb 2 and the VL and VH domains of gpA33 mAb 1. The molecule was designated "**EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb 1**." The amino acid sequence of the first polypeptide chain of this Tri-Specific Binding Molecule is (**SEQ ID NO:292**):

DIVLTQSHRS MSTSVGDRVN ITCKASQDVT TAVAWYQQKP GQSPKLLIFW
ASTRHAGVPD RFTGSGSGTD FTLTISSVQA GDLALYYCQQ HYSTPYTFGG
GTKLEIKGGG SGGGGEVQLV ESGGGLVQPG GSLRLSCAAS GFTFSTYAMN
WVRQAPGKGL EWVGRIRSKY NNYATYYADS VKGRFTISRD DSKNSLYLQM
NSLKTEDTAV YYCVRHGNFG NSYVSWFAYW GQGTLVTVSS GGCGGGEVAA
LEKEVAALEK EVAALEKEVA ALEKGGGDKT HTCPPCPAPE AAGGPSVFLF
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP
REPQVYTLPP SREEMTKNQV SLWCLVKGFY PSDIAVEWES NGQPENNYKT
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL
SPGK

[00421] In **SEQ ID NO:292**, amino acid residues 1-107 correspond to the amino acid sequence of the VL Domain of EphA2 mAb 3 (**SEQ ID NO:172**), residues 108-115 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 116-240 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 241-246 correspond to the GGCGGG linker (**SEQ ID NO:34**), residues 247-274 correspond to an E-coil Domain (**SEQ ID NO:39**), residues 275-277 are the linker GGG, residues 278-287 are the linker DKTHTCPPCP (**SEQ ID NO:48**), and residues 288-504 are the "knob-bearing" CH2-CH3 Domain (**SEQ ID NO:52**).

[00422] A polynucleotide that encodes **SEQ ID NO:292** is (**SEQ ID NO:293**):

gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga
cagggtcaac atcacctgca aggccagtca ggatgtgact actgctgtag
cctggtatca acaaaaacca gggcaatctc ctaaattact gattttctgg
gcatccaccc ggcacgctgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tttactctca ccatcagcag tgtgcaggct ggagacctgg
cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg
gggaccaagc tggaaataaa aggtggagga tccggcggcg gaggcgaggt
gcagctggtg gagtctgggg gaggcttggt ccagcctgga gggtccctga
gactctcctg tgcagcctct ggattcacct tcagcacata cgctatgaat
tgggtccgcc aggctccagg gaaggggctg gagtgggttg gaaggatcag
gtccaagtac aacaattatg caacctacta tgccgactct gtgaagggta
gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg
aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg
taacttcggc aattcttacg tgtcttggtt tgcttattgg ggacagggga
cactggtgac tgtgtcttcc ggaggatgtg gcggtggaga agtggccgca
ctggagaaag aggttgctgc tttggagaag gaggtcgctg cacttgaaaa
ggaggtcgca gccctggaga aaggcggcgg ggacaaaact cacacatgcc
caccgtgccc agcacctgaa gccgcggggg gaccgtcagt cttcctcttc
cccccaaaac ccaaggacac cctcatgatc tcccggaccc ctgaggtcac
atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc aagttcaact
ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag
gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag
ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc
cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa
gaaccaggtc agcctgtggt gcctggtcaa aggcttctat cccagcgaca
tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct
caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg
tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg
tctccgggta aa

[00423] The amino acid sequence of the second polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:294**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGEV QLVESGGGSV KPGGSLKLSC AASGFTFTDH
YMYWVRQTPE KRLEWVATIS DGGSFTSYPD SVKGRFTISR DIAKNNLYLQ
MSSLKSEDTA MYYCTRDESD RPFPYWGQGT LVTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00424] In **SEQ ID NO:294**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 3 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the amino acid sequence of the VH Domain of EphA2 mAb 3 (**SEQ ID NO:177**), residues 237-242 correspond to the linker GGCGGG (**SEQ ID NO:34**), and residues 243-270 are a K-coil Domain (**SEQ ID NO:40**).

[00425] A polynucleotide that encodes **SEQ ID NO:294** is (**SEQ ID NO:295**):

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg
tggagaagtg cagctggtgg agtctggggg aggctcagtg aagcctggag
ggtccctgaa actctcctgt gcagcctctg gattcacttt cactgaccat
tacatgtatt gggttcgcca gactccggaa aagaggctgg agtgggtcgc
aaccattagt gatggcggta gtttcacctc ctatccagac agtgtgaagg
ggcgattcac catctccaga gacattgcca agaacaacct gtacctccaa
atgagcagtc tgaagtctga ggacacagcc atgtattact gtacaagaga
tgagagcgat aggccgtttc cttactgggg ccaagggact ctggtcactg
tctcctccgg aggatgtggc ggtggaaaag tggccgcact gaaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

[00426] The amino acid sequence of the third polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:296**):

QVQLVQSGAE VKKPGASVKV SCKASGYTFT GSWMNWVRQA PGQGLEWIGR
IYPGDGETNY NGKFKDRVTI TADKSTSTAY MELSSLRSED TAVYYCARIY
GNNVYFDVWG QGTTVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPEAAGGP SVFLFPPKPK

DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV
YTLPPSREEM TKNQVSLSCA VKGFYPSDIA VEWESNGQPE NNYKTTPPVL
DSDGSFFLVS KLTVDKSRWQ QGNVFSCSVM HEALHNRYTQ KSLSLSPGK

[00427] In **SEQ ID NO:296**, amino acid residues 1-119 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 120-217 correspond to a modified CH1 Domain (**SEQ ID NO:208**), residues 218-232 correspond to a linker (**SEQ ID NO:209**), and residues 233-449 correspond to the "hole-bearing" CH2-CH3 Domain (**SEQ ID NO:53**).

[00428] A polynucleotide that encodes **SEQ ID NO:296** is (**SEQ ID NO:297**):

caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag
cgtgaaggtc tcctgcaaag catcaggcta tacatttaca ggcagctgga
tgaactgggt gaggcaggct ccaggacagg gactggagtg gatcgggcgc
atctaccctg gagacggcga aactaactat aatggaaagt tcaaagaccg
agtgaccatc acagccgata agtctactag taccgcctac atggagctga
gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac
ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt
ctcctccgcc tccaccaagg gcccatcggt cttccccctg gcaccctcct
ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag
cggcgtgcac accttcccgg ctgtcctaca gtcctcagga ctctactccc
tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt
tgagcccaaa tcttgtgaca aaactcacac atgcccaccg tgcccagcac
ctgaagccgc ggggggaccg tcagtcttcc tcttcccccc aaaacccaag
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga
cgtgagccac gaagaccctg aggtcaagtt caactggtac gtggacggcg
tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa
tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca
tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagcct
gagttgcgca gtcaaaggct tctatcccag cgacatcgcc gtggagtggg
agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag
caggtggcag caggggaacg tcttctcatg ctccgtgatg catgaggctc
tgcacaaccg ctacacgcag aagagcctct ccctgtctcc gggtaaa

[00429] The amino acid sequence of the fourth polypeptide chain of EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb 1 is (**SEQ ID NO:298**):

DIQLTQSPSF LSASVGDRVT ITCSARSSIS FMYWYQQKPG KAPKLLIYDT
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYCQQW SSYPLTFGQG
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD

NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL
SSPVTKSFNR GEC

[00430] In **SEQ ID NO:298**, amino acid residues 1-106 correspond to the amino acid sequence of the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), and residues 107-213 correspond to the CL Kappa Domain (**SEQ ID NO:210**).

[00431] A polynucleotide that encodes **SEQ ID NO:298** is (**SEQ ID NO:299**):

gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga
tcgagtgact attacttgct ctgctaggtc ctcaatcagc ttcatgtact
ggtatcagca gaagcccggc aaagcaccta agctgctgat ctacgacaca
agcaacctgg cctccggggt gccatctcgg ttctctggca gtgggtcagg
aactgagttt accctgacaa ttagctccct ggaggctgaa gatgccgcta
cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt
cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc
tgctgaataa cttctatccc agagaggcca aagtacagtg gaaggtggat
aacgccctcc aatcgggtaa ctcccaggag agtgtcacag agcaggacag
caaggacagc acctacagcc tcagcagcac cctgacgctg agcaaagcag
actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg
agctcgcccg tcacaaagag cttcaacagg ggagagtgt

IV. Reference Antibodies and Diabodies

[00432] In order to assist in the characterization of the Tri-Specific Binding Molecules of the present invention, the following reference diabodies were constructed.

Q. DR5 mAb 1 x CD3 mAb 2 Diabody

[00433] An exemplary bi-specific diabody composed of two polypeptide chains was constructed having the VL and VH domains of anti-human DR5 antibody DR5 mAb 1 and the VL and VH domains of CD3 mAb 2. The diabody was designated "**DR5 mAb 1 x CD3 mAb 2 diabody**." The amino acid sequence of the first polypeptide chain of this diabody is (**SEQ ID NO:140**):

DIVLTQSPAS LAVSLGQRAT ISCRASKSVS SSGYSYMHWY QQKPGQPPKV
LIFLSSNLDS GVPARFSGSG SGTDFTLNIH PVEDGDAATY YCQHSRDLPP
TFGGGTKLEI KGGGSGGGGE VQLVESGGGL VQPGGSLRLS CAASGFTFST
YAMNWVRQAP GKGLEWVGRI RSKYNNYATY YADSVKGRFT ISRDDSKNSL
YLQMNSLKTE DTAVYYCVRH GNFGNSYVSW FAYWGQGTLV TVSSASTKGE
VAACEKEVAA LEKEVAALEK EVAALEK

[00434] In **SEQ ID NO:140**, amino acid residues 1-111 correspond to the amino acid sequence of the VL Domain of DR5 mAb 1 (**SEQ ID NO:3**), residues 112-119 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 120-244 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 245-249 correspond to the ASTKG linker (**SEQ ID NO:47**) and residues 250-277 correspond to a cysteine-containing E-coil Domain (**SEQ ID NO:41**). A polynucleotide that encodes **SEQ ID NO:140** is **SEQ ID NO:141**:

gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca
gagggccacc atctcatgca gggccagcaa aagtgtcagt tcctctggct
atagttatat gcactggtac caacagaaac caggacagcc acccaaagtc
ctcatctttc tttcatccaa cctagattct ggggtccctg ccaggttcag
tggcagtggg tctgggacag acttcaccct caacatccat cctgtggagg
atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg
acgttcggtg gaggcaccaa gctggaaatc aaaggaggcg gatccggcgg
cggaggcgag gtgcagctgg tggagtctgg gggaggcttg gtccagcctg
gagggtccct gagactctcc tgtgcagcct ctggattcac cttcagcaca
tacgctatga attgggtccg ccaggctcca gggaaggggc tggagtgggt
tggaaggatc aggtccaagt acaacaatta tgcaacctac tatgccgact
ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg
tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg
tgtgagacac ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt
ggggacaggg gacactggtg actgtgtctt ccgcctccac caagggcgaa
gtggccgcat gtgagaaaga ggttgctgct ttggagaagg aggtcgctgc
acttgaaaag gaggtcgcag ccctggagaa a

[00435] The amino acid sequence of the second polypeptide chain of the DR5 mAb 1 x CD3 mAb 2 diabody is (**SEQ ID NO:142**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGEV KFLESGGGLV QPGGSLKLSC VASGFDFSRY
WMSWVRQAPG KGLEWIGEIN PDSNTINYTP SLKDKFIISR DNAKNTLYLQ
MTKVRSEDTA LYYCTRRAYY GNPAWFAYWG QGTLVTVSAA STKGKVAACK
EKVAALKEKV AALKEKVAAL KE

[00436] In **SEQ ID NO:142**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-239 correspond to the amino acid sequence of the VH Domain of DR5 mAb 1 (**SEQ ID NO:8**), except that the C-terminal serine residue of **SEQ ID NO:8** has been replaced with an alanine residue), residues 240-244 correspond to an

ASTKG linker (**SEQ ID NO:47**), and residues 245-272 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**). A polynucleotide that encodes **SEQ ID NO:142** is **SEQ ID NO:143**:

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
gggggtggca caaaactgac tgtgctggga ggtggtggat ccggcggcgg
aggcgaggtg aagtttctcg agtctggagg tggcctggtg cagcctggag
gatccctgaa actctcctgt gtagcctcag gattcgattt tagtagatac
tggatgagtt gggtccggca ggctccaggg aaagggctag aatggattgg
agaaattaat ccagatagca atacgataaa ctatacgcca tctctaaagg
ataaattcat catctccaga gacaacgcca aaaatacgct gtatctgcaa
atgaccaaag tgagatctga ggacacagcc ctttattatt gtacaagaag
ggcctactat ggtaacccgg cctggtttgc ttactggggc caagggactc
tggtcactgt ctctgcagcc tccaccaagg gcaaagtggc cgcatgtaag
gagaaagttg ctgctttgaa agagaaggtc gccgcactta aggaaaaggt
cgcagccctg aaagag

R. DR5 mAb 2 x CD3 mAb 2 Diabody

[00437] An exemplary bi-specific diabody composed of two polypeptide chains was constructed having the VL and VH domains of anti-human DR5 antibody DR5 mAb 2 and the VL and VH domains of CD3 mAb 2. The diabody was designated "**DR5 mAb 2 x CD3 mAb 2 diabody**." The amino acid sequence of the first polypeptide chain of this diabody is (**SEQ ID NO:144**):

DIVMTQSHKF MSTSVGDRVS ITCKASQDVN TAVAWYQQKP GQSPKLLIYW
ASTRHTGVPD RFTGSGSGTD YTLTIKSVQA EDLTLYYCQQ HYITPWTFGG
GTKLEIKGGG SGGGGEVQLV ESGGGLVQPG GSLRLSCAAS GFTFSTYAMN
WVRQAPGKGL EWVGRIRSKY NNYATYYADS VKGRFTISRD DSKNSLYLQM
NSLKTEDTAV YYCVRHGNFG NSYVSWFAYW GQGTLVTVSS ASTKGEVAAC
EKEVAALEKE VAALEKEVAA LEK

[00438] In **SEQ ID NO:144**, amino acid residues 1-107 correspond to the amino acid sequence of the VL Domain of DR5 mAb 2 (**SEQ ID NO:13**), residues 108-115 correspond to intervening spacer peptide (Linker 1) (**SEQ ID NO:33**), residues 116-240 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 241-245 correspond to an ASTKG linker (**SEQ ID NO:47**) and residues 246-273 correspond to a cysteine-containing E-

coil Domain (**SEQ ID NO:41**). A polynucleotide that encodes **SEQ ID NO:144** is **SEQ ID NO:145**:

gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga
cagggtcagc atcacctgca aggccagtca ggatgtgaat actgctgtag
cctggtatca acaaaaacca gggcaatctc ctaaactact gatttactgg
gcatccaccc ggcacactgg agtccctgat cgcttcacag gcagtggatc
tgggacagat tatacactca ccatcaaaag tgtgcaggct gaagacctga
cactttatta ctgtcagcaa cactatatca ctccgtggac gttcggtgga
ggcaccaagc tggaaatcaa aggaggcgga tccggcggcg gaggcgaggt
gcagctggtg gagtctgggg gaggcttggt ccagcctgga gggtccctga
gactctcctg tgcagcctct ggattcacct tcagcacata cgctatgaat
tgggtccgcc aggctccagg gaaggggctg gagtgggttg gaaggatcag
gtccaagtac aacaattatg caacctacta tgccgactct gtgaagggta
gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg
aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg
taacttcggc aattcttacg tgtcttggtt tgcttattgg ggacagggga
cactggtgac tgtgtcttcc gcctccacca agggcgaagt ggccgcatgt
gagaaagagg ttgctgcttt ggagaaggag gtcgctgcac ttgaaaagga
ggtcgcagcc ctggagaaa

[00439] The amino acid sequence of the second polypeptide chain of the DR5 mAb 2 x CD3 mAb 2 diabody is (**SEQ ID NO:146**):

QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF
GGGTKLTVLG GGGSGGGGKV QLQQSGAELV KPGASVKLSC KASGYTFTEY
ILHWVKQKSG QGLEWIGWFY PGNNNIKYNE KFKDKATLTA DKSSSTVYME
LSRLTSEDSA VYFCARHEQG PGYFDYWGQG TTLTVSSAST KGKVAACKEK
VAALKEKVAA LKEKVAALKE

[00440] In **SEQ ID NO:146**, amino acid residues 1-110 correspond to the amino acid sequence of the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of DR5 mAb 2 (**SEQ ID NO:18**), residues 238-242 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 243-270 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**). A polynucleotide that encodes **SEQ ID NO:146** is **SEQ ID NO:147**:

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac
tgtgaccctg acatgcagat ccagcacagg cgcagtgacc acatctaact
acgccaattg ggtgcagcag aagccaggac aggcaccaag gggcctgatc
gggggtacaa acaaaagggc tccctggacc cctgcacggt tttctggaag
tctgctgggc ggaaaggccg ctctgactat taccggggca caggccgagg
acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc

ggggggtggca caaaactgac tgtgctggga gggggtggat ccggcggcgg
aggcaaggtc cagctgcagc agtctggagc tgaactggtg aaacccgggg
catcagtgaa gctgtcctgc aaggcttctg ggtacacctt cactgagtat
attttacact gggtaaagca gaagtctgga cagggtcttg agtggattgg
gtggttttat cctggaaata ataatataaa gtacaatgag aaattcaagg
acaaggccac actgactgcg gacaaatcct ccagcacagt ctatatggaa
cttagtagat tgacatctga agactctgcg gtctatttct gtgcaagaca
cgaacaagga ccaggttact ttgactactg gggccaaggc accactctca
cagtctcctc cgcctccacc aagggcaaag tggccgcatg taaggagaaa
gttgctgctt tgaaagagaa ggtcgccgca cttaaggaaa aggtcgcagc
cctgaaagag

S. DR5 mAb 3 x CD3 mAb 2 Diabody

[00441] An exemplary bi-specific diabody composed of two polypeptide chains was constructed having the VL and VH domains of anti-human DR5 antibody DR5 mAb 3 and the VL and VH domains of CD3 mAb 2. The amino acid sequence of the first polypeptide chain of the diabody had the sequence (**SEQ ID NO:148**) (CDR residues are shown underlined):

SELTQDPAVS VALGQTVRIT C**SGDSLRSYY AS**WYQQKPGQ APVLVIY**GAN**
NRPSGIPDRF SGSSSGNTAS LTITGAQAED EADYYC**NSAD SSGNHVV**FGG
GTKLTVLGGG GSGGGGEVQL VESGGGLVQP GGSLRLSCAA SGFTFS**TYAM**
NWVRQAPGKG LEWVG**RIRSK YNNYATYYAD SVKG**RFTISR DDSKNSLYLQ
MNSLKTEDTA VYYCVR**HGNF GNSYVSWFAY** WGQGTLVTVS SASTKGEVAA
CEKEVAALEK EVAALEKEVA ALEK

[00442] In **SEQ ID NO:148**, amino acid residues 1-108 correspond to the VL Domain of DR5 mAb 3 (**SEQ ID NO:54**), residues 109-116 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 117-241 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 242-246 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 247-275 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**).

[00443] The amino acid sequence of the second polypeptide chain of the diabody had the sequence (**SEQ ID NO:149**) (CDR residues are shown underlined):

QAVVTQEPSL TVSPGGTVTL TC**RSSTGAVT TSNYAN**WVQQ KPGQAPRGLI
G**GTNKRAP**WT PARFSGSLLG GKAALTITGA QAEDEADYYC **ALWYSNLWV**F
GGGTKLTVLG GGGSGGGGEV QLVQSGGGVE RPGGSLRLSC AAS**GFTFDDY**
AMSWVRQAPG KGLEWVSG**IN WQGGSTGYAD SVKG**RVTISR DNAKNSLYLQ

MNSLRAEDTA VYYCAK**ILGA GRGWYFDY**WG KGTTVTVSSA STKGKVAACK EKVAALKEKV AALKEKVAAL KE

[00444] In **SEQ ID NO:149**, amino acid residues 1-110 correspond to the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-239 correspond to the amino acid sequence of the VH Domain of DR5 mAb 3 (**SEQ ID NO:58**), residues 240-244 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 245-272 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**).

T. DR5 mAb 4 x CD3 mAb 2 Diabody

[00445] An exemplary bi-specific diabody composed of two polypeptide chains was constructed having the VL and VH domains of anti-human DR5 antibody DR5 mAb 4 and the VL and VH domains of CD3 mAb 2. The amino acid sequence of the first polypeptide chain of the diabody had the sequence (**SEQ ID NO:150**) (CDR residues are shown underlined):

EIVLTQSPGT LSLSPGERAT LSC**RASQGIS RSYLA**WYQQK PGQAPSLLIY **GASSRAT**GIP DRFSGSGSGT DFTLTISRLE PEDFAVYYC**Q QFGSSPWT**FG QGTKVEIKGG GSGGGGEVQL VESGGGLVQP GGSLRLSCAA SGFTFS**TYAM N**WVRQAPGKG LEWVG**RIRSK YNNYATYYAD SVKG**RFTISR DDSKNSLYLQ MNSLKTEDTA VYYCVR**HGNF GNSY**VSWFAY WGQGTLVTVS SASTKGEVAA CEKEVAALEK EVAALEKEVA ALEK

[00446] In **SEQ ID NO:150**, amino acid residues 1-108 correspond to the VL Domain of DR5 mAb 4 (**SEQ ID NO:62**), residues 109-116 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 117-241 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 242-246 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 247-275 correspond to a cysteine-containing E-coil Domain (**SEQ ID NO:41**).

[00447] The amino acid sequence of the second polypeptide chain of the diabody had the sequence (**SEQ ID NO:151**) (CDR residues are shown underlined):

QAVVTQEPSL TVSPGGTVTL TC**RSSTGAVT TSNYAN**WVQQ KPGQAPRGLI G**GTNKRAP**WT PARFSGSLLG GKAALTITGA QAEDEADYYC **ALWYSNLWV**F GGGTKLTVLG GGGSGGGGQV QLQESGPGLV KPSQTLSLTC TVS**GGSISSG**

DYFWSWIRQL PGKGLEWIG**H IHNSGTTYYN PSLKS**RVTIS VDTSKKQFSL
RLSSVTAADT AVYYCAR**DRG GDYYYGMDV**W GQGTTVTVSS ASTKGKVAAC
KEKVAALKEK VAALKEKVAA LKE

[00448] In **SEQ ID NO:151**, amino acid residues 1-110 correspond to the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-240 correspond to the amino acid sequence of the VH Domain of DR5 mAb 4 (**SEQ ID NO:66**), residues 241-245 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 246-273 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**).

U. Reference gpA33 x CD3 mAb 2 Diabody

[00449] To further exemplify the bi-specific Tri-Specific Binding Molecules of the present invention, a diabody composed of two polypeptide chains was constructed using the VL and VH domains of gpA33 mAb 1 and CD3 mAb 2. The amino acid sequence of the first polypeptide chain of the diabody had the sequence (**SEQ ID NO:316**) (CDR residues are shown underlined):

DIQLTQSPSF LSASVGDRVT ITC**SARSSIS FMY**WYQQKPG KAPKLLIY**DT**
SNLASGVPSR FSGSGSGTEF TLTISSLEAE DAATYYC**QQW SSYPLT**FGQG
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFS**TYAMN**W
VRQAPGKGLE WVG**RIRSKYN NYATYYADSV KG**RFTISRDD SKNSLYLQMN
SLKTEDTAVY YCVR**HGNFGN SYVSWFAY**WG QGTLVTVSSA STKGEVAACE
KEVAALEKEV AALEKEVAAL EK

[00450] In **SEQ ID NO:316**, amino acid residues 1-106 correspond to the VL Domain of gpA33 mAb 1 (**SEQ ID NO:181**), residues 107-114 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 115-239 correspond to the amino acid sequence of the VH Domain of CD3 mAb 2 having the D65G substitution (**SEQ ID NO:112**), residues 240-244 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 245-272 correspond to a cysteine-containing E-coil Domain (**SEQ ID NO:41**).

[00451] The amino acid sequence of the second polypeptide chain of the diabody had the sequence (**SEQ ID NO:317**) (CDR residues are shown underlined):

QAVVTQEPSL TVSPGGTVTL TC**RSSTGAVT TSNYAN**WVQQ KPGQAPRGLI
G**GTNKRAP**WT PARFSGSLLG GKAALTITGA QAEDEADYYC **ALWYSNLWV**F

GGGTKLTVLG GGGSGGGGQV QLVQSGAEVK KPGASVKVSC KAS**GYTFTGS**
WMNWVRQAPG QGLEWIG**RIY PGDGETNYNG KFKD**RVTITA DKSTSTAYME
LSSLRSEDTA VYYCAR**IYGN NVYFDV**WGQG TTVTVSSAST KGKVAACKEK
VAALKEKVAA LKEKVAALKE

[00452] In **SEQ ID NO:317**, amino acid residues 1-110 correspond to the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-237 correspond to the amino acid sequence of the VH Domain of gpA33 mAb 1 (**SEQ ID NO:186**), residues 238-242 correspond to an ASTKG linker (**SEQ ID NO:47**), and residues 243-270 correspond to a cysteine-containing K-coil Domain (**SEQ ID NO:42**).

V. Reference Anti-Fluorescein Antibody

[00453] The anti-fluorescein antibody 4-4-20 (Gruber, M. et al. (1994) "Efficient Tumor Cell Lysis Mediated By A Bi-specific Single Chain Antibody Expressed In Escherichia coli," J. Immunol. 152(11):5368-5374; Bedzyk, W.D. et al. (1989) "Comparison Of Variable Region Primary Structures Within An Anti-Fluorescein Idiotype Family," J. Biol. Chem. 264(3): 1565-1569) was used in control diabodies. The amino acid sequences of the variable light and variable heavy Domains of anti-fluorescein antibody 4-4-20 are as follows:

[00454] Amino Acid Sequence Of The Variable Light Chain Domain Of Anti-Fluorescein Antibody 4-4-20 (**SEQ ID NO:138**) (CDR residues are underlined):

DVVMTQTPFS LPVSLGDQAS ISC**RSSQSLV HSNGNTYLR**W YLQKPGQSPK
VLIY**KVSNRF S**GVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFC**SQSTHVP**
WTFGGGTKLE IK

[00455] Amino Acid Sequence Of The Variable Heavy Chain Domain Of Anti-Fluorescein Antibody 4-4-20 (SEQ ID NO:**139**) (CDR residues are underlined):

EVKLDETGGG LVQPGRPMKL SCVA**SGFTFS DYWMN**WVRQS PEKGLEWVA**Q**
IRNKPYNYET YYSDSVKGRF TISRDDSKSS VYLQMNNLRV EDMGIYYCTG
SYYGMDYWGQ GTSVTVSS

V. Methods of Production

[00456] The Tri-Specific Binding Molecules of the present invention can be created from the polynucleotides and/or sequences of antibodies that are

immunospecific for DR5, a desired Cancer Antigen, and a desired Effector Cell by methods known in the art, for example, synthetically or recombinantly. One method of producing such peptide agonists, antagonists and modulators involves chemical synthesis of the polypeptide, followed by treatment under oxidizing conditions appropriate to obtain the native conformation, that is, the correct disulfide bond linkages. This can be accomplished using methodologies well-known to those skilled in the art (see, *e.g.*, Kelley, R. F. *et al.* (1990) In: GENETIC ENGINEERING PRINCIPLES AND METHODS, Setlow, J.K. Ed., Plenum Press, N.Y., vol. 12, pp 1-19; Stewart, J.M *et al.* (1984) SOLID PHASE PEPTIDE SYNTHESIS, Pierce Chemical Co., Rockford, IL; see also United States Patents Nos. 4,105,603; 3,972,859; 3,842,067; and 3,862,925).

[00457] Polypeptides of the invention may be conveniently prepared using solid phase peptide synthesis (Merrifield, B. (1986) "S*olid Phase Synthesis*," Science 232(4748):341-347; Houghten, R.A. (1985) "*General Method For The Rapid Solid-Phase Synthesis Of Large Numbers Of Peptides: Specificity Of Antigen-Antibody Interaction At The Level Of Individual Amino Acids*," Proc. Natl. Acad. Sci. (U.S.A.) 82(15):5131-5135; Ganesan, A. (2006) "*Solid-Phase Synthesis In The Twenty-First Century*," Mini Rev. Med. Chem. 6(1):3-10).

[00458] In yet another alternative, suitable antibodies having one or more of the CDRs of a desired anti-DR5 antibody, anti-Cancer Antigen antibody or anti-Effector Cell antibody may be obtained through the use of commercially available mice that have been engineered to express specific human immunoglobulin proteins. Transgenic animals that are designed to produce a more desirable (e.g., fully human antibodies) or more robust immune response may also be used for generation of humanized or human antibodies. Examples of such technology are XENOMOUSE™ (Abgenix, Inc., Fremont, CA) and HUMAB-MOUSE® and TC MOUSE™ (both from Medarex, Inc., Princeton, NJ).

[00459] In an alternative, antibodies may be made recombinantly and expressed using any method known in the art. Antibodies may be made recombinantly by first isolating the antibodies made from host animals, obtaining the gene sequence, and using the gene sequence to express the antibody recombinantly in host cells (*e.g.*,

CHO cells). Another method that may be employed is to express the antibody sequence in plants {e.g., tobacco) or transgenic milk. Suitable methods for expressing antibodies recombinantly in plants or milk have been disclosed (see, for example, Peeters *et al.* (2001) "*Production Of Antibodies And Antibody Fragments In Plants*," Vaccine 19:2756; Lonberg, N. *et al.* (1995) "*Human Antibodies From Transgenic Mice*," Int. Rev. Immunol 13:65-93; and Pollock *et al.*(1999) "*Transgenic Milk As A Method For The Production Of Recombinant Antibodies*," J. Immunol Methods 231:147-157). Suitable methods for making derivatives of antibodies, *e.g.*, humanized, single-chain, etc. are known in the art. In another alternative, antibodies may be made recombinantly by phage display technology (see, for example, U.S. Patent Nos. 5,565,332; 5,580,717; 5,733,743; 6,265,150; and Winter, G. *et al.* (1994) "*Making Antibodies By Phage Display Technology*," Annu. Rev. Immunol. 12.433-455).

[00460] The antibodies or protein of interest may be subjected to sequencing by Edman degradation, which is well-known to those of skill in the art. The peptide information generated from mass spectrometry or Edman degradation can be used to design probes or primers that are used to clone the protein of interest.

[00461] An alternative method of cloning the protein of interest is by "panning" using purified DR5, and/or a desired Cancer Antigen, and/or a molecule expressed on the surface of a desired Effector Cell (or portions of any such molecules), for cells expressing an antibody or protein of interest that possesses one or more CDRs so as to be capable of binding to DR5, or such desired Cancer Antigen or Effector Cell molecule. The "panning" procedure may be conducted by obtaining a cDNA library from tissues or cells that express DR5, overexpressing the cDNAs in a second cell type, and screening the transfected cells of the second cell type for a specific binding to DR5 in the presence or absence of a known antibody that is capable of binding to such molecule (*e.g.*, DR5 mAb 1 or DR5 mAb 2 in the case of panning for new anti-DR5 antibodies, *etc.*). Detailed descriptions of the methods used in cloning mammalian genes coding for cell surface proteins by "panning" can be found in the art (see, for example, Aruffo, A. *et al.* (1987) "*Molecular Cloning Of A CD28 cDNA By A High-Efficiency COS Cell Expression System*," Proc. Natl. Acad. Sci. (U.S.A.)

84:8573-8577 and Stephan, J. *et al.* (1999) "*Selective Cloning Of Cell Surface Proteins Involved In Organ Development: Epithelial Glycoprotein Is Involved In Normal Epithelial Differentiation*," Endocrinol. 140:5841-5854).

[00462] Vectors containing polynucleotides of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE- dextran, or other substances; microprojectile bombardment; lipofection; and infection (e.g., where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell.

[00463] Any host cells capable of overexpressing heterologous DNAs can be used for the purpose of isolating the genes encoding the antibody, polypeptide or protein of interest. Non-limiting examples of suitable mammalian host cells include but are not limited to COS, HeLa, and CHO cells. Preferably, the host cells express the cDNAs at a level of about 5-fold higher, more preferably 10-fold higher, even more preferably 20-fold higher than that of the corresponding endogenous antibody or protein of interest, if present, in the host cells. Screening the host cells for a specific binding to DR5 is effected by an immunoassay or FACS. A cell overexpressing the antibody or protein of interest can be identified.

[00464] The invention includes polypeptides comprising an amino acid sequence of the antibodies of this invention. The polypeptides of this invention can be made by procedures known in the art. The polypeptides can be produced by proteolytic or other degradation of the antibodies, by recombinant methods (i.e., single or fusion polypeptides) as described above or by chemical synthesis. Polypeptides of the antibodies, especially shorter polypeptides up to about 50 amino acids, are conveniently made by chemical synthesis. Methods of chemical synthesis are known in the art and are commercially available. For example, an anti-DR5 polypeptide could be produced by an automated polypeptide synthesizer employing the solid phase method.

[00465] The invention includes modifications to any such antibodies (or to any of their polypeptide fragments that bind to DR5, the Cancer Antigen or the effector cell, as the case may be) and the agonists, antagonists, and modulators of such molecules, including functionally equivalent antibodies and fusion polypeptides that do not significantly affect the properties of such molecules as well as variants that have enhanced or decreased activity. Modification of polypeptides is routine practice in the art and need not be described in detail herein. Examples of modified polypeptides include polypeptides with conservative substitutions of amino acid residues, one or more deletions or additions of amino acids which do not significantly deleteriously change the functional activity, or use of chemical analogs. Amino acid residues which can be conservatively substituted for one another include but are not limited to: glycine/alanine; serine/threonine; valine/isoleucine/leucine; asparagine/glutamine; aspartic acid/glutamic acid; lysine/arginine; and phenylalanine/tyrosine. These polypeptides also include glycosylated and non-glycosylated polypeptides, as well as polypeptides with other post-translational modifications, such as, for example, glycosylation with different sugars, acetylation, and phosphorylation. Preferably, the amino acid substitutions would be conservative, i.e., the substituted amino acid would possess similar chemical properties as that of the original amino acid. Such conservative substitutions are known in the art, and examples have been provided above. Amino acid modifications can range from changing or modifying one or more amino acids to complete redesign of a region, such as the variable region. Changes in the variable region can alter binding affinity and/or specificity. Other methods of modification include using coupling techniques known in the art, including, but not limited to, enzymatic means, oxidative substitution and chelation. Modifications can be used, for example, for attachment of labels for immunoassay, such as the attachment of radioactive moieties for radioimmunoassay. Modified polypeptides are made using established procedures in the art and can be screened using standard assays known in the art.

[00466] The invention encompasses fusion proteins comprising one or more of the polypeptides of this invention. In one embodiment, a fusion polypeptide is provided that comprises a light chain, a heavy chain or both a light and heavy chain. In another embodiment, the fusion polypeptide contains a heterologous immunoglobulin

constant region. In another embodiment, the fusion polypeptide contains a light chain variable region and a heavy chain variable region of an antibody produced from a publicly-deposited hybridoma. For purposes of this invention, an antibody fusion protein contains one or more polypeptide domains that specifically bind to DR5, a Cancer Antigen, or an effector cell (as the case may be) and another amino acid sequence to which it is not attached in the native molecule, for example, a heterologous sequence or a homologous sequence from another region.

VI. Uses of the Trispecific Binding Molecules of the Present Invention

[00467] The Tri-Specific Binding Molecules of the present invention provide a general therapy for cancer. The cancers that may be treated by such molecules include cancers characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine

cancer. The Tri-Specific Binding Molecules of the present invention may be used in the treatment of colorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer and rectal cancer.

[00468] The Tri-Specific Binding Molecules of the present invention augment the cancer therapy provided by an antibody directed to a Cancer Antigen that is characteristic of cells of a target tumor by being additionally able to bind to DR5 molecules arrayed on the surface of such tumor cells. The utility of the invention is particularly seen in circumstances in which the density of the Cancer Antigen is low, or when the binding kinetics of the anti-Cancer Antigen antibody is suboptimal (or insufficient) to promote a clinically sufficient therapeutic response. In such cases, the ability of the molecules of the present invention to bind both the Cancer Antigen and DR5 of the tumor cells provides enhanced binding (via avidity) that is sufficient to promote a clinically sufficient therapeutic response. Additionally, by also possessing a Binding Domain capable of binding to a molecule on the surface of an immune system effector cell, the Tri-Specific Binding Molecules of the present invention permit the co-localization of such immune system cells to the tumor cells, thereby promoting a cytotoxic response against the tumor cells via redirected killing.

[00469] As shown in **Table 2**, Tri-Specific Binding Molecules of the present invention that possess particular combinations of Cancer Antigen-Binding Domains have preferred utility in the treatment of specific cancers.

Table 2

Cancer Antigen-Binding Domains		**Preferred Utility**
gpA33	DR5	Treatment Of Colorectal Cancer
gpA33	EphA2	
gpA33	B7-H3	
gpA33	BST2	
5T4	EphA2	Broadly Applicable To Treatment Of Many Types Of Cancers
5T4	CEACAM5	
5T4	B7-H3	
5T4	DR5	
B7-H3	CEACAM5	
B7-H3	CEACAM6	

Table 2		
Cancer Antigen-Binding Domains		**Preferred Utility**
B7-H3	IL1Rα2	Glioblastoma, Melanoma
EphA2	IL1Rα2	
EphA2	DR5	Broadly Applicable To Treatment Of Many Types Of Cancers
EphA2	CEACAM5	
EphA2	CEACAM6	
ITGB6	B7-H3	
ITGB6	DR5	
ITGB6	BST2	
BST2	CEACAM5	
BST2	EGFR	

[00470] In addition to their utility in therapy, the Tri-Specific Binding Molecules of the present invention may be detectably labeled and used in the diagnosis of cancer or in the imaging of tumors and tumor cells.

VII. Pharmaceutical Compositions

[00471] The compositions of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, impure or non-sterile compositions) and pharmaceutical compositions (*i.e.*, compositions that are suitable for administration to a subject or patient) which can be used in the preparation of unit dosage forms. Such compositions comprise a prophylactically or therapeutically effective amount of the Tri-Specific Binding Molecules of the present invention, or a combination of such agents and a pharmaceutically acceptable carrier. Preferably, compositions of the invention comprise a prophylactically or therapeutically effective amount of the Tri-Specific Binding Molecules of the present invention and a pharmaceutically acceptable carrier. The invention particularly encompasses such pharmaceutical compositions in which the Tri-Specific Binding Molecule has a DR5-Binding Domain of:

(1) a DR5 mAb 1 antibody;

(2) a DR5 mAb 2 antibody;

(3) a DR5 mAb 3 antibody;

(4) a DR5 mAb 4 antibody;

(5) a DR5 mAb 5 antibody;

(6) a DR5 mAb 6 antibody;

(7) a DR5 mAb 7 antibody; or

(8) a DR5 mAb 8 antibody

(or a humanized derivative of any such antibodies).

[00472] The invention further particularly encompasses such pharmaceutical compositions in which the Tri-Specific Binding Molecule has a Cancer Antigen-Binding Domain that:

(A) binds to an epitope of EphA2, especially wherein the Tri-Specific Binding Molecule has a Cancer Antigen-Binding Domain of EphA2 mAb 1, EphA2 mAb 2 or EphA2 mAb 3, or a humanized or chimeric variant thereof; or

(B) binds to an epitope of gpA33, especially wherein the Tri-Specific Binding Molecule has a Cancer Antigen-Binding Domain of gpA33 mAb 1, or a humanized or chimeric variant thereof; or

(C) binds to an epitope of Her2, especially wherein the Tri-Specific Binding Molecule has a Cancer Antigen-Binding Domain of Her2 mAb 1 or trastuzumab, or a humanized or chimeric variant thereof; or

(D) binds to an epitope of B7-H3, especially wherein the Tri-Specific Binding Molecule has a Cancer Antigen-Binding Domain of B7-H3 mAb 1, B7-H3 mAb 2, or B7-H3 mAb 3, or a humanized or chimeric variant thereof.

[00473] The invention further particularly encompasses such pharmaceutical compositions in which the Tri-Specific Binding Molecule has an Effector Cell-Binding Domain that binds to CD2, CD3, CD17, CD20, CD22, CD32B, CD64, BCR/CD79, the T cell Receptor or the NKG2D Receptor. The invention further particularly encompasses such pharmaceutical compositions in which the Tri-Specific Binding Molecule has an Effector Cell-Binding Domain of antibody: Lo-CD2a, CD3 mAb 2, OKT3, 3G8, A9, HD37, rituximab, epratuzumab, CD32B mAb 1, CD64 mAb 1, CD79 mAb 1, BMA 031, KYK-1.0, or KYK-2.0.

[00474] The invention specifically contemplates Tri-Specific Binding Molecules, pharmaceutical compositions that comprise such binding molecule and uses of such Tri-Specific Binding Molecules, in which:

(1) the DR5 Binding Domain is a DR5 binding domain of any anti-DR5 antibody;

(2) the Cancer Binding Domain is any of the Cancer Antigens disclosed herein;

and

(3) the Effector Cell-Binding Domains binds to any of CD2, CD3, CD17, CD20, CD22, CD32B, CD64, BCR/CD79, the T cell Receptor or the NKG2D Receptor.

[00475] The invention further specifically contemplates Tri-Specific Binding Molecules, pharmaceutical compositions that comprise such binding molecule and uses of such Tri-Specific Binding Molecules, in which:

(1) the DR5 Binding Domain is a DR5 binding domain of any anti-DR5 antibody;

(2) the Cancer Binding Domain is any of: EphA1, gpA33, Her2, or B7-H3;

and

(3) the Effector Cell-Binding Domains binds to any of CD2, CD3, CD17, CD20, CD22, CD32B, CD64, BCR/CD79, the T cell Receptor or the NKG2D Receptor.

[00476] The invention particularly contemplates each of the Tri-Specific Binding Molecules, as well as pharmaceutical compositions that comprise such binding molecule and uses of such Tri-Specific Binding Molecules, in which:

(1) the DR5 Binding Domain is a DR5 binding domain of any of: a DR5 mAb 1 antibody, a DR5 mAb 2 antibody, a DR5 mAb 3 antibody, a DR5 mAb 4 antibody, a DR5 mAb 5 antibody, a DR5 mAb 6 antibody, a DR5 mAb 7 antibody, or a DR5 mAb 8 antibody;

(2) the Cancer Antigen-Binding Domain is a binding domain of any of: EphA2 mAb 1, EphA2 mAb 2, EphA2 mAb 3, gpA33 mAb 1, Her2 mAb 1, trastuzumab, B7-H3 mAb 1, B7-H3 mAb 2, or B7-H3 mAb 3;

and

(3) the Effector Cell-Binding Domain is a binding domain of any of: Lo-CD2a, CD3 mAb 2, OKT3, 3G8, A9, HD37, rituximab, epratuzumab,

CD32B mAb 1, CD64 mAb 1, CD79 mAb 1, BMA 031, KYK-1.0, or KYK-2.0.

As 8 anti-DR5 Binding Domain antibodies, 9 anti-Cancer Antigen-Binding Domain antibodies and 14 anti-Effector Cell-Binding Domain antibodies are listed, such specific contemplation encompasses all (8 x 9 x 14 =) 1,008 combinations of such binding domains.

[00477] The invention also encompasses such pharmaceutical compositions that additionally include a second therapeutic antibody (*e.g.*, tumor-specific monoclonal antibody) that is specific for a particular cancer antigen, and a pharmaceutically acceptable carrier.

[00478] In a specific embodiment, the term "**pharmaceutically acceptable**" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "**carrier**" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like.

[00479] Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry

lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[00480] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include, but are not limited to those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, *etc.*, and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

[00481] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with a Tri-Specific Binding Molecule of the present invention (and more preferably, any of the specific binding molecules discussed or exemplified above). Additionally, one or more other prophylactic or therapeutic agents useful for the treatment of a disease can also be included in the pharmaceutical pack or kit. The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00482] The present invention provides kits that can be used in the above methods. A kit can comprise any of the Tri-Specific Binding Molecules of the present invention. The kit can further comprise one or more other prophylactic and/or therapeutic agents useful for the treatment of cancer, in one or more containers; and/or the kit can further comprise one or more cytotoxic antibodies that bind one or more cancer antigens associated with cancer. In certain embodiments, the other

prophylactic or therapeutic agent is a chemotherapeutic. In other embodiments, the prophylactic or therapeutic agent is a biological or hormonal therapeutic.

VIII. Methods of Administration

[00483] The compositions of the present invention may be provided for the treatment, prophylaxis, and amelioration of one or more symptoms associated with a disease, disorder or infection by administering to a subject an effective amount of a fusion protein or a conjugated molecule of the invention, or a pharmaceutical composition comprising a fusion protein or a conjugated molecule of the invention. In a preferred aspect, such compositions are substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side effects). In a specific embodiment, the subject is an animal, preferably a mammal such as non-primate (*e.g.*, bovine, equine, feline, canine, rodent, *etc.*) or a primate (*e.g.*, monkey such as, a cynomolgus monkey, human, *etc.*). In a preferred embodiment, the subject is a human.

[00484] Various delivery systems are known and can be used to administer the compositions of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or fusion protein, receptor-mediated endocytosis (See, *e.g.*, Wu *et al.* (1987) *"Receptor-Mediated In Vitro Gene Transformation By A Soluble DNA Carrier System,"* J. Biol. Chem. 262:4429-4432), construction of a nucleic acid as part of a retroviral or other vector, *etc.*

[00485] Methods of administering a molecule of the invention include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, the Tri-Specific Binding Molecules of the present invention are administered intramuscularly, intravenously, or subcutaneously. The compositions may be administered by any convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, *etc.*) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition,

pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Patent Nos. 6,019,968; 5,985, 320; 5,985,309; 5,934,272; 5,874,064; 5,855,913; 5,290,540; and 4,880,078; and PCT Publication Nos. WO 92/19244; WO 97/32572; WO 97/44013; WO 98/31346; and WO 99/66903, each of which is incorporated herein by reference in its entirety.

[00486] The invention also provides that the Tri-Specific Binding Molecules of the present invention are packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of the molecule. In one embodiment, such molecules are supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a subject. Preferably, the Tri-Specific Binding Molecules of the present invention are supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 5 μg, more preferably at least 10 μg, at least 15 μg, at least 25 μg, at least 50 μg, at least 100 μg, or at least 200 μg.

[00487] The lyophilized Tri-Specific Binding Molecules of the present invention should be stored at between 2 and 8°C in their original container and the molecules should be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, such molecules are supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the molecule, fusion protein, or conjugated molecule. Preferably, such Tri-Specific Binding Molecules when provided in liquid form are supplied in a hermetically sealed container in which the molecules are present at a concentration of least 1 μg/ml, more preferably at least 2.5 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 50 μg/ml, or at least 100 μg/ml.

[00488] The amount of the composition of the invention which will be effective in the treatment, prevention or amelioration of one or more symptoms associated with a disorder can be determined by standard clinical techniques. The precise dose to be employed in the formulation will also depend on the route of administration, and the

seriousness of the condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[00489] For the Tri-Specific Binding Molecules monovalent diabodies encompassed by the invention, the dosage administered to a patient is preferably determined based upon the body weight (kg) of the recipient subject. The dosage administered is typically from at least about 0.3 ng/kg per day to about 0.9 ng/kg per day, from at least about 1 ng/kg per day to about 3 ng/kg per day, from at least about 3 ng/kg per day to about 9 ng/kg per day, from at least about 10 ng/kg per day to about 30 ng/kg per day, from at least about 30 ng/kg per day to about 90 ng/kg per day, from at least about 100 ng/kg per day to about 300 ng/kg per day, from at least about 200 ng/kg per day to about 600 ng/kg per day, from at least about 300 ng/kg per day to about 900 ng/kg per day, from at least about 400 ng/kg per day to about 800 ng/kg per day, from at least about 500 ng/kg per day to about 1000 ng/kg per day, from at least about 600 ng/kg per day to about 1000 ng/kg per day, from at least about 700 ng/kg per day to about 1000 ng/kg per day, from at least about 800 ng/kg per day to about 1000 ng/kg per day, from at least about 900 ng/kg per day to about 1000 ng/kg per day, or at least about 1,000 ng/kg per day.

[00490] In another embodiment, the patient is administered a treatment regimen comprising one or more doses of such prophylactically or therapeutically effective amount of a Tri-Specific Binding Molecule of the present invention, wherein the treatment regimen is administered over 2 days, 3 days, 4 days, 5 days, 6 days or 7 days. In certain embodiments, the treatment regimen comprises intermittently administering doses of the prophylactically or therapeutically effective amount of the Tri-Specific Binding Molecules of the present invention (for example, administering a dose on day 1, day 2, day 3 and day 4 of a given week and not administering doses of the prophylactically or therapeutically effective amount of the Tri-Specific Binding Molecule

[00491] Especially encompassed is the administration of such Tri-Specific Binding Molecules that comprise any of the specific combinations of DR5 Binding Domains,

Cancer Antigen-Binding Domains and Effector Cell-Binding Domains discussed above, on day 5, day 6 and day 7 of the same week). Typically, there are 1, 2, 3, 4, 5 or more courses of treatment. Each course may be the same regimen or a different regimen.

[00492] In another embodiment, the administered dose escalates over the first quarter, first half or first two-thirds or three-quarters of the regimen(s) (*e.g.*, over the first, second, or third regimens of a 4 course treatment) until the daily prophylactically or therapeutically effective amount of the Tri-Specific Binding Molecule is achieved. **Table 3** provides 5 examples of different dosing regimens described above for a typical course of treatment.

Table 3

Regimen	Day	Diabody Dosage (ng diabody per kg subject weight per day)				
1	1, 2, 3, 4	100	100	100	100	100
	5, 6, 7	none	none	none	none	none
2	1, 2, 3, 4	300	500	700	900	1,000
	5, 6, 7	none	none	none	none	none
3	1, 2, 3, 4	300	500	700	900	1,000
	5, 6, 7	none	none	none	none	none
4	1, 2, 3, 4	300	500	700	900	1,000
	5, 6, 7	none	none	none	none	none

[00493] The dosage and frequency of administration of a Tri-Specific Binding Molecule of the present invention may be reduced or altered by enhancing uptake and tissue penetration of the molecule by modifications such as, for example, lipidation.

[00494] The dosage of a Tri-Specific Binding Molecule of the invention administered to a patient may be calculated for use as a single agent therapy. Alternatively, the molecule may be used in combination with other therapeutic compositions and the dosage administered to a patient are lower than when said molecules are used as a single agent therapy.

[00495] The pharmaceutical compositions of the invention may be administered locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a molecule of

the invention, care must be taken to use materials to which the molecule does not absorb.

[00496] The compositions of the invention can be delivered in a vesicle, in particular a liposome (*See* Langer (1990) *"New Methods Of Drug Delivery,"* Science 249:1527-1533); Treat *et al.*, in LIPOSOMES IN THE THERAPY OF INFECTIOUS DISEASE AND CANCER, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 3 17-327).

[00497] The compositions of the invention can be delivered in a controlled-release or sustained-release system. Any technique known to one of skill in the art can be used to produce sustained-release formulations comprising one or more of the Tri-Specific Binding Molecule(s) of the invention. *See*, *e.g.*, U.S. Patent No. 4,526,938; PCT publication WO 91/05548; PCT publication WO 96/20698; Ning *et al.* (1996) *"Intratumoral Radioimmunotheraphy Of A Human Colon Cancer Xenograft Using A Sustained-Release Gel,"* Radiotherapy & Oncology 39:179-189, Song *et al.* (1995) *"Antibody Mediated Lung Targeting Of Long-Circulating Emulsions,"* PDA Journal of Pharmaceutical Science & Technology 50:372-397; Cleek *et al.* (1997) *"Biodegradable Polymeric Carriers For A bFGF Antibody For Cardiovascular Application,"* Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854; and Lam *et al.* (1997) *"Microencapsulation Of Recombinant Humanized Monoclonal Antibody For Local Delivery,"* Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in its entirety. In one embodiment, a pump may be used in a controlled-release system (*See* Langer, *supra*; Sefton, (1987) *"Implantable Pumps,"* CRC Crit. Rev. Biomed. Eng. 14:201-240; Buchwald *et al.* (1980) *"Long-Term, Continuous Intravenous Heparin Administration By An Implantable Infusion Pump In Ambulatory Patients With Recurrent Venous Thrombosis,"* Surgery 88:507-516; and Saudek *et al.* (1989) *"A Preliminary Trial Of The Programmable Implantable Medication System For Insulin Delivery,"* N. Engl. J. Med. 321:574-579). In another embodiment, polymeric materials can be used to achieve controlled-release of the molecules (*see e.g.*, MEDICAL APPLICATIONS OF CONTROLLED RELEASE, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); CONTROLLED DRUG BIOAVAILABILITY, DRUG PRODUCT DESIGN AND

PERFORMANCE, Smolen and Ball (eds.), Wiley, New York (1984); Levy *et al.* (1985) *"Inhibition Of Calcification Of Bioprosthetic Heart Valves By Local Controlled-Release Diphosphonate,"* Science 228:190-192; During *et al.* (1989) *"Controlled Release Of Dopamine From A Polymeric Brain Implant: In Vivo Characterization,"* Ann. Neurol. 25:351-356; Howard *et al.* (1989) *"Intracerebral Drug Delivery In Rats With Lesion-Induced Memory Deficits,"* J. Neurosurg. 7(1):105-112); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253). Examples of polymers used in sustained-release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. A controlled-release system can be placed in proximity of the therapeutic target (*e.g.*, the lungs), thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in MEDICAL APPLICATIONS OF CONTROLLED RELEASE, *supra*, vol. 2, pp. 115-138 (1984)). Polymeric compositions useful as controlled-release implants can be used according to Dunn *et al.* (See U.S. 5,945,155). This particular method is based upon the therapeutic effect of the in situ controlled-release of the bioactive material from the polymer system. The implantation can generally occur anywhere within the body of the patient in need of therapeutic treatment. A non-polymeric sustained delivery system can be used, whereby a non-polymeric implant in the body of the subject is used as a drug delivery system. Upon implantation in the body, the organic solvent of the implant will dissipate, disperse, or leach from the composition into surrounding tissue fluid, and the non-polymeric material will gradually coagulate or precipitate to form a solid, microporous matrix (See U.S. 5,888,533).

[00498] Controlled-release systems are discussed in the review by Langer (1990, *"New Methods Of Drug Delivery,"* Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained-release formulations comprising one or more therapeutic agents of the invention. See, *e.g.*, U.S. Patent No. 4,526,938; International Publication Nos. WO 91/05548 and WO 96/20698; Ning *et*

al. (1996) *"Intratumoral Radioimmunotheraphy Of A Human Colon Cancer Xenograft Using A Sustained-Release Gel,"* Radiotherapy & Oncology 39:179-189, Song *et al.* (1995) *"Antibody Mediated Lung Targeting Of Long-Circulating Emulsions,"* PDA Journal of Pharmaceutical Science & Technology 50:372-397; Cleek *et al.* (1997) *"Biodegradable Polymeric Carriers For A bFGF Antibody For Cardiovascular Application,"* Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854; and Lam *et al.* (1997) *"Microencapsulation Of Recombinant Humanized Monoclonal Antibody For Local Delivery,"* Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in its entirety.

[00499] Where the composition of the invention is a nucleic acid encoding a Tri-Specific Binding Molecule of the present invention, the nucleic acid can be administered *in vivo* to promote expression of its encoded Tri-Specific Binding Molecule by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (*See* U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (See *e.g.*, Joliot *et al.* (1991) *"Antennapedia Homeobox Peptide Regulates Neural Morphogenesis,"* Proc. Natl. Acad. Sci. (U.S.A.) 88:1864-1868), *etc.* Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

[00500] Treatment of a subject with a therapeutically or prophylactically effective amount of a Tri-Specific Binding Molecule of the present invention can include a single treatment or, preferably, can include a series of treatments. In a preferred example, a subject is treated with such a diabody one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. The pharmaceutical compositions of the invention can be administered once a day, twice a day, or three times a day. Alternatively, the pharmaceutical compositions can be administered once a week, twice a week, once every two weeks, once a month, once

every six weeks, once every two months, twice a year or once per year. It will also be appreciated that the effective dosage of the molecules used for treatment may increase or decrease over the course of a particular treatment.

Examples:

[00501] Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention unless specified. It will be apparent to those skilled in the art that many modifications, both to materials and methods, can be practiced without departing from the scope of the present disclosure.

W. Example 1: Characterization of Anti-Human DR5 Monoclonal Antibodies DR5 mAb 1 and DR5 mAb 2

[00502] Two monoclonal antibodies were isolated as being capable of immunospecifically binding to human DR5, and accorded the designations "DR5 mAb 1" and "DR5 mAb 2". As discussed above, the CDRs of these antibodies were found to differ. In order to determine whether the antibodies bound to different DR5 epitopes, a human DR5-Fc fusion protein was prepared and was coated to an immobilized surface. DR5 mAb 1 (1 μg/mL) was biotinylated and incubated with either a control IgG or with DR5 mAb 2 (10 μg/mL), and the ability of the IgG or DR5 mAb 2 antibody to compete for binding (to human DR5-Fc fusion protein) with DR5 mAb 1 was assessed by measuring the amount of immobilized biotinylated antibody. Additionally, the ability of the IgG or DR5 mAb 1 antibody to compete for binding with biotinylated DR5 mAb 2 was assessed. The results of this experiment are shown in **Table 4**.

Table 4

1 μg/mL DR5-Fc Fusion coat		10 μg/mL Competitor mAb		
		mIgG	DR5 mAb 1	DR5 mAb 2
1 μg/mL biotinylated DR5 mAb	DR5 mAb 1	2.162	self	0.826
	DR5 mAb 2	2.102	2.377	self

[00503] The results of this experiment indicate that the biotinylated antibody was capable of binding to the DR5 protein even in the presence of excess amounts of the non-biotinylated antibody. Thus, the results show that DR5 mAb 1 and DR5 mAb 2 bind to different epitopes of DR5.

[00504] In order to further characterize the DR5 mAb 1 and DR mAb 2 antibodies, their ability to block binding between DR5 and the TRAIL ligand as assessed. Thus, biotinylated DR5 mAb 1, biotinylated DR5 mAb 2 or biotinylated DR5-Fc fusion (each at 2 μg/mL) were separately incubated with immobilized DR5-Fc fusion (1 μg/mL) in the presence of either buffer or histidine tagged TRAIL (20 μg/mL). The amount of immobilized biotinylated antibody was assessed. The results of this experiment are shown in **Table 5**.

Table 5

2 μg/mL Biotinylated DR5 mAb	1 μg/mL DR5-Fc fusion coat		1 μg/mL TRAIL-His coat
	20 μg/mL TRAIL-His	Buffer	
DR5 mAb 1	1.939	2.118	0.007
DR5 mAb 2	2.052	2.052	0.008
DR5-Fc fusion	--	--	0.288

[00505] The results show that the amount of DR5 mAb 1 or DR5 mAb 2 bound to the immobilized DR5-Fc was not affected by the presence of the histidine tagged TRAIL, thus indicating that neither DR5 mAb 1 nor DR5 mAb 2 block the TRAIL ligand binding site of DR5. Additionally, neither antibody was capable of binding to the histidine tagged TRAIL ligand.

X. Example 2: Species Specificity of Anti-Human DR5 Monoclonal Antibodies DR5 mAb 1 and DR5 mAb 2

[00506] In order to assess the species specificity of anti-human DR5 monoclonal antibodies DR5 mAb 1 and DR5 mAb 2, the ability of the antibodies to bind to human DR5 was compared with their ability to bind cynomolgus monkey (*Macaca fascicularis*) DR5. The results of this experiment are shown in **Figure 6**. The results show that both antibodies are capable of binding to cynomolgus monkey DR5, but that they each exhibit higher binding affinity for human DR5.

[00507] The kinetics of binding was investigated using Biacore Analysis, as shown in **Figure 7**. Bi-specific DR5 x CD3 diabodies were incubated with His-tagged DR5 and the kinetics of binding was determined via Biacore analysis. The diabodies employed were DR5 mAb 1 x CD3 mAb 2 (**Figure 7, Panels A and E**), DR5 mAb 2 x CD3 mAb 2 (**Figure 7, Panels B and F**), DR5 mAb 3 x CD3 mAb 2 (**Figure 7, Panels C and G**), and DR5 mAb 4 x CD3 mAb 2 (**Figure 7, Panels D and H**). **Figure 7, Panels A-D** show the results for human DR5. **Figure 7, Panels E-H** show the results for cynomolgus monkey DR5. The calculated ka, kd and KD are presented in **Table 6**.

Table 6

Anti-DR Antibody	Human			Cynomolgus Monkey		
	ka	kd	KD (nM)	ka	kd	KD (nM)
DR mAb 1	8.5×10^{6}	1.2×10^{-3}	0.14	4.0×10^{6}	1.3×10^{-1}	32.5
DR mAb 2	3.4×10^{5}	2.1×10^{-4}	0.62	2.4×10^{5}	1.0×10^{-4}	0.42
DR mAb 3	4.2×10^{6}	3.7×10^{-2}	8.8	3.3×10^{6}	4.4×10^{-2}	13.3
DR mAb 4	5.4×10^{6}	1.7×10^{-2}	3.2	2.5×10^{6}	4.1×10^{-2}	16.4

[00508] The results demonstrate that DR5 mAb 1 and DR5 mAb 2 exhibit altered kinetics of binding relative to reference antibodies DR5 mAb 3 and DR5 mAb 4.

Y. Example 3: Unexpected Superiority of DR5 mAb 1 and DR5 mAb 2

[00509] The ability of DR5-binding molecules DR5 mAb 1 and DR5 mAb 2 of the present invention to mediate cytotoxicity was compared with that of the reference anti-DR5 antibodies: DR5 mAb 3 and DR5 mAb 4. In order to make such a comparison, a bi-specific DR5 x CD3 diabody containing the VL and VH Domains of these antibodies and the VL and VH Domains of CD3 mAb 2 were prepared. The prepared diabodies were: DR5 mAb 1 x CD3 mAb 2; DR5 mAb 2 x CD3 mAb 2; DR5 mAb 3 x CD3 mAb 2; and DR5 mAb 4 x CD3 mAb 2.

[00510] The employed control diabody contained the VL and VH domains of anti-fluorescein antibody 4-4-20 (respectively, **SEQ ID NOs:138 and 139**) and the VL and VH domains of CD3 mAb 2 (respectively, **SEQ ID NOs:102 and 108**), and was designated as the anti-fluorescein x anti-CD3 control diabody "**4-4-20 x CD3 mAb 2**." The diabody was composed of two polypeptide chains. The first polypeptide

chain of the diabody had the amino acid sequence (**SEQ ID NO:300**) (CDRs are shown in underline):

DVVMTQTPFS LPVSLGDQAS ISC**RSSQSLV HSNGNTYLR**W YLQKPGQSPK
VLIY**KVSNRF S**GVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFC**SQSTHVP**
WTFGGGTKLE IKGGGSGGGG EVQLVESGGG LVQPGGSLRL SCAASGFTFN
TYAMNWVRQA PGKGLEWVA**R IRSKYNNYAT YYADSVKD**RF TISRDDSKNS
LYLQMNSLKT EDTAVYYCVR **HGNFGNSYVS WFAY**WGQGTL VTVSSGGCGG
GEVAALEKEV AALEKEVAAL EKEVAALEK

[00511] In **SEQ ID NO:300**, amino acid residues 1-112 correspond to the VL Domain of anti-fluorescein antibody 4-4-20 (**SEQ ID NO:138**), residues 113-120 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 121-245 correspond to the VH Domain of CD3 mAb 2 (**SEQ ID NO:108**), residues 246-251 are a cysteine-containing spacer peptide (GGCGGG) (**SEQ ID NO:34**), and residues 252-280 correspond to an E-coil Domain (**SEQ ID NO:39**).

[00512] The second polypeptide chain of the diabody had the amino acid sequence (**SEQ ID NO:301**) (CDRs are shown in underline):

QAVVTQEPSL TVSPGGTVTL TC**RSSTGAVT TSNYAN**WVQQ KPGQAPRGLI
G**GTNKRAP**WT PARFSGSLLG GKAALTITGA QAEDEADYYC **ALWYSNLWV**F
GGGTKLTVLG GGGSGGGGEV KLDETGGGLV QPGRPMKLSC VA**SGFTFSDY**
WMNWVRQSPE KGLEWVA**QIR NKPYNYETYY SDSVKG**RFTI SRDDSKSSVY
LQMNNLRVED MGIYYCTG**SY YGMDY**WGQGT SVTVSSGGCG GGKVAALKEK
VAALKEKVAA LKEKVAALKE

[00513] In **SEQ ID NO:301**, amino acid residues 1-110 correspond to the VL Domain of CD3 mAb 2 (**SEQ ID NO:104**), residues 111-118 correspond to the intervening spacer peptide GGGSGGGG (Linker 1) (**SEQ ID NO:33**), residues 119-236 correspond to the VH Domain of anti-fluorescein antibody 4-4-20 (**SEQ ID NO:139**), residues 237-242 are a cysteine-containing spacer peptide (GGCGGG) (**SEQ ID NO:34**), and residues 243-270 correspond to a K-coil Domain (**SEQ ID NO:40**).

[00514] Target tumor cells were incubated with one of these diabodies or with the control diabody (4-4-20 x CD3 mAb 2) in the presence of peripheral blood mononuclear cells (**PBMC**) and A549 adenocarcinomic human alveolar basal epithelial cells for 24 hours at an effector to target cell ratio of 20:1. The percentage cytotoxicity was determined by measuring the release of lactate dehydrogenase (LDH) into the media by damaged cells.

[00515] The results of this investigation are shown in **Figure 8**. Similar results were obtained using SKMES human lung cancer cells, DU145 human prostate cancer cells, A375 human malignant melanoma cells, SKBR3 human HER2-overexpressing breast carcinoma cells, and JIMT human breast carcinoma cells. The results indicate that the VL and VH domains of DR5 mAb 1 and DR5 mAb 2 are significantly and unexpectedly more potent in inducing cytotoxicity than those of the reference DR5 mAbs.

Z. Example 4: The Trispecific Binding Molecules Mediate Coordinated and Simultaneous Binding to Target Cells

[00516] The ability of Tri-Specific Binding Molecules of the present inventon to bind to target cells was investigated. The employed trispecific molecules were: EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1; EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1; and gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1. As shown in **Figure 9A**, those Tri-Specific Binding Molecules that comprise an EphA2 Cancer Antigen-Binding Domain were found to be capable of binding to EphA2-expressing CHO target cells. As shown in **Figure 9B**, those Tri-Specific Binding Molecules that comprise a DR5 Cancer Antigen-Binding Domain were found to be capable of binding to DR5-expressing CHO target cells. As shown in **Figure 9C**, those Tri-Specific Binding Molecules that comprise an EphA2 Cancer Antigen-Binding *or* a DR5 Cancer Binding Domain were found to be capable of binding to DU145 cells. DU145 cells are a human prostate cell line that express both EphA2 and DR5, but not gpA33. The above-described reference gpA33 mAb 1 x CD3 mAb 2 diabody was used as a control.

[00517] Significantly, the data show that when *both* of the two Cancer Antigen-Binding Domains of a Tri-Specific Binding Molecule of the present invention are able to bind to a target cell, such dual binding is associated with a synergistic (*e.g.*, a 5-25 fold) enhancement in target binding.

AA. Example 5: The Trispecific Binding Molecules Mediate Cytotoxicity of Bound Target Cells

[00518] The ability of Tri-Specific Binding Molecules of the present inventon to mediate the cytotoxicity of bound target cells in the presence of cytotoxic lymphocytes was investigated. The employed trispecific molecules were: EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1; EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1; and gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1. The above-described reference gpA33 mAb 1 x CD3 mAb 2 diabody and the 4-4-20 x CD3 mAb 2 diabody were used as controls.

[00519] As shown in **Figure 10A**, those Tri-Specific Binding Molecules that comprise an EphA2 Cancer Antigen-Binding Domain, and thus were able to bind to bind to EphA2-expressing CHO cells, were able to mediate the cytotoxicity of such cells in the presence of the cytotoxic lymphocytes. As shown in **Figure 10B**, those Tri-Specific Binding Molecules that comprise a DR5 Cancer Antigen-Binding Domain, and thus were able to bind to bind to DR5-expressing CHO cells, were found to be capable of mediating cytotoxicity of DR5-expressing CHO target cells in the presence of the cytotoxic lymphocytes.

[00520] As shown in **Figure 10C**, those Tri-Specific Binding Molecules that comprise an EphA2 Cancer Antigen-Binding *or* a DR5 Cancer Binding Domain, and thus are capable of binding to DU145 cells, were able to mediate the cytotoxicity of such cells in the presence of the cytotoxic lymphocytes. Significantly, the data show that when *both* of the two Cancer Antigen-Binding Domains of a Tri-Specific Binding Molecule of the present invention are able to bind to a target cell, such dual binding is associated with a synergistic enhancement in target binding. Thus, EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1, which is capable of binding to *both* EphA2 *and* DR5, mediated substantially greater cytotoxicity than EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 or gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1, which were capable of binding to only EphA2 or DR5 molecules of the DU146 cells (since such cells lack gpA33).

[00521] In this regard, at approximately the EC50 of EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1, no cytotoxic lymphocyte response is seen for either EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 or gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1. At approximately the EC90 of EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1, EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1 shows only an EC15, and gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1 shows no cytotoxic lymphocyte response at all.

[00522] All publications and patents mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference in its entirety. While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

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What Is Claimed Is:

1. A Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

(I) four different polypeptide chains covalently complexed together;

(II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;

(III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(IV) a Fc Domain, wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain); or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3 Domain);

(E) a fourth polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Cysteine-Containing Domain);

(F) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy

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Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III: and

(G) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III} Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

2. The Tri-Specific Binding Molecule of claim 1, wherein the Cysteine-Containing Domain of the third polypeptide chain is chosen from a CH1 Domain and/or a Hinge Domain and the Cysteine-Containing Domain of the fourth polypeptide chain is a CL Domain.

3. The Tri-Specific Binding Molecule of claim 1 or claim 2, wherein (i) the first polypeptide chain and the second polypeptide chain are covalently bonded to one another; (ii) the first polypeptide chain and the third polypeptide chain are covalently bonded to one another; and (iii) the third polypeptide chain and the fourth polypeptide chain are covalently bonded to one another.

4. A Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

(I) three different polypeptide chains covalently complexed together;

(II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;

(III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(IV) a Fc Domain; wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain); or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3 Domain); or

(Cysteine-Containing Domain 1)—(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain 2)— (Cysteine-Containing Domain)—(CH2-CH3 Domain);

(E) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III; and

(F) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III} Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

5. The Tri-Specific Binding Molecule of claim 4, wherein the Cysteine-Containing Domain 1 of the third polypeptide chain is a CL Domain and the Cysteine-Containing Domain 2 of the third polypeptide chain is chosen from a CH1 Domain and/or a Hinge Domain.

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6. The Tri-Specific Binding Molecule of any one of claims 1-5, wherein:

the Linker 2 comprises a cysteine residue, or

the Heterodimer-Promoting Domain comprises a cysteine residue, or

the Linker 2 comprises a cysteine residue and the Heterodimer-Promoting Domain comprises a cysteine residue.

7. The Tri-Specific Binding Molecule of any one of claims 1-6, wherein:

the CH2-CH3 Domain of the first polypeptide chain is a knob-bearing CH2-CH3 Domain and the CH2-CH3 Domain of the third polypeptide chain is a hole-bearing CH2-CH3 Domain; or

the CH2-CH3 Domain of the third polypeptide chain is a knob-bearing CH2-CH3 Domain and the CH2-CH3 Domain of the first polypeptide chain is a hole-bearing CH2-CH3 Domain.

8. The Tri-Specific Binding Molecule of any one of claims 1-7, wherein the CH2-CH3 Domain of the first polypeptide chain and the third polypeptide chain comprise at least one amino acid substitution, relative to the sequence of SEQ ID NO:1, and the Fc Domain formed from their association exhibits altered FcγR-mediated effector function.

9. The Tri-Specific Binding Molecule of any one of claims 1-8, wherein:

the Heterodimer-Promoting Domain on the first polypeptide chain is an E-coil Domain and the Heterodimer-Promoting Domain on the second polypeptide chain is a K-coil Domain; or

the Heterodimer-Promoting Domain on the first polypeptide chain is an K-coil Domain and the Heterodimer-Promoting Domain on the second polypeptide chain is a E-coil Domain.

10. The Tri-Specific Binding Molecule of any one of claims 1-9, wherein:

the Linker 1 comprises the sequence of SEQ ID NO: 33;

the Linker 2 comprises the sequence of SEQ ID NO: 34 or 47;

the Heterodimer-Promoting Domain comprises the sequence of SEQ ID NO: 35, 36, 37, 38, 39, 40, 41 or 42;

the Linker 3 comprises the sequence of SEQ ID NO: 46, 47, 48, 49, 50, 51, 152, or GCG or GGG;

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the Linker 4 comprises the sequence of SEQ ID NO: 50 or 152;

the CH2-CH3 Domain comprises the sequence of SEQ ID NO: 52 or 53;

the CH1-Hinge Domain comprises the sequence of SEQ ID NO: 207, 208 or 209;

the Cysteine-Containing Domain comprises the sequence of SEQ ID NO: 34, 36, 38, 48, 210 or 211; or

combination of the foregoing.

11. The Tri-Specific Binding Molecule of claim 10, wherein the Heterodimer-Promoting Domain of SEQ ID NO: 41 or 42 is present when Linker 2 comprises the sequence of SEQ ID NO: 47, or the Heterodimer-Promoting Domain of SEQ ID NO: 39, 40, 41 or 42 is present when Linker 2 comprises the sequence of SEQ ID NO: 34.

12. The Tri-Specific Binding Molecule of any one of claims 1-11, wherein:

(A) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the second Cancer Antigen and an epitope of the Effector Cell Antigen;

(B) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the second Cancer Antigen;

(C) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of second Cancer Antigen, an epitope of the first Cancer Antigen, and an epitope of the Effector Cell Antigen;

(D) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the second Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the first Cancer Antigen;

(E) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of the first Cancer Antigen, and an epitope of the second Cancer Antigen; or

(F) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of second Cancer Antigen, and an epitope of the first Cancer Antigen.

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13. The Tri-Specific Binding Molecule of any one of claims 1-12, wherein the Effector Cell Antigen is CD2, CD3, CD16, CD19, CD20, CD22, CD32B, CD64, B cell Receptor (BCR), T cell Receptor (TCR), or NKG2D Receptor.

14. The Tri-Specific Binding Molecule of any of claims 1-13, wherein:

(A) the epitope of an Effector Cell Antigen is a CD2 epitope recognized by antibody Lo-CD2a;

(B) the epitope of an Effector Cell Antigen is a CD3 epitope recognized by antibody OKT3, M291, YTH12.5, Anti-CD3 mAb 1 or Anti-CD3 mAb 2;

(C) the epitope of an Effector Cell Antigen is a CD16 epitope recognized by antibody 3G8 or A9;

(D) the epitope of an Effector Cell Antigen is a CD19 epitope recognized by antibody MD1342, MEDI-551, blinatumomab or HD37;

(E) the epitope of an Effector Cell Antigen is a CD20 epitope recognized by antibody rituximab, ibritumomab, ofatumumab, and tositumomab;

(F) the epitope of an Effector Cell Antigen is a CD22 epitope recognized by antibody epratuzumab;

(G) the epitope of an Effector Cell Antigen is a CD32B epitope recognized by antibody CD32B mAb 1;

(H) the epitope of an Effector Cell Antigen is a CD64 epitope recognized by antibody CD64 mAb 1;

(I) the epitope of an Effector Cell Antigen is a BCR/CD79 epitope recognized by antibody CD79 mAb 1;

(J) the epitope of an Effector Cell Antigen is a TCR epitope recognized by antibody BMA 031;

(K) the epitope of an Effector Cell Antigen is a NKG2D Receptor epitope recognized by antibody KYK-2.0; or

(L) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen and the Antigen-Binding Domain that is capable of immunospecifically binding to the epitope comprises the six CDRs of SEQ ID NO:102 and 103; 104 and 108; 104 and 112; 114 and 115; 116 and 117; 118 and 119; 120 and 121; 122 and 123; 124 and 125; 126 and 127; 128 and 129; 130 and 131; 132 and 133; 134 and 135; or 136 and 137; or comprises one or more of SEQ ID NO: 102-104, 108, 112, 114 and 115-137.

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15. The Tri-Specific Binding Molecule of any one of claims 1-14, wherein the first Cancer Antigen and the second Cancer Antigen are independently chosen from: colon cancer antigen 19.9; a gastric cancer mucin; antigen 4.2; glycoprotein A33 (gpA33); ADAM-9; gastric cancer antigen AH6; ALCAM; malignant human lymphocyte antigen APO-1; cancer antigen B1; B7-H3; beta-catenin; blood group ALe^b/Le^y; Burkitt's lymphoma antigen-38.13, colonic adenocarcinoma antigen C14; ovarian carcinoma antigen CA125; Carboxypeptidase M; CD5; CD19; CD20; CD22; CD23; CD25; CD27; CD28; CD30; CD33; CD36; CD45; CD46; CD52; CD79a/CD79b; CD103; CD317; CDK4; carcinoembryonic antigen (CEA); CEACAM5; CEACAM6; CO17-1A; CO-43 (blood group Le^b); CO-514 (blood group Le^a); CTA-1; CTLA4; Cytokeratin 8; antigen D1.1; antigen $D_1$56-22; DR5; E_1 series (blood group B); EGFR (Epidermal Growth Factor Receptor); Ephrin receptor A2 (EphA2); ErbB1; ErbB3; ErbB4; GAGE-1; GAGE-2; GD2/GD3/GM2; lung adenocarcinoma antigen F3; antigen FC10.2; G49, ganglioside GD2; ganglioside GD3; ganglioside GM2; ganglioside GM3; G_{D2}; G_{D3}; GICA 19-9; G_{M2}; gp100; human leukemia T cell antigen Gp37; melanoma antigen gp75; gpA33; HER2 antigen ($p185^{HER2}$); human milk fat globule antigen (HMFG); human papillomavirus-E6/human papillomavirus-E7; high molecular weight melanoma antigen (HMW-MAA); I antigen (differentiation antigen) I(Ma); Integrin Alpha-V-Beta-6 Integrinβ6 (ITGB6); Interleukin-13; Receptor α2 (IL13Rα2); JAM-3; KID3; KID31; KS 1/4 pan-carcinoma antigen; human lung carcinoma antigens L6 and L20; LEA; LUCA-2; M1:22:25:8; M18; M39; MAGE-1; MAGE-3; MART; MUC-1; MUM-1; Myl; N-acetylglucosaminyltransferase; neoglycoprotein; NS-10; OFA-1; OFA-2; Oncostatin M; p15; melanoma-associated antigen p97; polymorphic epithelial mucin (PEM); polymorphic epithelial mucin antigen (PEMA); PIPA; prostate-specific antigen (PSA); prostate-specific membrane antigen (PSMA); prostatic acid phosphate; R_{24}; ROR1; sphingolipids; SSEA-1; SSEA-3; SSEA-4; sTn; T cell receptor derived peptide; T_5A_7; TAG-72; TL5 (blood group A); TNF-α receptor; TNF-ß receptor; TNF-γ receptor; TRA-1-85 (blood group H); Transferrin Receptor; tumor-specific transplantation antigen (TSTA), oncofetal antigen-alpha-fetoprotein (AFP); VEGF, VEGFR; VEP8; VEP9; VIM-D5; and Y hapten, Le^y; and 5T4.

16. The Tri-Specific Binding Molecule of claim 15, wherein one of Epitope I, Epitope II or Epitope III is an epitope of a Cancer Antigen and the Antigen-Binding Domain that is capable of immunospecifically binding to the epitope comprises the six CDRs of SEQ ID

NO: 3 and 8; 13 and 18; 23 and 31; 25 and 31; 27 and 31; 29 and 31; 54 and 58; 62 and 66; 70 and 74; 78 and 82; 86 and 90; 94 and 98; 153 and 158; 163 and 167; 172 and 177; 181 and 186; 191 and 192; 193 and 194; 195 and 196; 197 and 198; 199 and 200; 201 and 202; 203 and 204; 205 and 206; 302 and 303; 304 and 305; 306 and 307; 308 and 309; 310 and 311; 312 and 313; 314 and 315; or 321 and 322; or comprises one or more of SEQ ID NO: 3, 8, 13, 18, 23, 25, 27, 29, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 153, 158, 163, 167, 172, 177, 181, 186, 191-206, 302-315, 321 and 322.

17. A nucleic acid composition comprising polynucleotides that encode polypeptide chains of the Tri-Specific Binding Molecule of any one of claims 1-16.

18. A pharmaceutical composition comprising the Tri-Specific Binding Molecule of any one of claims 1-16, and a pharmaceutically acceptable carrier, excipient or diluent.

19. A Tri-Specific Binding Molecule of any one of claims 1-16 or a composition of claim 18, for use as a medicament.

20. Use of a Tri-Specific Binding Molecule of any one of claims 1-16 or a composition of claim 18 to treat a cancer.

21. A method of treating cancer in a patient or subject including the step of administering the Tri-Specific Binding Molecule of any one of claims 1-16 or the composition of claim 18 to the patient or subject to thereby treat the cancer.

22. The use of claim 20 or the method of claim 21, wherein the cancer is characterized by the presence of a cancer cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's

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Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, or a uterine cancer.

23. The use or the method of claim 22, wherein the cancer is a colorectal cancer, a hepatocellular carcinoma, a glioma, a kidney cancer, a breast cancer, a multiple myeloma, bladder cancer, a neuroblastoma, a sarcoma, a non-Hodgkin's lymphoma, a non-small cell lung cancer, an ovarian cancer, a pancreatic cancer, a rectal cancer, acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphoma (NHL), mantel cell leukemia (MCL), small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.

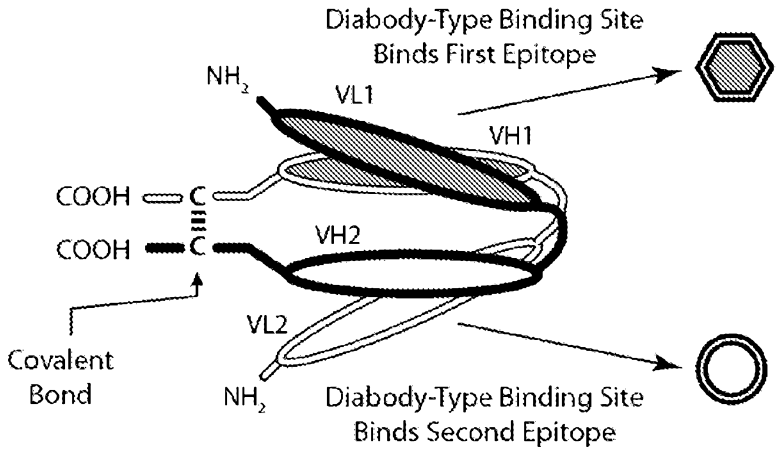


Figure 1A

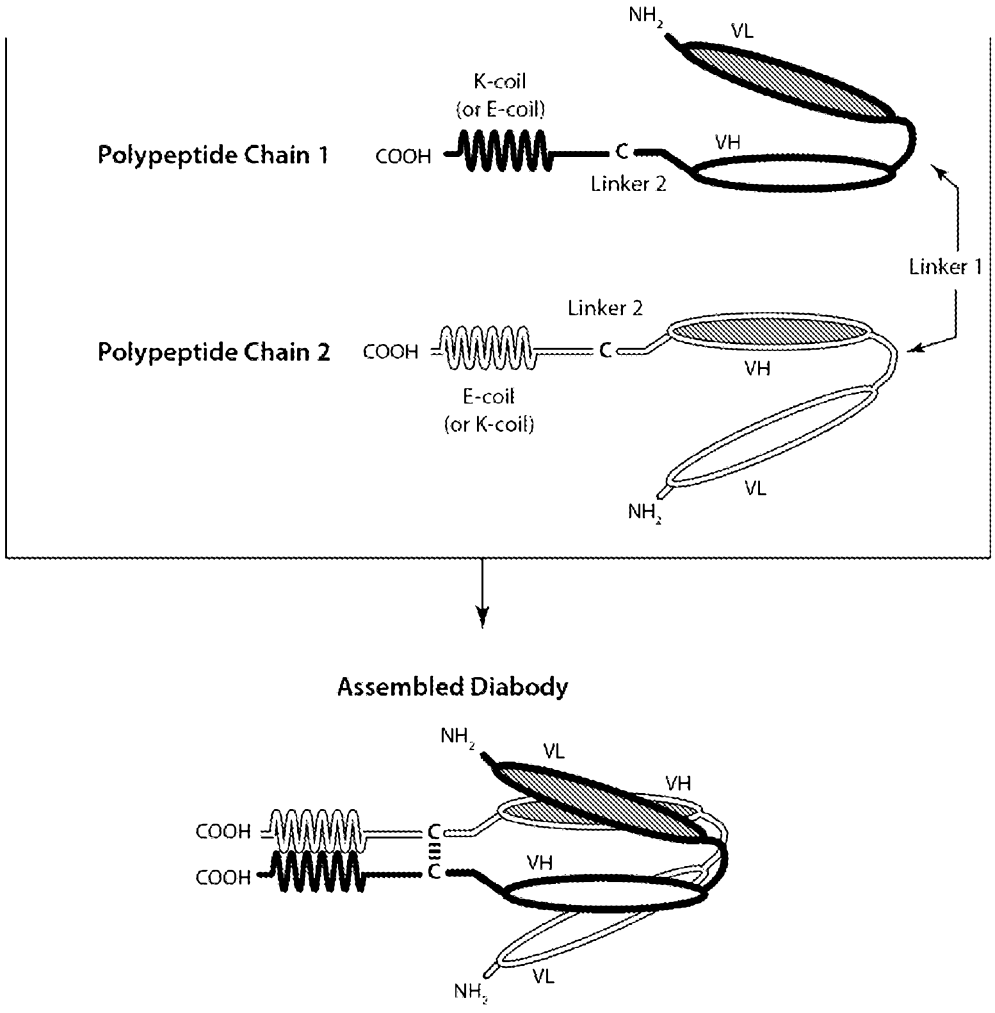


Figure 1B

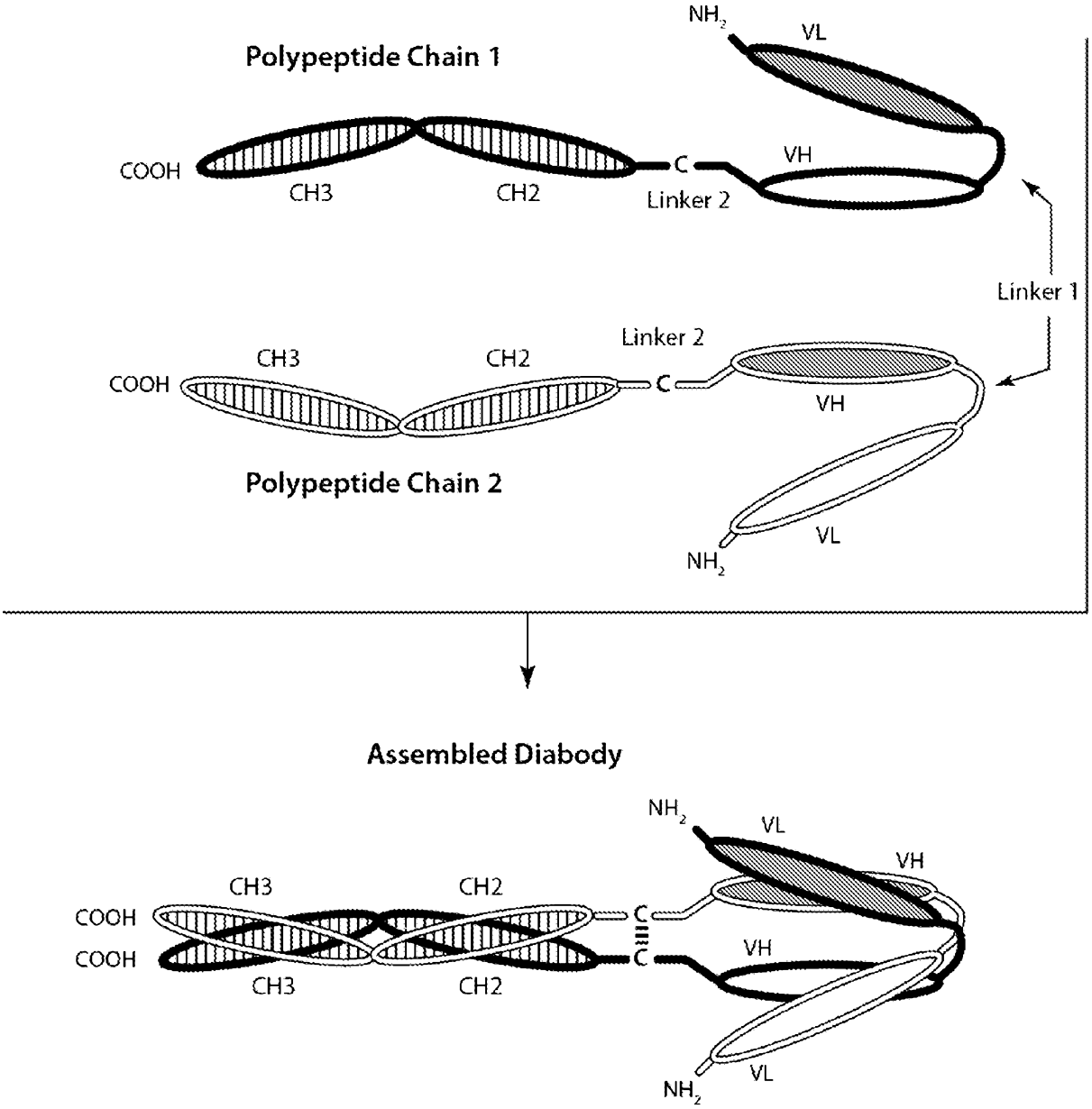


Figure 2A

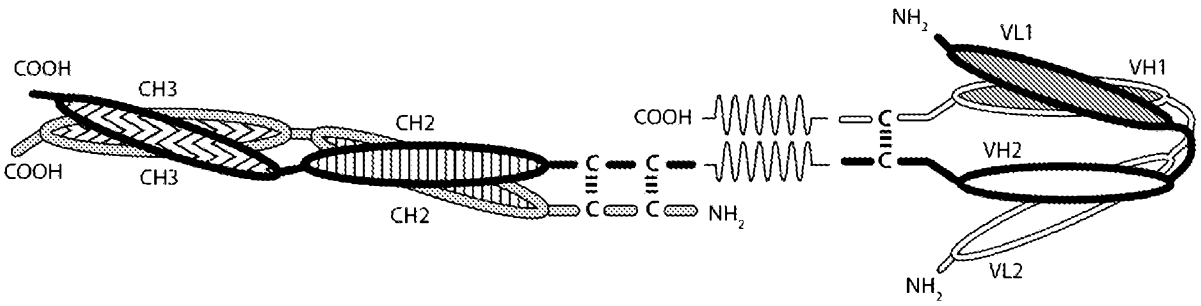


Figure 2B

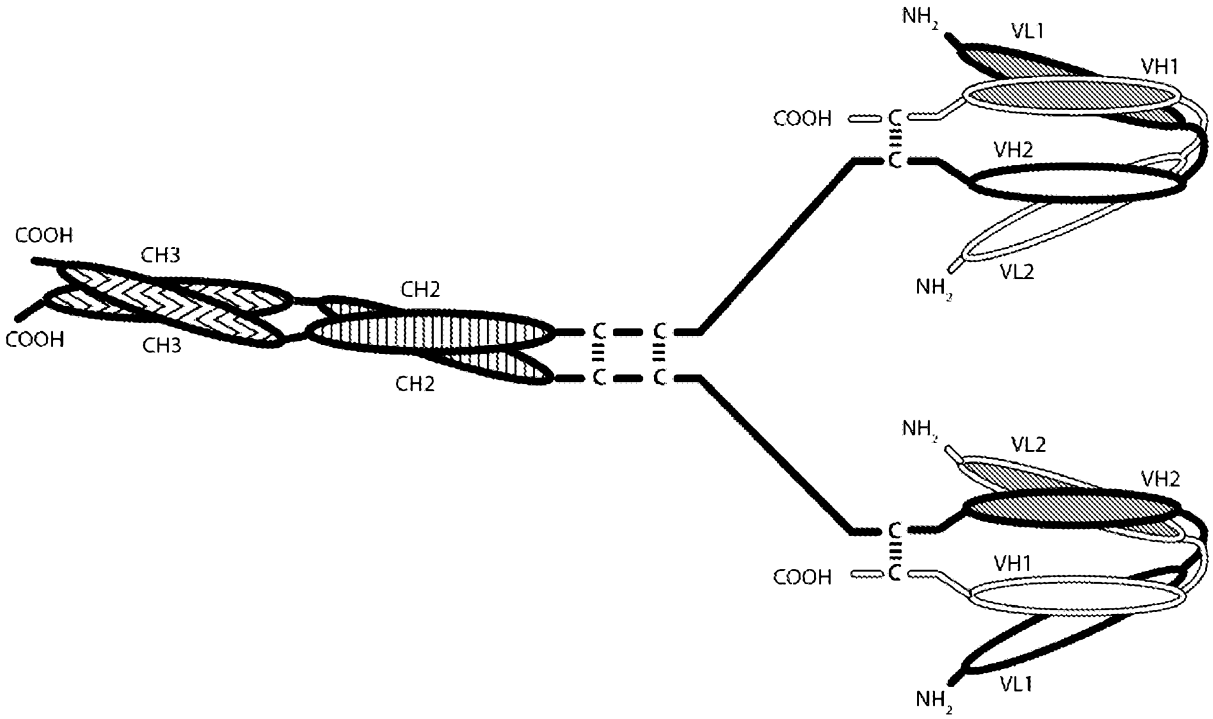

NH2
VL1
VH1
COOH
VH2
COOH
CH3
CH2
NH2
VL2
COOH
CH3
CH2
NH2
VL2
VH2
COOH
VH1
NH2
VL1

Figure 3A

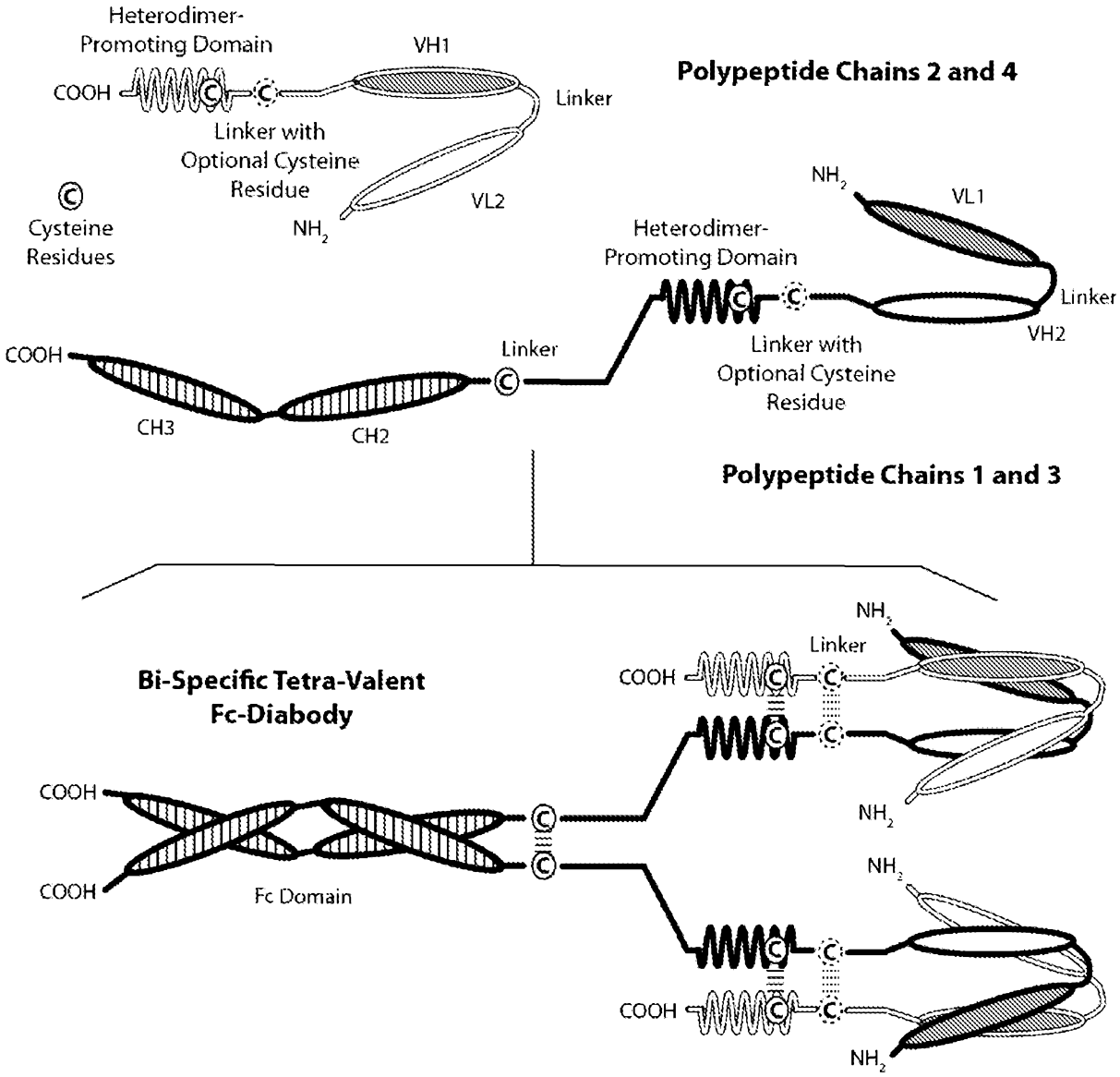

Heterodimer-
Promoting Domain
VH1
COOH
Linker
Linker with
Optional Cysteine
Residue
VL2
NH2
Cysteine
Residues
Polypeptide Chains 2 and 4
NH2
VL1
Heterodimer-
Promoting Domain
Linker
VH2
Linker with
Optional Cysteine
Residue
COOH
Linker
CH3
CH2
Polypeptide Chains 1 and 3
Bi-Specific Tetra-Valent
Fc-Diabody
NH2
Linker
COOH
COOH
Fc Domain
NH2
NH2
COOH
NH2

Figure 3B

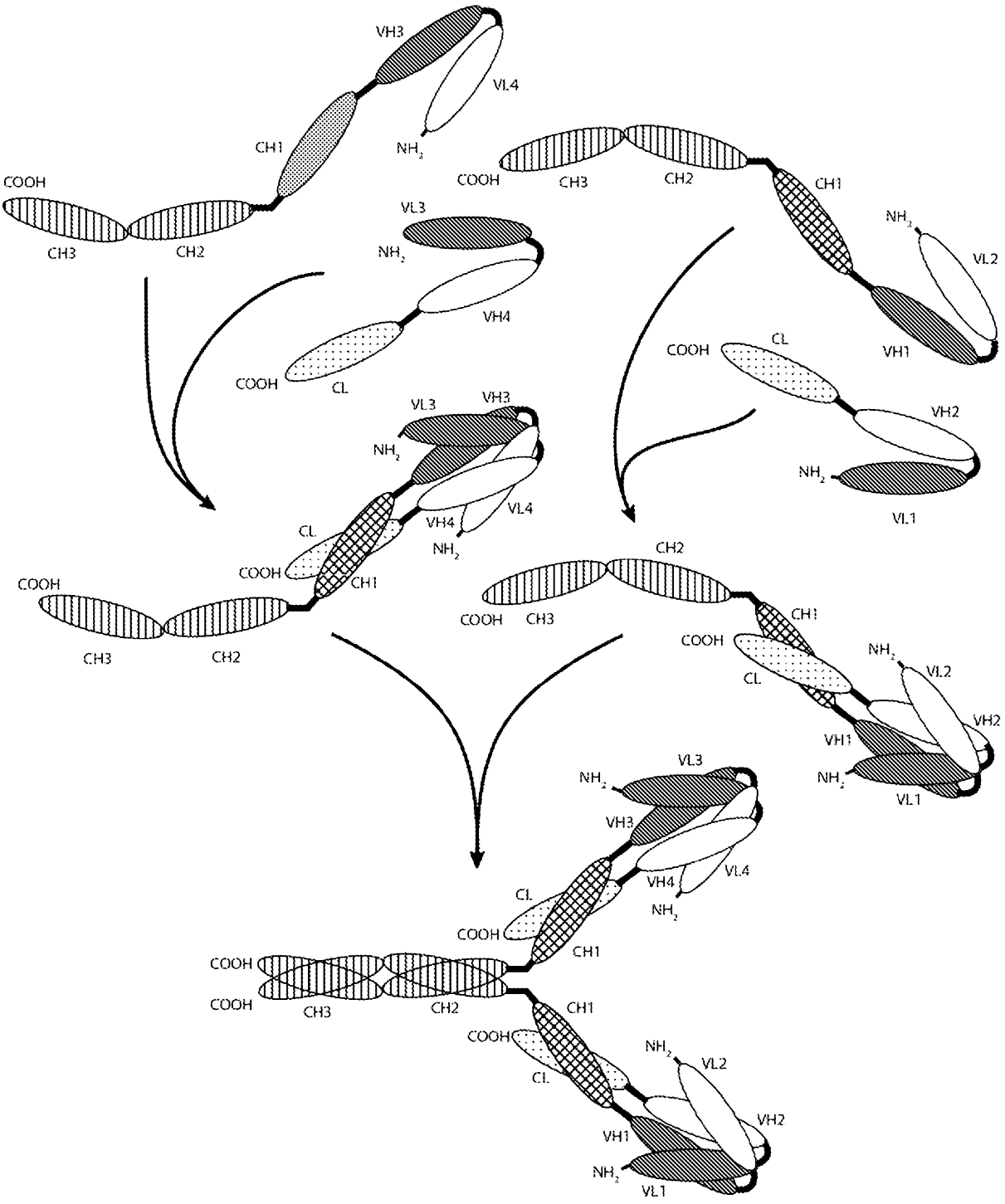

VH3
VL4
CH1
NH2
COOH
CH3
CH2
VL3
NH2
VH4
COOH
CL
COOH
CH3
CH2
CH1
NH2
VL2
VH1
COOH
CL
VH2
NH2
VL1
VL3
VH3
NH2
VH4
VL4
CL
COOH
CH1
NH2
COOH
CH3
CH2
CH2
COOH
CH3
CH1
COOH
CL
NH2
VL2
VH2
VH1
NH2
VL1
VL3
NH2
VH3
VH4
VL4
NH2
CL
COOH
CH1
COOH
COOH
CH3
CH2
CH1
COOH
CL
NH2
VL2
VH2
VH1
NH2
VL1

Figure 3C

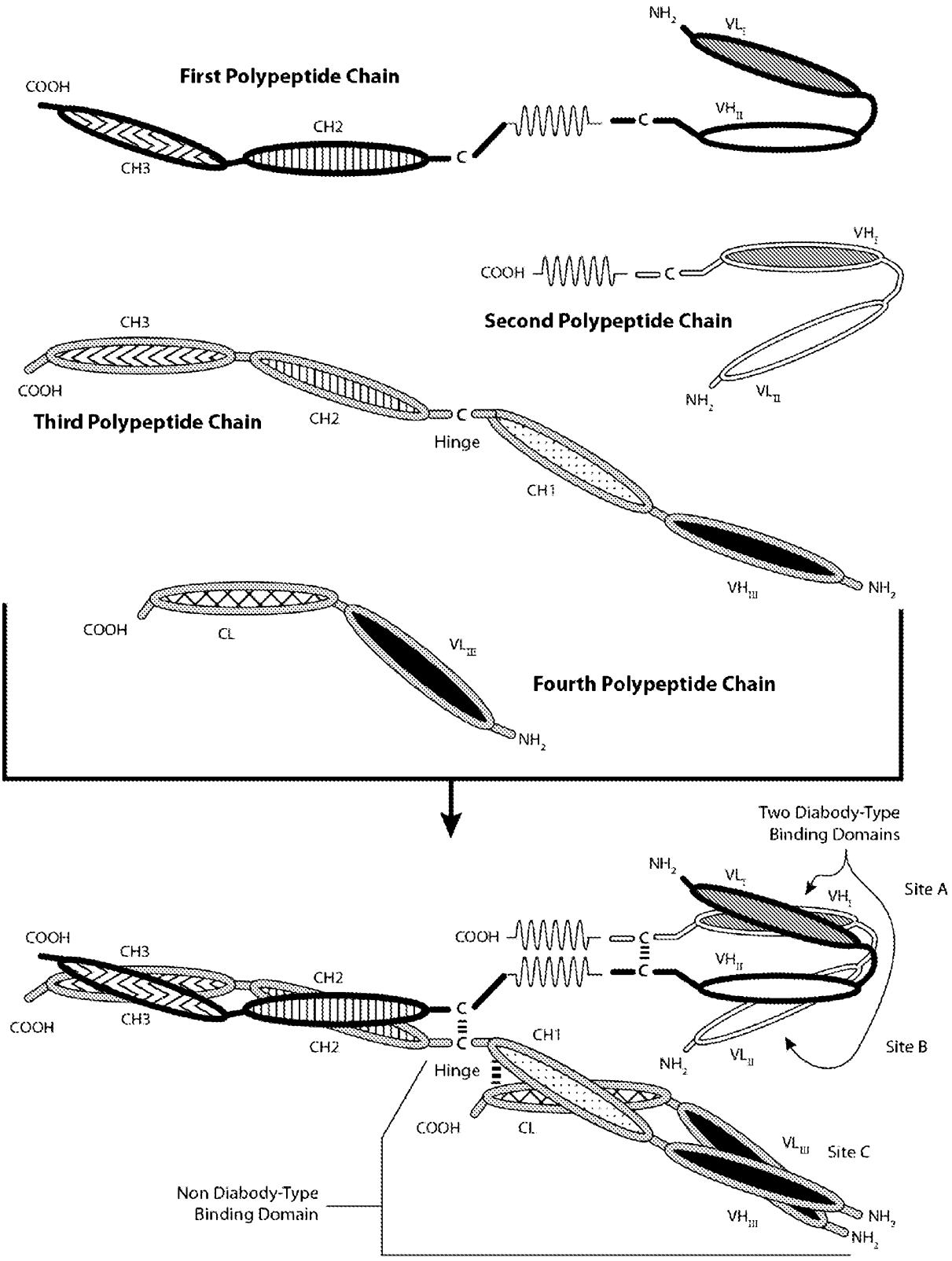

First Polypeptide Chain
COOH
CH2
CH3
C
NH2
VL
VH
Second Polypeptide Chain
Third Polypeptide Chain
Hinge
CH1
Fourth Polypeptide Chain
CL
Two Diabody-Type Binding Domains
Site A
Site B
Site C
Non Diabody-Type Binding Domain

Figure 4A

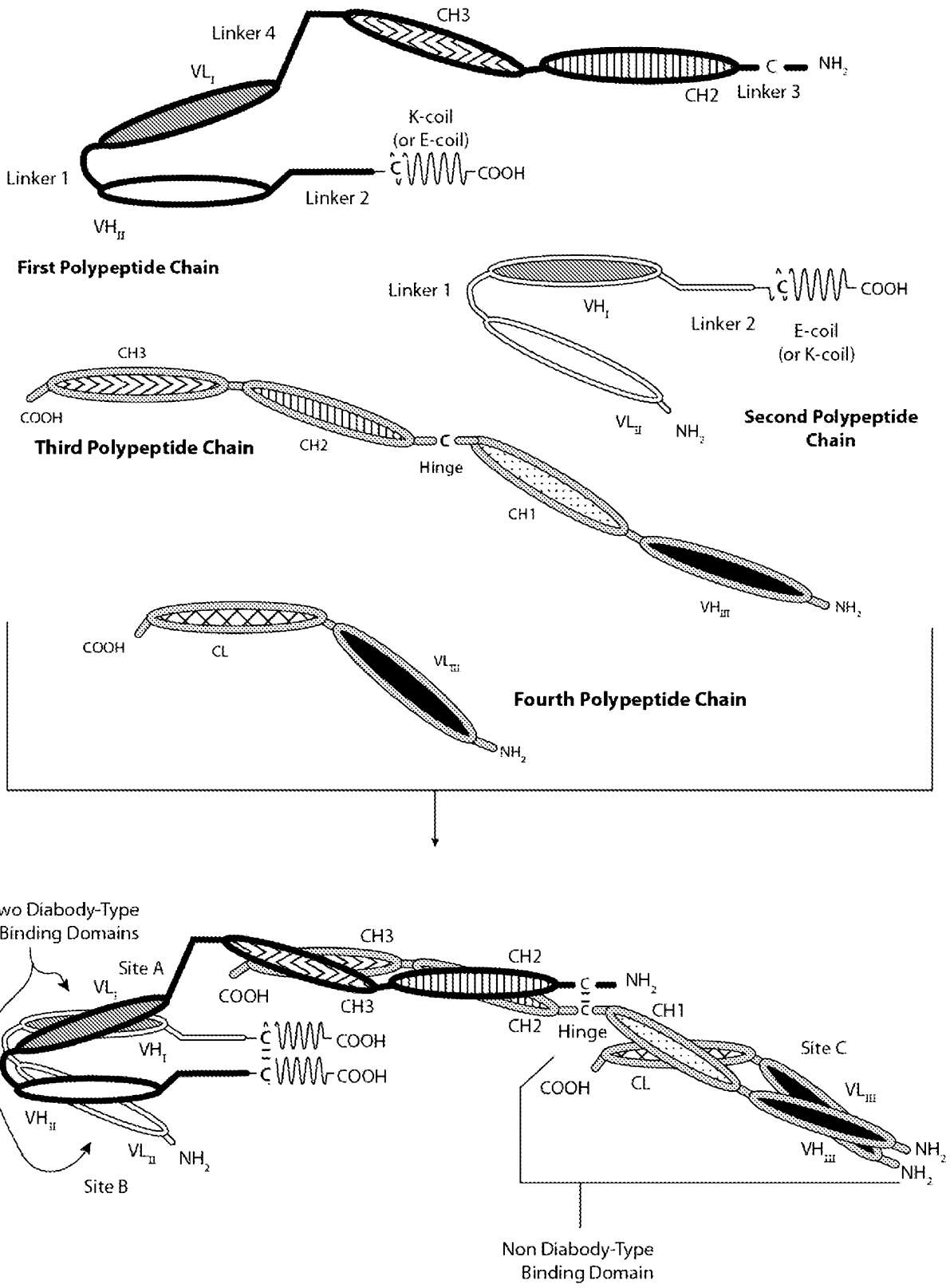

CH3
Linker 4
VL
C
NH2
CH2
Linker 3
K-coil
(or E-coil)
Linker 1
COOH
Linker 2
VH
First Polypeptide Chain
Linker 1
VH
COOH
Linker 2
E-coil
(or K-coil)
CH3
COOH
VL
NH2
Second Polypeptide Chain
Third Polypeptide Chain
CH2
C
Hinge
CH1
VH
NH2
COOH
CL
VL
Fourth Polypeptide Chain
NH2
Two Diabody-Type
Binding Domains
Site A
VL
CH3
CH2
C
NH2
COOH
CH3
CH1
CH2
Hinge
VH
COOH
COOH
Site C
CL
COOH
VL
VH
NH2
VL
NH2
NH2
Site B
Non Diabody-Type
Binding Domain

Figure 4B

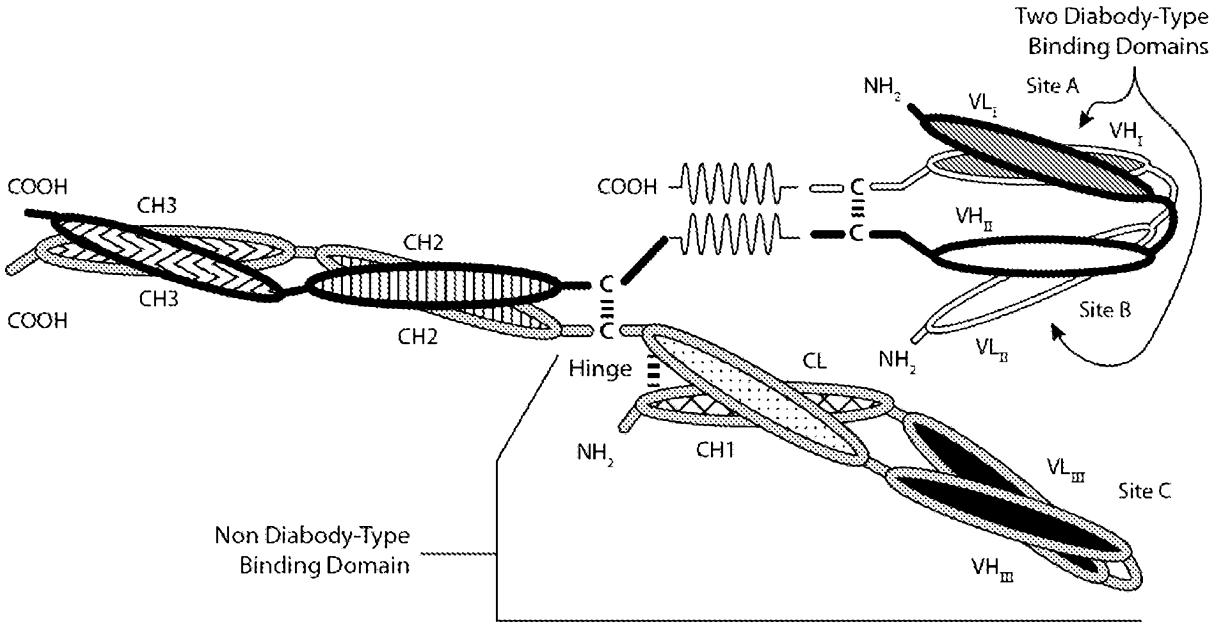


Figure 4C

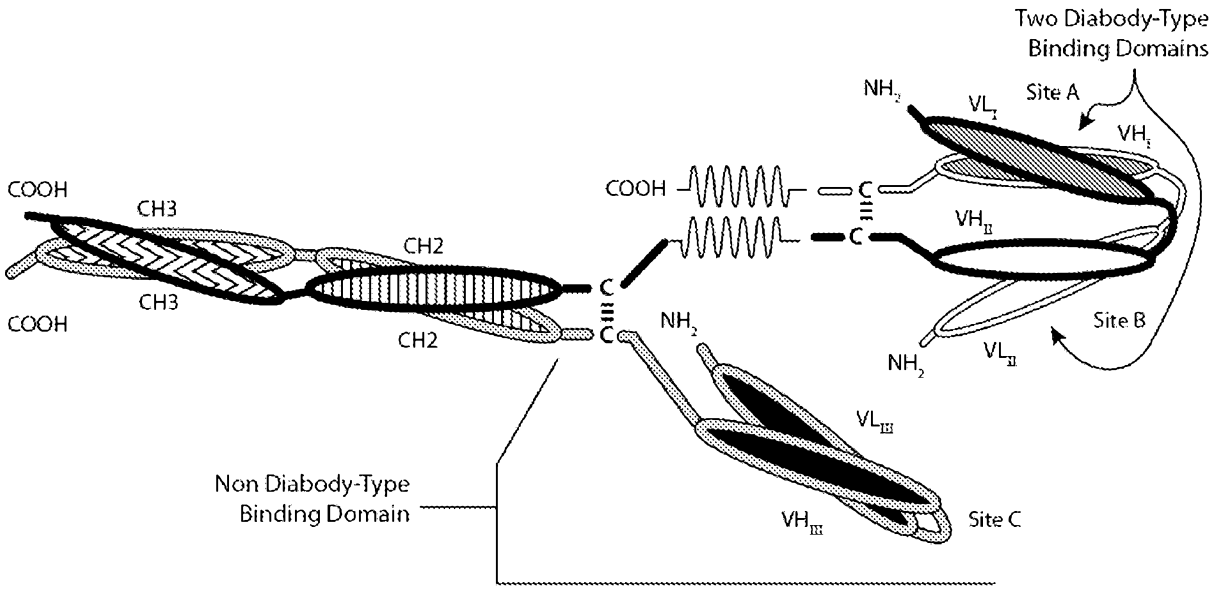


Figure 4D

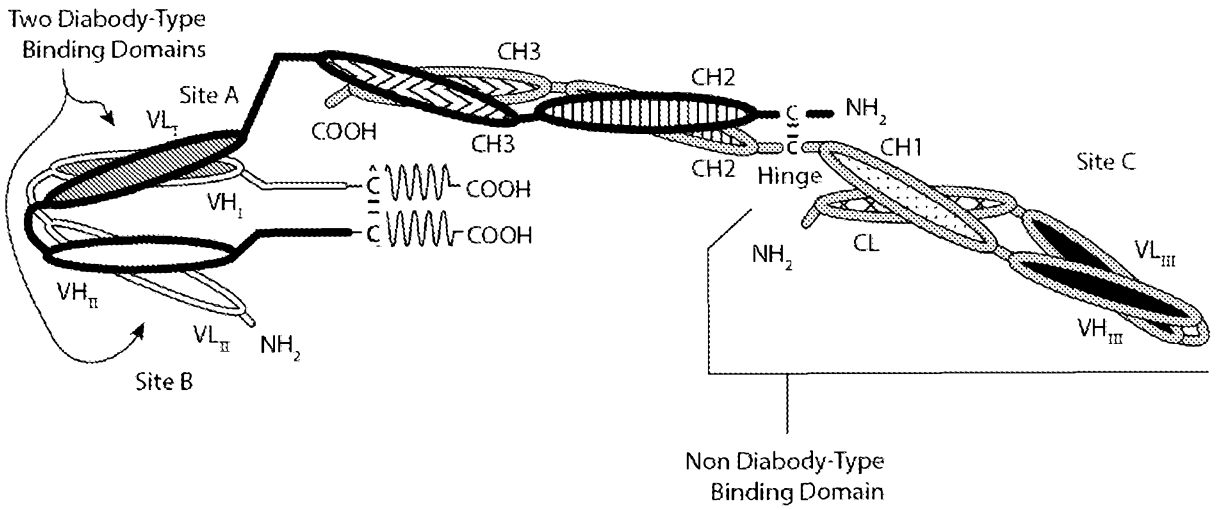


Figure 4E

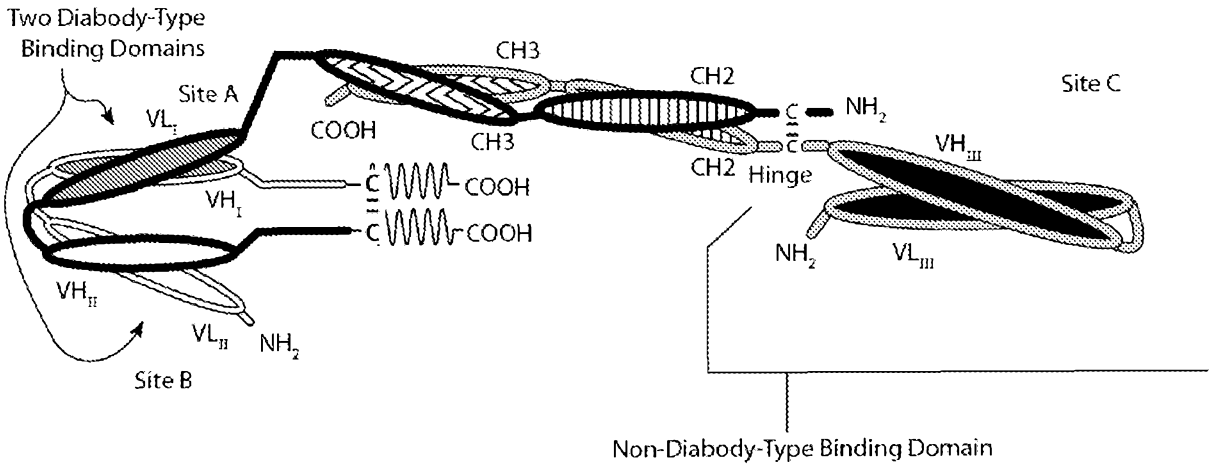


Figure 4F

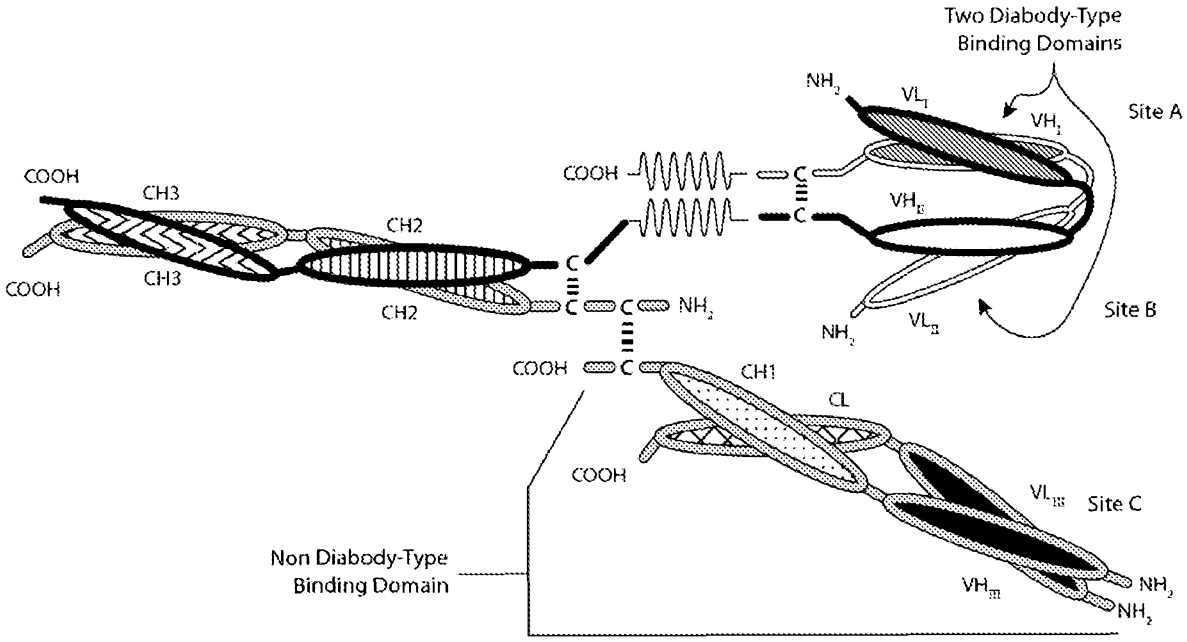

Two Diabody-Type
Binding Domains
Site A
Site B
Site C
Non Diabody-Type
Binding Domain
COOH
CH3
CH2
CH1
CL
NH2

Figure 4G

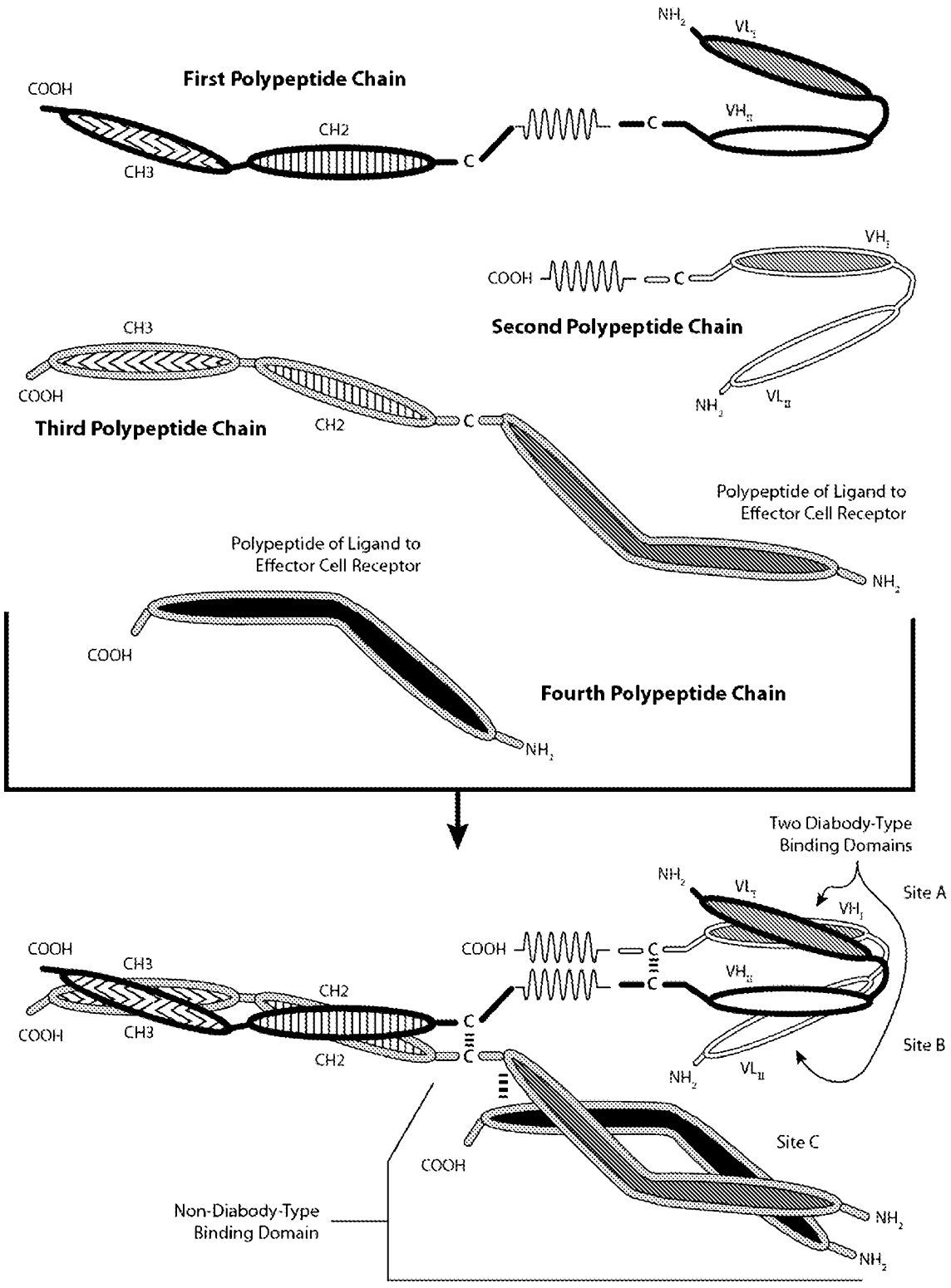

First Polypeptide Chain
COOH
CH2
CH3
C
NH2
VL1
VH2
Second Polypeptide Chain
COOH
C
VH1
NH2
VL2
Third Polypeptide Chain
COOH
CH3
CH2
C
Polypeptide of Ligand to Effector Cell Receptor
NH2
Polypeptide of Ligand to Effector Cell Receptor
COOH
Fourth Polypeptide Chain
NH2
Two Diabody-Type Binding Domains
Site A
Site B
Site C
Non-Diabody-Type Binding Domain

Figure 5A

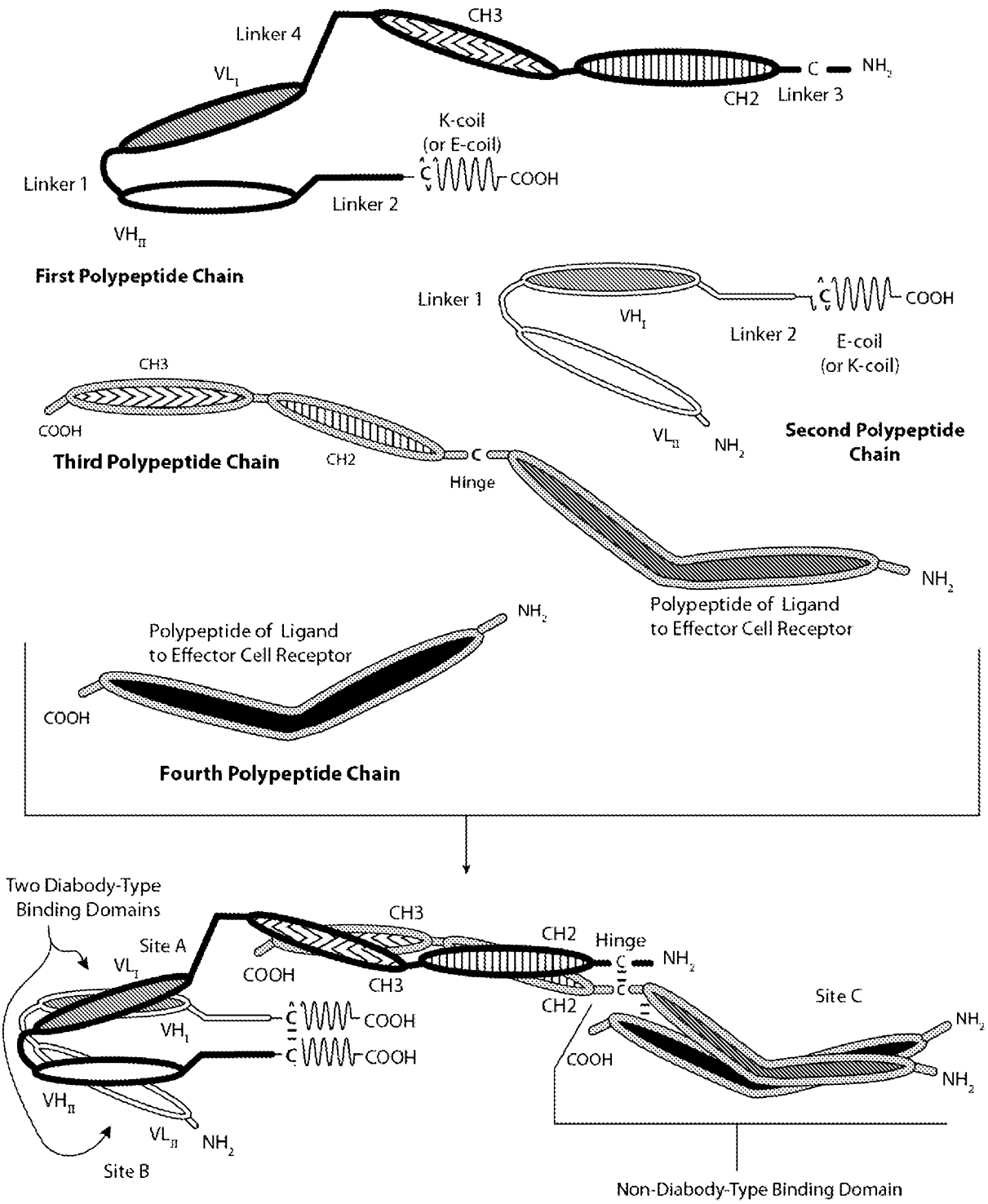

CH3
Linker 4
VL
C
NH2
CH2
Linker 3
K-coil
(or E-coil)
Linker 1
COOH
Linker 2
VH
First Polypeptide Chain
Linker 1
VH
COOH
Linker 2
E-coil
(or K-coil)
VL
NH2
Second Polypeptide Chain
CH3
COOH
Third Polypeptide Chain
CH2
C
Hinge
NH2
Polypeptide of Ligand
to Effector Cell Receptor
NH2
Polypeptide of Ligand
to Effector Cell Receptor
COOH
Fourth Polypeptide Chain
Two Diabody-Type
Binding Domains
Site A
VL
CH3
CH2
Hinge
NH2
COOH
CH3
CH2
VH
COOH
COOH
Site C
NH2
VH
COOH
NH2
VL
NH2
Site B
Non-Diabody-Type Binding Domain

Figure 5B

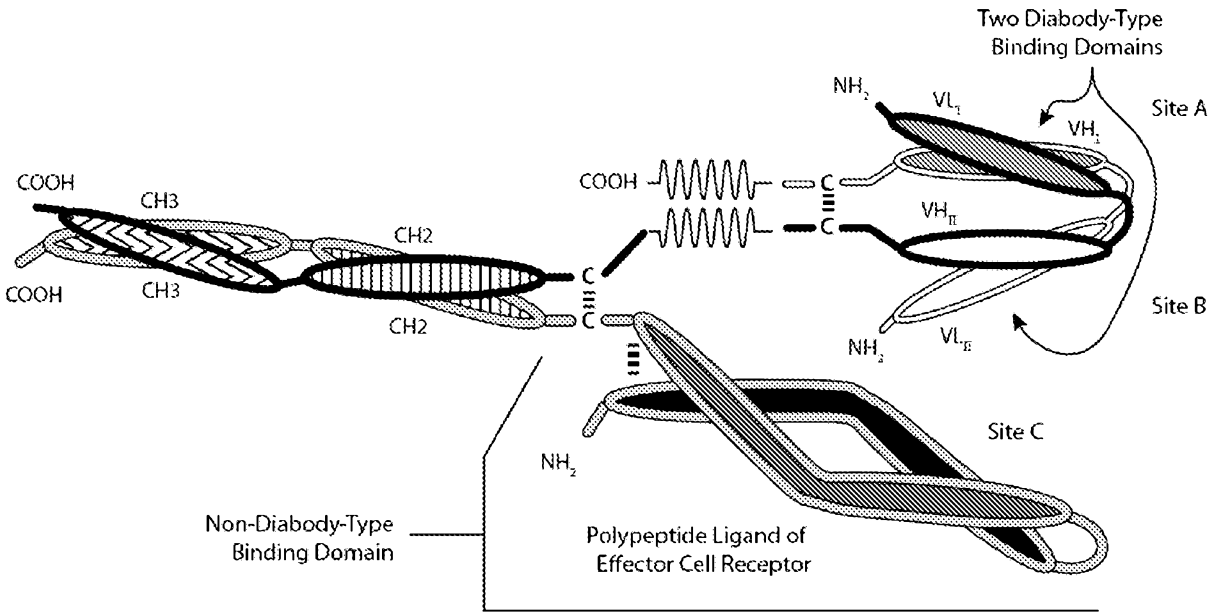


Figure 5C

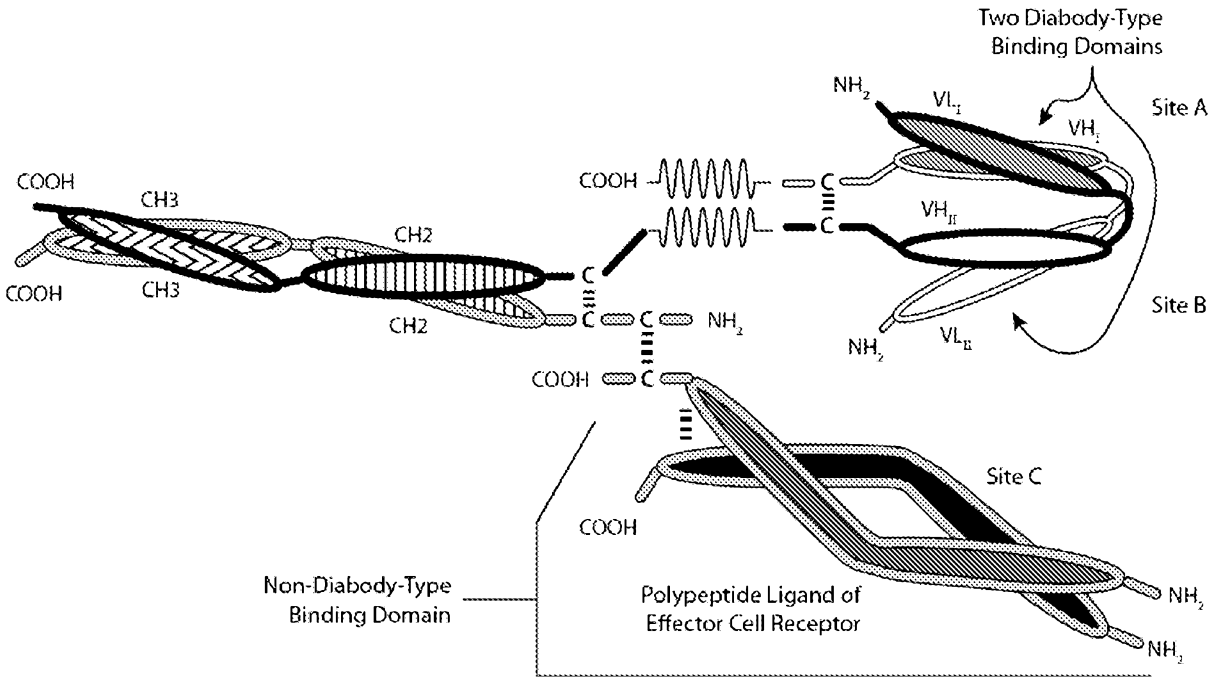


Figure 5D

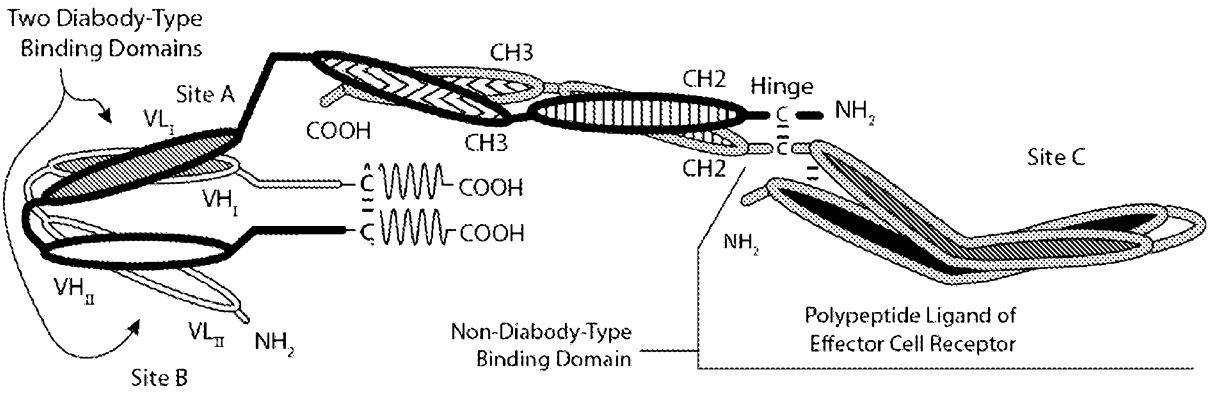

Two Diabody-Type
Binding Domains
Site A
VL
VH
VH
VL
NH2
Site B
COOH
CH3
CH3
CH2
CH2
Hinge
NH2
COOH
COOH
NH2
Site C
Non-Diabody-Type
Binding Domain
Polypeptide Ligand of
Effector Cell Receptor

Figure 5E

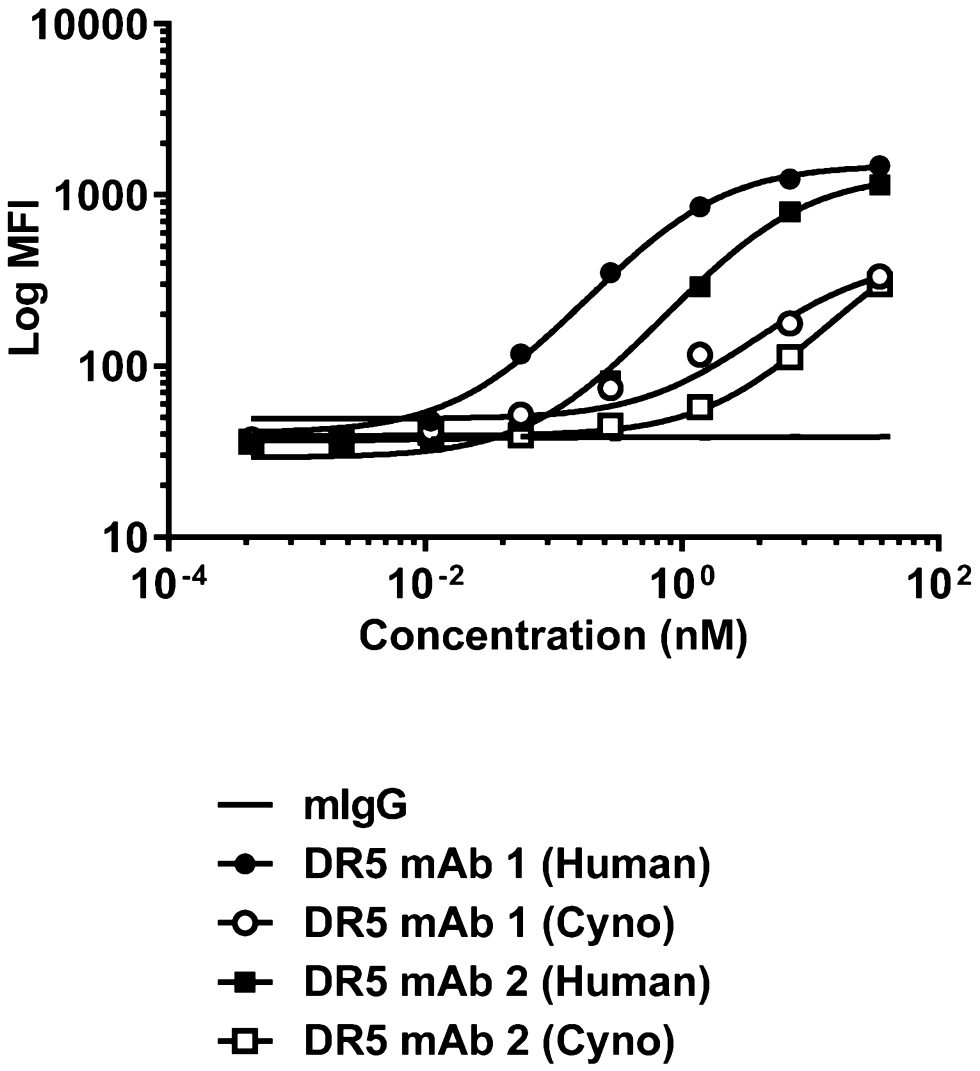

10000
1000
100
10
Log MFI
10-4
10-2
100
102
Concentration (nM)
mIgG
DR5 mAb 1 (Human)
DR5 mAb 1 (Cyno)
DR5 mAb 2 (Human)
DR5 mAb 2 (Cyno)

Figure 6

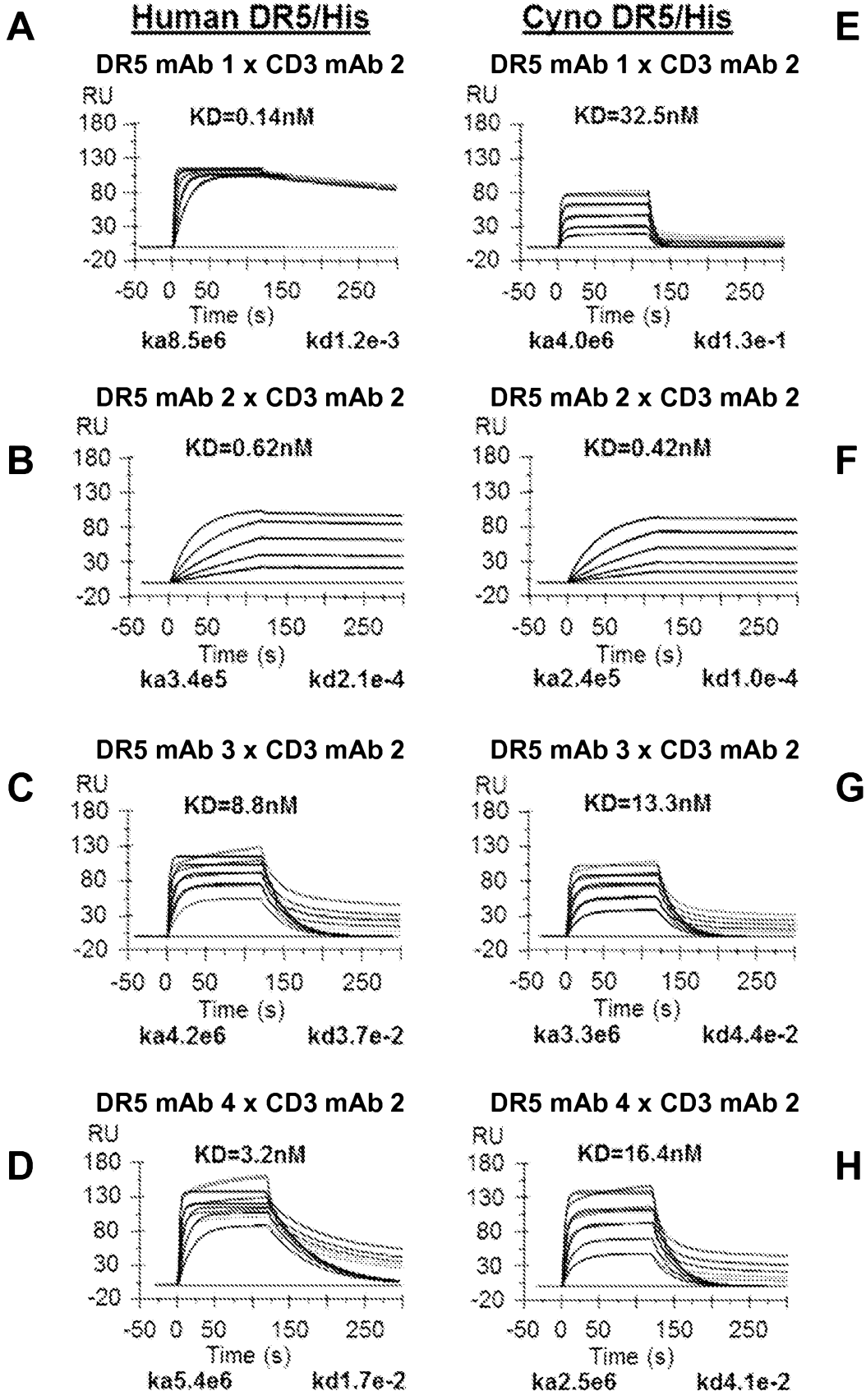

A
Human DR5/His
Cyno DR5/His
E
DR5 mAb 1 x CD3 mAb 2
KD=0.14nM
ka8.5e6 kd1.2e-3
DR5 mAb 1 x CD3 mAb 2
KD=32.5nM
ka4.0e6 kd1.3e-1
DR5 mAb 2 x CD3 mAb 2
B
KD=0.62nM
ka3.4e5 kd2.1e-4
DR5 mAb 2 x CD3 mAb 2
KD=0.42nM
F
ka2.4e5 kd1.0e-4
DR5 mAb 3 x CD3 mAb 2
C
KD=8.8nM
ka4.2e6 kd3.7e-2
DR5 mAb 3 x CD3 mAb 2
KD=13.3nM
G
ka3.3e6 kd4.4e-2
DR5 mAb 4 x CD3 mAb 2
D
KD=3.2nM
ka5.4e6 kd1.7e-2
DR5 mAb 4 x CD3 mAb 2
KD=16.4nM
H
ka2.5e6 kd4.1e-2
RU
180
130
80
30
-20
-50 0 50 150 250
Time (s)

Figure 7

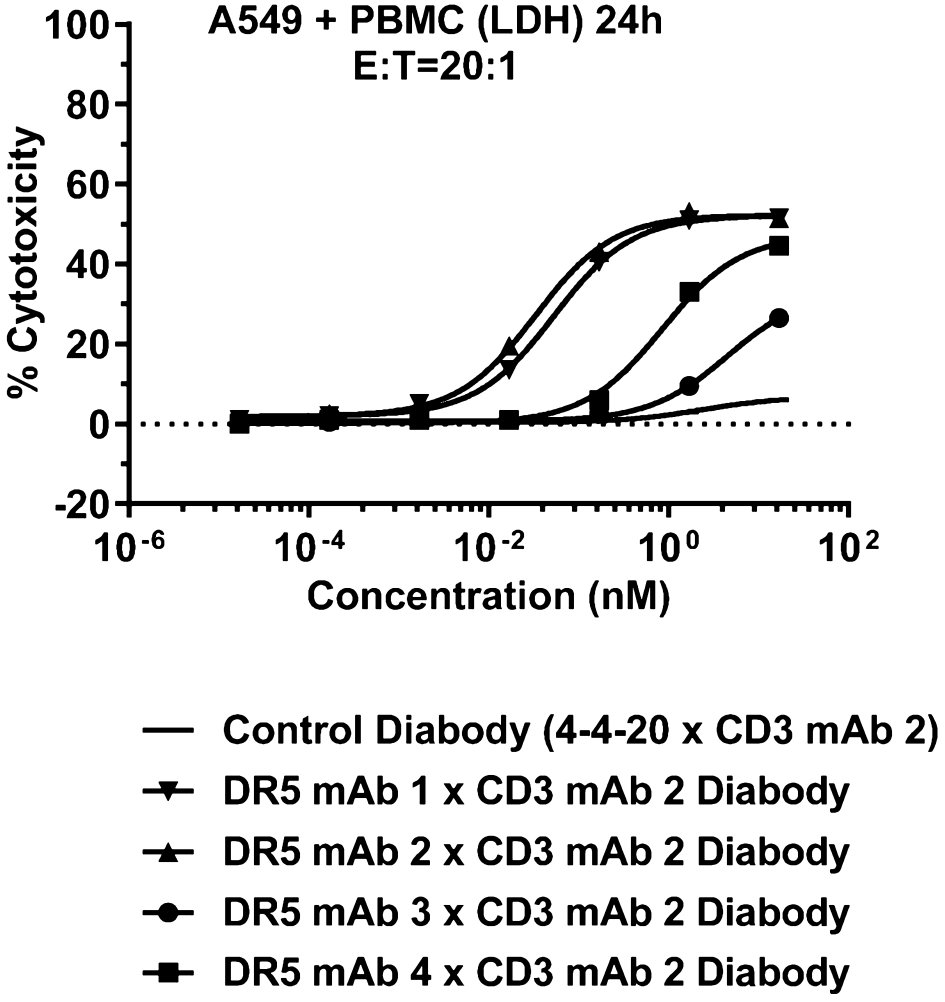

A549 + PBMC (LDH) 24h
E:T=20:1
% Cytotoxicity
100
80
60
40
20
0
-20
10-6
10-4
10-2
100
102
Concentration (nM)
Control Diabody (4-4-20 x CD3 mAb 2)
DR5 mAb 1 x CD3 mAb 2 Diabody
DR5 mAb 2 x CD3 mAb 2 Diabody
DR5 mAb 3 x CD3 mAb 2 Diabody
DR5 mAb 4 x CD3 mAb 2 Diabody

Figure 8

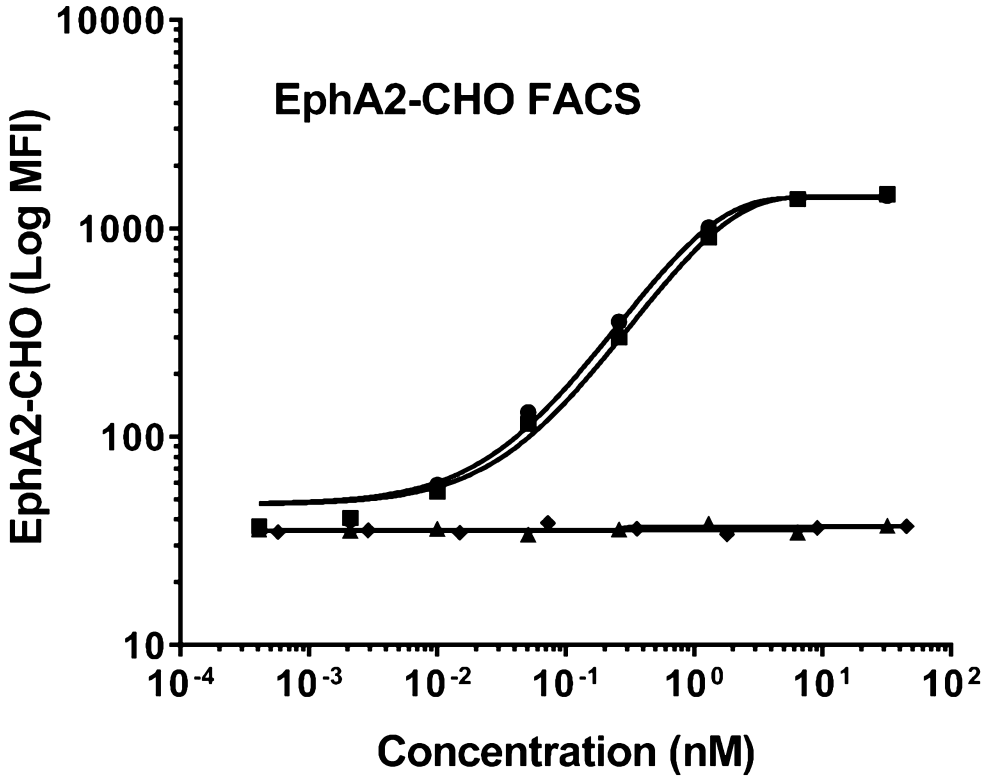

EphA2-CHO FACS
EphA2-CHO (Log MFI)
10000
1000
100
10
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2

Figure 9A

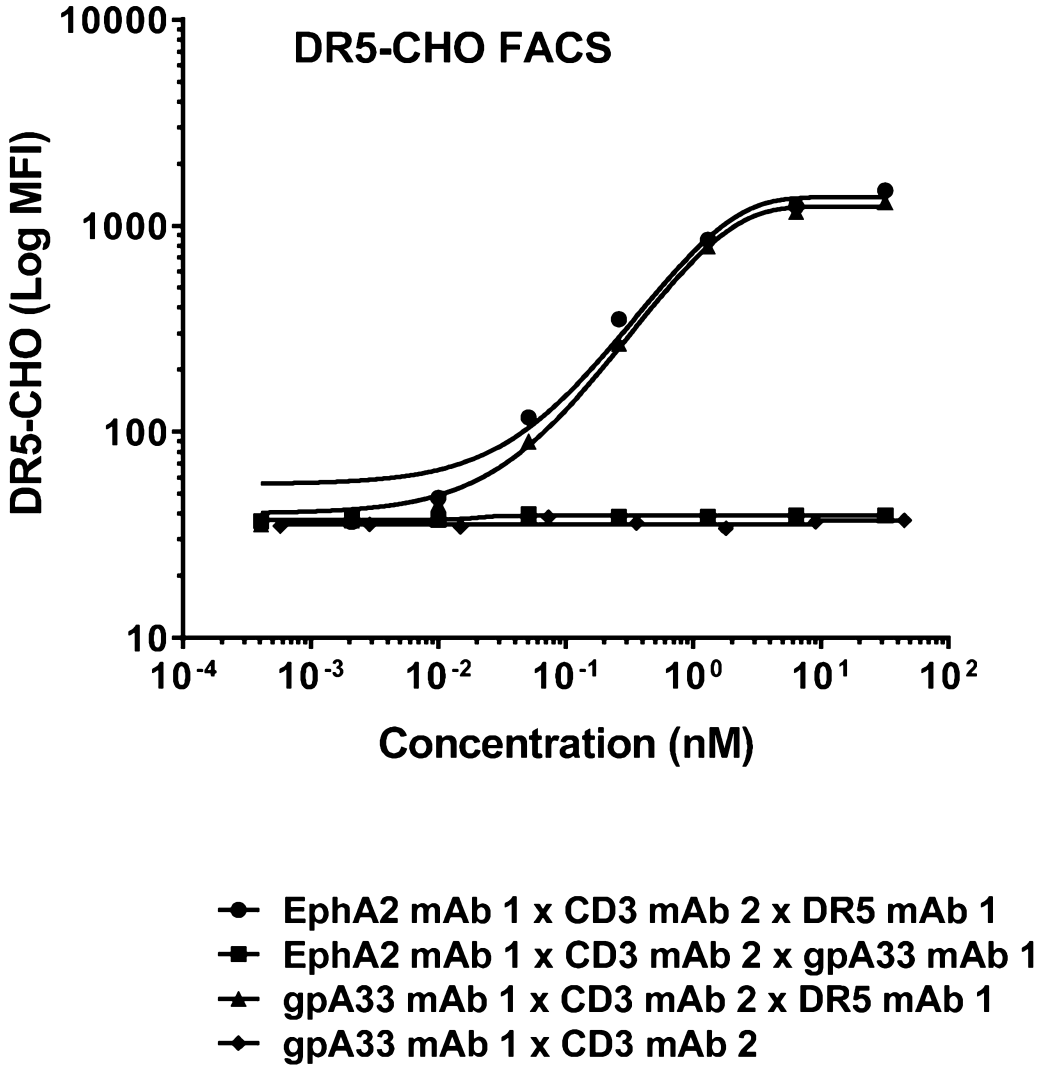

DR5-CHO FACS
DR5-CHO (Log MFI)
10000
1000
100
10
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2

Figure 9B

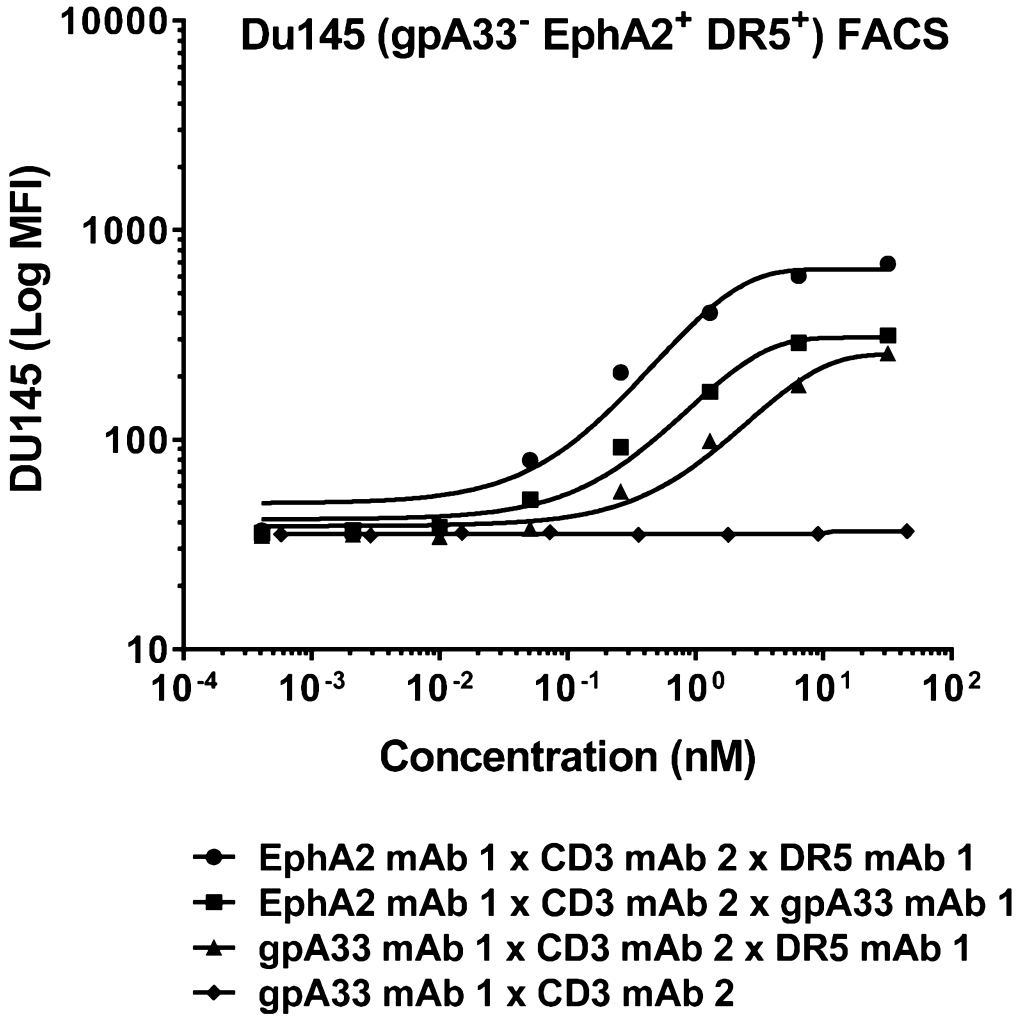

Du145 (gpA33- EphA2+ DR5+) FACS
DU145 (Log MFI)
10000
1000
100
10
10-4
10-3
10-2
10-1
100
101
102
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2

Figure 9C

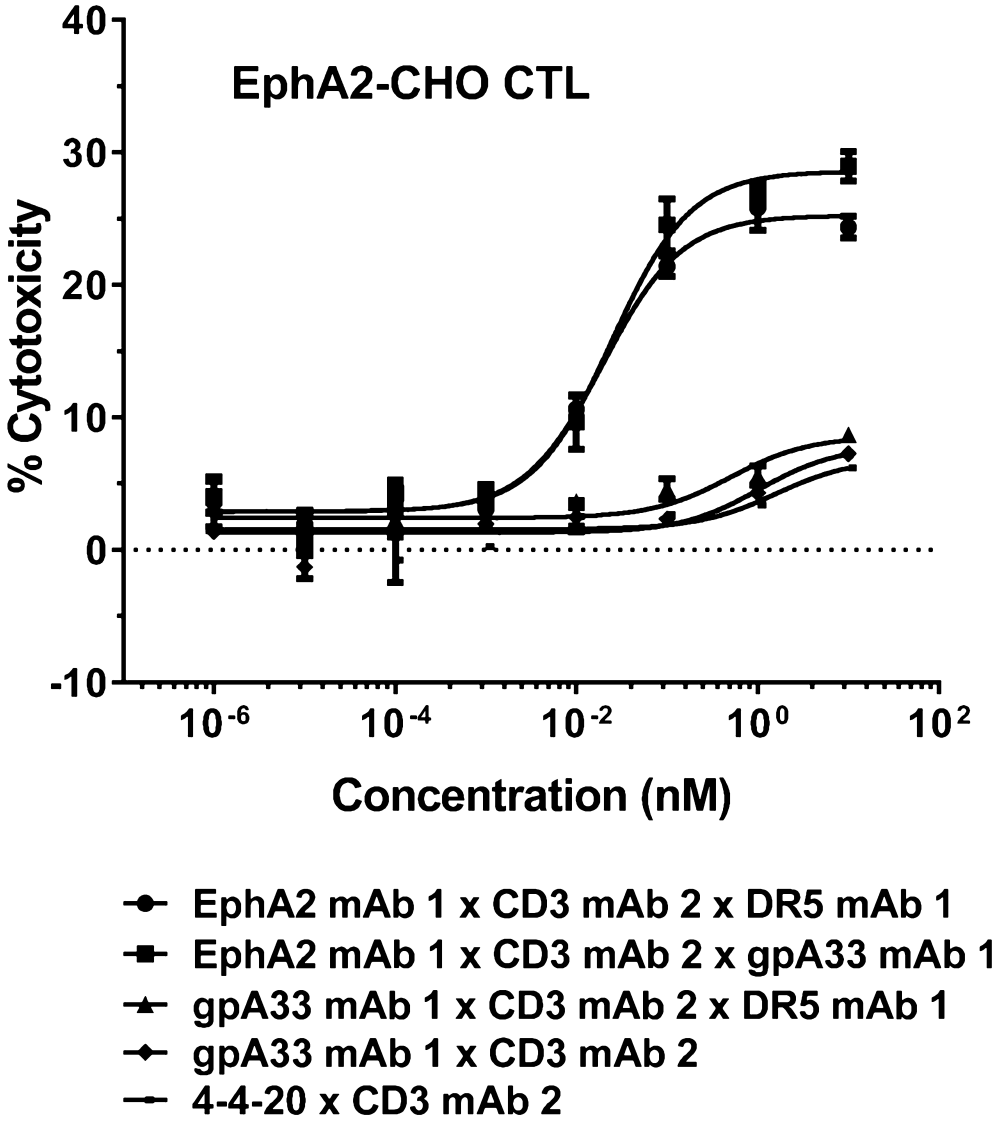

EphA2-CHO CTL
% Cytotoxicity
40
30
20
10
0
-10
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2
4-4-20 x CD3 mAb 2

Figure 10A

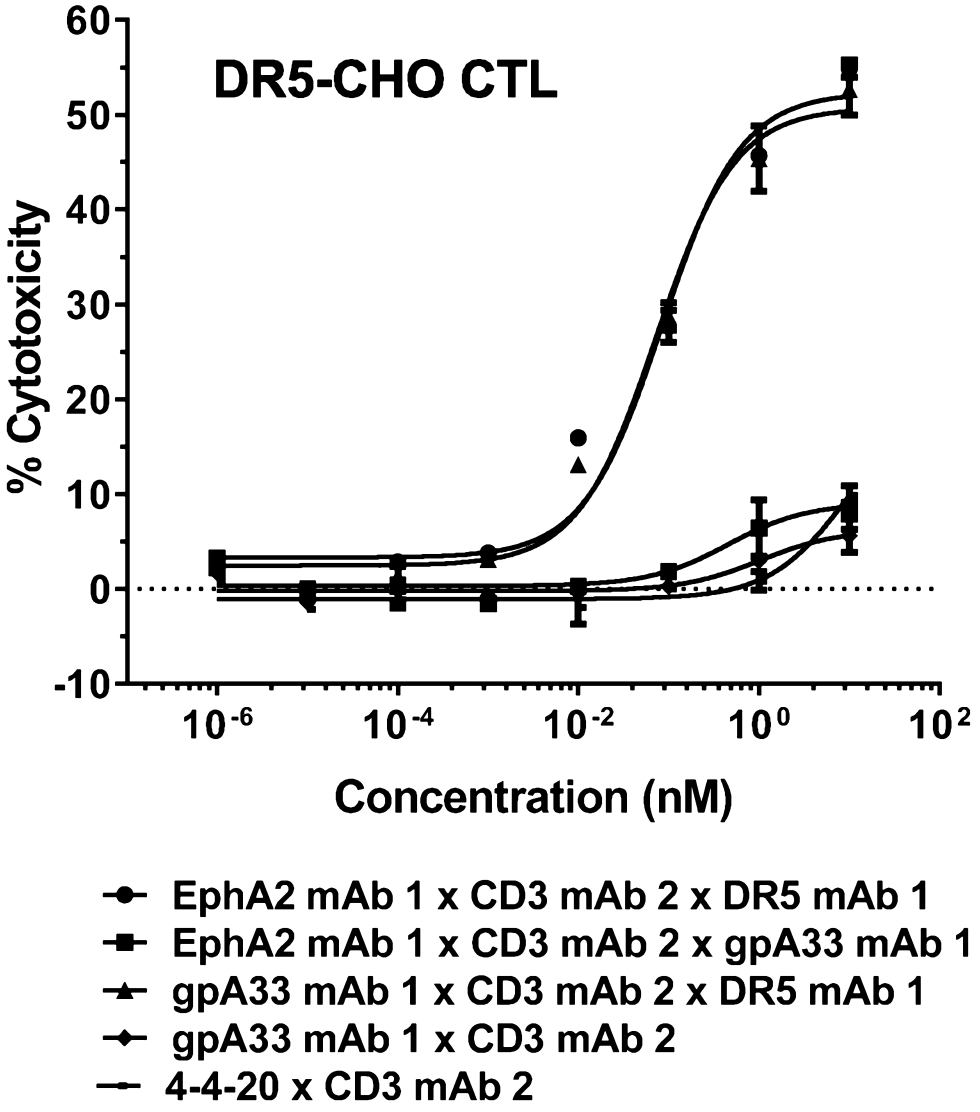

DR5-CHO CTL
% Cytotoxicity
60
50
40
30
20
10
0
-10
10^{-6}
10^{-4}
10^{-2}
10^{0}
10^{2}
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2
4-4-20 x CD3 mAb 2

Figure 10B

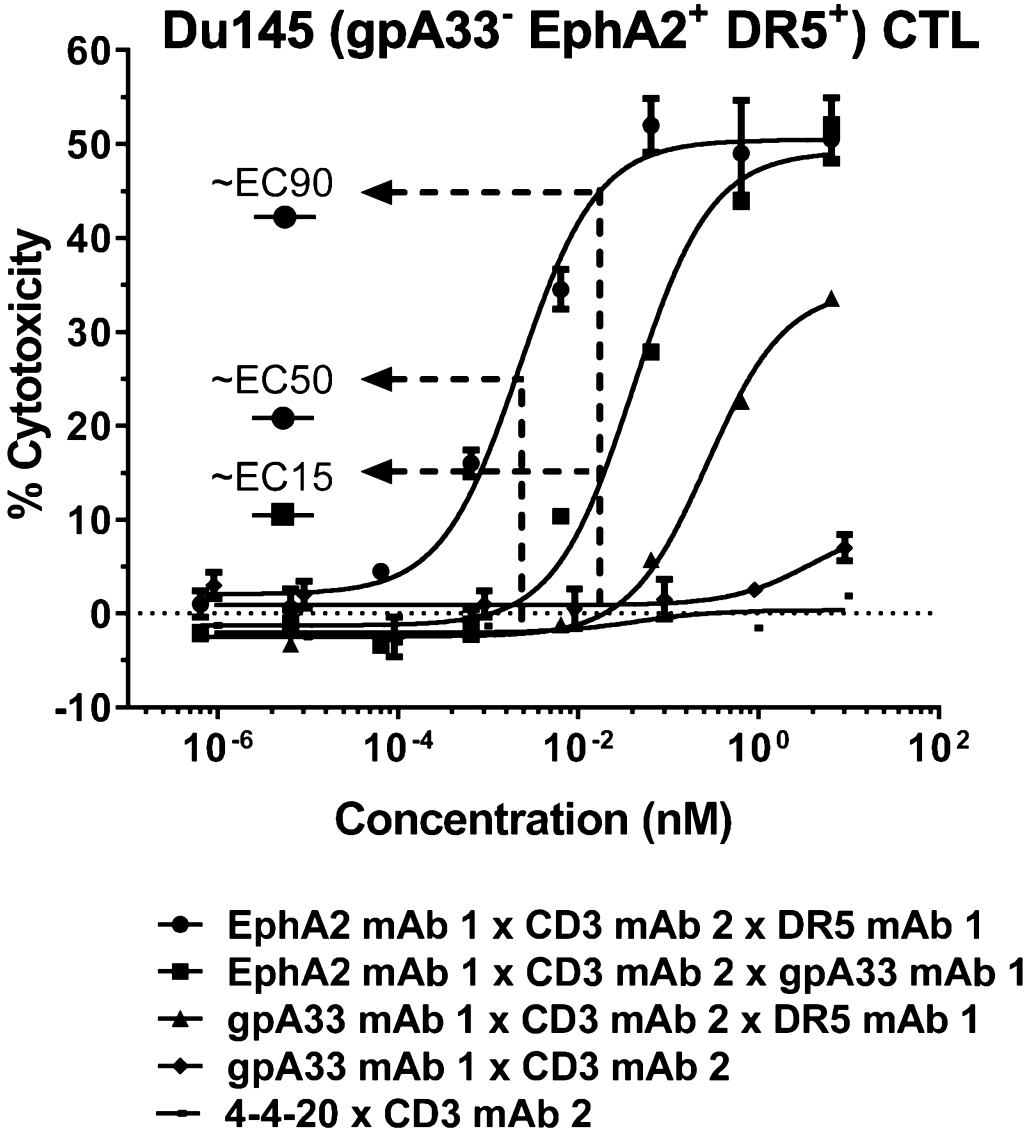

Du145 (gpA33- EphA2+ DR5+) CTL
% Cytotoxicity
60
50
40
30
20
10
0
-10
~EC90
~EC50
~EC15
10-6
10-4
10-2
100
102
Concentration (nM)
EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1
EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb 1
gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1
gpA33 mAb 1 x CD3 mAb 2
4-4-20 x CD3 mAb 2

Figure 10C

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SEQUENCE LISTING

<110> MacroGenics, Inc.

<120> Tri-Specific Binding Molecules That Specifically Bind to Multiple
Cancer Antigens and Methods of Use Therof

<130> MAC-0060-US

<140> 15/313,765
<141> 2016-11-23

<150> PCT/US2015/033081
<151> 2015-05-29

<150> US 62/107,824
<151> 2015-01-26

<150> US 62/008,229
<151> 2014-06-05

<150> US 62/004,571
<151> 2014-05-29

<160> 322

<170> PatentIn version 3.5

<210> 1
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<212> PRT
<213> Homo sapiens

<220>
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<223> Human Wild-Type IgG CH2-CH3 Domain

<400> 1

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1 5 10 15

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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190
```

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Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
210 215

<210> 2
<211> 440
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(440)
<223> Human DR5 Precursor (NCBI Sequence NP_003833.4)

<400> 2

Met Glu Gln Arg Gly Gln Asn Ala Pro Ala Ala Ser Gly Ala Arg Lys
1 5 10 15

Arg His Gly Pro Gly Pro Arg Glu Ala Arg Gly Ala Arg Pro Gly Leu
20 25 30

Arg Val Pro Lys Thr Leu Val Leu Val Val Ala Ala Val Leu Leu Leu
35 40 45

Val Ser Ala Glu Ser Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln
50 55 60

Gln Arg Val Ala Pro Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu
65 70 75 80

Cys Pro Pro Gly His His Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser
85 90 95

Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe

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```
                100                 105                 110

Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro
        115                 120                 125

Cys Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe
    130                 135                 140

Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys
145                 150                 155                 160

Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile
                165                 170                 175

Glu Cys Val His Lys Glu Ser Gly Thr Lys His Ser Gly Glu Ala Pro
            180                 185                 190

Ala Val Glu Glu Thr Val Thr Ser Ser Pro Gly Thr Pro Ala Ser Pro
        195                 200                 205

Cys Ser Leu Ser Gly Ile Ile Ile Gly Val Thr Val Ala Ala Val Val
    210                 215                 220

Leu Ile Val Ala Val Phe Val Cys Lys Ser Leu Leu Trp Lys Lys Val
225                 230                 235                 240

Leu Pro Tyr Leu Lys Gly Ile Cys Ser Gly Gly Gly Gly Asp Pro Glu
                245                 250                 255

Arg Val Asp Arg Ser Ser Gln Arg Pro Gly Ala Glu Asp Asn Val Leu
            260                 265                 270

Asn Glu Ile Val Ser Ile Leu Gln Pro Thr Gln Val Pro Glu Gln Glu
        275                 280                 285
```

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```
Met Glu Val Gln Glu Pro Ala Glu Pro Thr Gly Val Asn Met Leu Ser
    290                 295                 300

Pro Gly Glu Ser Glu His Leu Leu Glu Pro Ala Glu Ala Glu Arg Ser
305                 310                 315                 320

Gln Arg Arg Arg Leu Leu Val Pro Ala Asn Glu Gly Asp Pro Thr Glu
                325                 330                 335

Thr Leu Arg Gln Cys Phe Asp Asp Phe Ala Asp Leu Val Pro Phe Asp
            340                 345                 350

Ser Trp Glu Pro Leu Met Arg Lys Leu Gly Leu Met Asp Asn Glu Ile
        355                 360                 365

Lys Val Ala Lys Ala Glu Ala Ala Gly His Arg Asp Thr Leu Tyr Thr
    370                 375                 380

Met Leu Ile Lys Trp Val Asn Lys Thr Gly Arg Asp Ala Ser Val His
385                 390                 395                 400

Thr Leu Leu Asp Ala Leu Glu Thr Leu Gly Glu Arg Leu Ala Lys Gln
                405                 410                 415

Lys Ile Glu Asp His Leu Leu Ser Ser Gly Lys Phe Met Tyr Leu Glu
            420                 425                 430

Gly Asn Ala Asp Ser Ala Met Ser
        435                 440
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<210> 3
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<212> PRT

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<213> Mus musculus

<220>
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Domain

<400> 3

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1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 4
<211> 15
<212> PRT
<213> Mus musculus

<220>

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<221> MISC_FEATURE
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Light Chain Variable
Domain CDRL1

<400> 4

Arg Ala Ser Lys Ser Val Ser Ser Ser Gly Tyr Ser Tyr Met His
1 5 10 15

<210> 5
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Light Chain Variable
Domain CDRL2

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Leu Ser Ser Asn Leu Asp Ser
1 5

<210> 6
<211> 9
<212> PRT
<213> Mus musculus

<220>
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Light Chain Variable
Domain CDRL3

<400> 6

Gln His Ser Arg Asp Leu Pro Pro Thr

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<210> 7
<211> 333
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(333)
<223> Polynucleotide Encoding Murine Anti-Human DR5 Antibody ("DR5 mAb
1") Light Chain Variable Domain

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gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc
60

atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac
120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct
180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat
240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg
300

acgttcggtg gaggcaccaa gctggaaatc aaa
333

<210> 8
<211> 121
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(121)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Heavy Chain
Variable

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Domain

<400> 8

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Glu Val Lys Phe Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Thr Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 9
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Heavy Chain Variable

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Domain CDRH1

<400> 9

Gly Phe Asp Phe Ser Arg Tyr Trp Met Ser
1 5 10

<210> 10
<211> 17
<212> PRT
<213> Mus musculus

<220>
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Heavy Chain Variable
Domain CDRH2

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Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu Lys
1 5 10 15

Asp

<210> 11
<211> 12
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 1") Heavy Chain Variable
Domain CDRH3

<400> 11

Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr

1 5 10

<210> 12
<211> 363
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(363)
<223> Polynucleotide Encoding Murine Anti-Human DR5 Antibody ("DR5 mAb
1") Heavy Chain Variable Domain

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tcctgtgtag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

ccagggaaag ggctagaatg gattggagaa attaatccag atagcaatac gataaactat 180

acgccatctc taaaggataa attcatcatc tccagagaca acgccaaaaa tacgctgtat 240

ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc 300

tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt cactgtctct 360

t c c 363

<210> 13
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE

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<222> (1)..(107)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Light Chain Variable
Domain

<400> 13

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Lys Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Thr Leu Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 14
<211> 11
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Light Chain Variable

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Domain CDRL1

<400> 14

Lys Ala Ser Gln Asp Val Asn Thr Ala Val Ala
1 5 10

<210> 15
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
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<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Light Chain Variable
Domain CDRL2

<400> 15

Trp Ala Ser Thr Arg His Thr
1 5

<210> 16
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Light Chain Variable
Domain CDRL3

<400> 16

Gln Gln His Tyr Ile Thr Pro Trp Thr
1 5

<210> 17

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<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(321)
<223> Polynucleotide Encoding Murine Anti-Human DR5 Antibody ("DR5 mAb
2") Light Chain Variable Domain

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gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga cagggtcagc
60

atcacctgca aggccagtca ggatgtgaat actgctgtag cctggtatca acaaaaacca
120

gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat
180

cgcttcacag gcagtggatc tgggacagat tatacactca ccatcaaaag tgtgcaggct
240

gaagacctga cactttatta ctgtcagcaa cactatatca ctccgtggac gttcggtgga
300

g g c a c c a a g c t g g a a a t c a a a
321

<210> 18
<211> 119
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(119)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Heavy Chain
Variable Domain

<400> 18

Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala

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1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Ile Leu His Trp Val Lys Gln Lys Ser Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Phe Tyr Pro Gly Asn Asn Asn Ile Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg His Glu Gln Gly Pro Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 19
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Heavy Chain Variable
Domain CDRH1

<400> 19

12 Dec 2018
2015266797

Gly Tyr Thr Phe Thr Glu Tyr Ile Leu His
1 5 10

<210> 20
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Heavy Chain Variable
Domain CDRH2

<400> 20

Trp Phe Tyr Pro Gly Asn Asn Asn Ile Lys Tyr Asn Glu Lys Phe Lys
1 5 10 15

Asp

<210> 21
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 2") Heavy Chain Variable
Domain CDRH3

<400> 21

His Glu Gln Gly Pro Gly Tyr Phe Asp Tyr
1 5 10

<210> 22

12 Dec 2018
2015266797

<211> 357
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(357)
<223> Polynucleotide Encoding Murine Anti-Human DR5 Antibody ("DR5 mAb
2") Heavy Chain Variable Domain

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60

tcctgcaagg cttctgggta caccttcact gagtatattt tacactgggt aaagcagaag
120

tctggacagg gtcttgagtg gattgggtgg ttttatcctg gaaataataa tataaagtac
180

aatgagaaat tcaaggacaa ggccacactg actgcggaca aatcctccag cacagtctat
240

atggaactta gtagattgac atctgaagac tctgcggtct atttctgtgc aagacacgaa
300

caaggaccag gttactttga ctactggggc caaggcacca ctctcacagt ctcctcc
357

<210> 23
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody ("hDR5 mAb 2 VL-2") Light
Chain
Variable Domain

<400> 23

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 24
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Humanized Anti-Human DR5 Antibody ("hDR5
mAb 2 VL-2") Light Chain Variable Domain

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gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga ccgcgtgact 60

attacttgta aagcttctca ggatgtcaac accgccgtgg cttggtacca gcagaagccc 120

ggtaaagcac ctaagctgct gatctattgg gccagcactc ggcacaccgg agtcccatct 180

aggttctctg gcagtggatc agggacagac tttaccctga caattagctc cctgcagccc
240

gaggatgtgg ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg
300

g g c a c a a a a a c t g g a a a t c a a a
321

<210> 25
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody ("hDR5 mAb 2 VL-3") Light Chain
Variable Domain

<400> 25

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 26
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Humanized Anti-Human DR5 Antibody ("hDR5
mAb 2 VL-3") Light Chain Variable Domain

<400> 26
gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga ccgcgtgact 60

attacttgtc gggcttctca ggatgtcaac accgccgtgg cttggtacca gcagaagccc 120

ggtaaagcac ctaagctgct gatctattgg gccagcactc ggcacaccgg agtcccagat 180

aggttctctg gcagtggatc agggacagac tttaccctga caattagctc cctgcagccc 240

gaggatgtgg ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg 300

g g c a c a a a a c t g g a a a t c a a a 321

<210> 27
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Murine Anti-Human DR5 Antibody ("DR5 mAb 4") Light Chain Variable
Domain

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<400> 27

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 28
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Humanized Anti-Human DR5 Antibody ("hDR5
mAb 2 VL-4") Light Chain Variable Domain

<400> 28
gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga ccgcgtgact 60

attacttgtc gggcttctca ggatgtcaac accgccgtgg cttggtacca gcagaagccc
120

ggtaaagcac ctaagctgct gatctattgg gccagcactc ggcacaccgg agtcccatct
180

aggttctctg gcagtggatc agggacagac tttaccctga caattagctc cctgcagcca
240

gaggatatcg ctacatacta ttgtcagcag cactacatca ctccttggac cttcggcggg
300

g g c a c a a a a c t g g a a a t c a a a
321

<210> 29
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody ("hDR5 mAb 2 VL-5") Light Chain
Variable Domain

<400> 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 30
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Humanized Anti-Human DR5 Antibody ("hDR5
mAb 2 VL-5") Light Chain Variable Domain

<400> 30
gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcggtga ccgcgtgact 60

attacttgtc gggcttctca ggatgtcaac accgccgtgg cttggtacca gcagaagccc 120

ggtaaagcac ctaagctgct gatctattgg gccagcactc ggcacaccgg agtcccagat 180

aggttctctg gcagtggatc agggacagac tttaccctga caattagctc cctgcagccc 240

gaggatatcg ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcggg 300

g g c a c a a a a c t g g a a a t c a a a 321

<210> 31
<211> 119
<212> PRT
<213> Artificial Sequence

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<220>
<223> Humanized Anti-Human DR5 Antibody ("hDR5 mAb 2 VH-2") Heavy Chain
Variable Domain

<400> 31

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Ile Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Phe Tyr Pro Gly Asn Asn Asn Ile Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Glu Gln Gly Pro Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 32
<211> 357
<212> DNA
<213> Artificial Sequence

12 Dec 2018
2015266797

<220>
<223> Polynucleotide Encoding Humanized Anti-Human DR5 Antibody ("hDR5
mAb 2 VH-2") Heavy Chain Variable Domain

<400> 32
caggtccagc tggtgcagag tggggcagag gtgaaaaagc caggggcatc agtgaaagtg 60

tcttgtaaag catcaggtta tacatttact gagtacatcc tgcactgggt gcgacaggca 120

ccaggacagg gactggaatg gatggggtgg ttctaccctg gcaacaacaa cattaagtac 180

aacgagaagt ttaaagaccg ggtgaccatc acagcggata agtctaccag tacagtctat 240

atggagctga gctccctgag aagcgaagac accgccgtct actattgcgc tcgccacgaa 300

cagggtccag gttactttga ttattggggg cagggaactc tggtcacagt cagctcc 357

<210> 33
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker 1

<400> 33

Gly Gly Gly Ser Gly Gly Gly Gly
1 5

<210> 34
<211> 6
<212> PRT
<213> Artificial Sequence

<220>

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<223> Cysteine-Containing Spacer Peptide ("Linker 2")

<400> 34

Gly Gly Cys Gly Gly Gly
1 5

<210> 35
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Peptide Variant of Human IgG Hinge Domain

<400> 35

Gly Val Glu Pro Lys Ser Cys
1 5

<210> 36
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Peptide Variant of Human IgG Hinge Domain

<400> 36

Val Glu Pro Lys Ser Cys
1 5

<210> 37
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Peptide Variant of Human IgG CL Domain

<400> 37

12 Dec 2018
2015266797

Gly Phe Asn Arg Gly Glu Cys
1 5

<210> 38
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Peptide Variant of Human IgG CL Domain

<400> 38

Phe Asn Arg Gly Glu Cys
1 5

<210> 39
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterodimer-Promoting "E-coil" Domain

<400> 39

Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val
1 5 10 15

Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys
20 25

<210> 40
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Heterodimer-Promoting "K-coil" Domain

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<400> 40

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu Lys Val
1 5 10 15

Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
20 25

<210> 41
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Heterodimer-Promoting "E-coil" Domain

<400> 41

Glu Val Ala Ala Cys Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val
1 5 10 15

Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys
20 25

<210> 42
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine-Containing Heterodimer-Promoting "K-coil" Domain

<400> 42

Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala Leu Lys Glu Lys Val
1 5 10 15

Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
20 25

<210> 43
<211> 46
<212> PRT
<213> Streptococcus dysgalactiae

<220>
<221> MISC_FEATURE
<222> (1)..(46)
<223> Albumin-Binding Domain 3 (ABD3) of Protein G of Streptococcus Strain G148

<400> 43

Leu Ala Glu Ala Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly
1 5 10 15

Val Ser Asp Tyr Tyr Lys Asn Leu Ile Asp Asn Ala Lys Ser Ala Glu
20 25 30

Gly Val Lys Ala Leu Ile Asp Glu Ile Leu Ala Ala Leu Pro
35 40 45

<210> 44
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant Deimmunized Albumin-Binding Domain 3 (ABD3) of Protein G of Streptococcus Strain G148

<400> 44

Leu Ala Glu Ala Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly
1 5 10 15

Val Ser Asp Tyr Tyr Lys Asn Ala Ala Asn Asn Ala Lys Thr Val Glu
20 25 30

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Gly Val Lys Ala Leu Ile Ala Glu Ile Leu Ala Ala Leu Pro
35 40 45

<210> 45
<211> 46
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant Deimmunized Albumin-Binding Domain 3 (ABD3) of Protein G
of Streptococcus Strain G148

<400> 45

Leu Ala Glu Ala Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly
1 5 10 15

Val Ser Asp Tyr Tyr Lys Asn Leu Ile Ser Asn Ala Lys Ser Val Glu
20 25 30

Gly Val Lys Ala Leu Ile Ala Glu Ile Leu Ala Ala Leu Pro
35 40 45

<210> 46
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Linker ("Linker 3")

<400> 46

Gly Gly Gly Ser
1

<210> 47
<211> 5

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<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Linker

<400> 47

Ala Ser Thr Lys Gly
1 5

<210> 48
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Linker

<400> 48

Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10

<210> 49
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Linker

<400> 49

Leu Glu Pro Lys Ser Ser
1 5

<210> 50
<211> 8
<212> PRT
<213> Artificial Sequence

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<220>
<223> Peptide Linker

<400> 50

Ala Pro Ser Ser Ser Pro Met Glu
1 5

<210> 51
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Linker

<400> 51

Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 52
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> "Knob-Bearing" Variant Human IgG Fc Domain

<400> 52

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

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```
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
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<210> 53

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<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> "Hole-Bearing" Variant Human IgG Fc Domain

<400> 53

```
Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
    130                 135                 140
```

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```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
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<210> 54
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Light Chain Variable Domain

<400> 54

```
Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr
1               5                   10                  15

Val Arg Ile Thr Cys Ser Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
            20                  25                  30

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly
        35                  40                  45
```

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Ala Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
50 55 60

Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp
65 70 75 80

Glu Ala Asp Tyr Tyr Cys Asn Ser Ala Asp Ser Ser Gly Asn His Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 55
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Light Chain Variable Domain CDRL1

<400> 55

Ser Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
1 5 10

<210> 56
<211> 7
<212> PRT
<213> Homo sapienss

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Light Chain Variable Domain CDRL2

<400> 56

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Gly Ala Asn Asn Arg Pro Ser
1 5

<210> 57
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Light Chain Variable Domain CDRL3

<400> 57

Asn Ser Ala Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> 58
<211> 121
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(121)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Heavy Chain Variable Domain

<400> 58

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Glu Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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Ser Gly Ile Asn Trp Gln Gly Gly Ser Thr Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Val Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ile Leu Gly Ala Gly Arg Gly Trp Tyr Phe Asp Tyr Trp Gly
100 105 110

Lys Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 59
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Heavy Chain Variable Domain CDRH1

<400> 59

Gly Phe Thr Phe Asp Asp Tyr Ala Met Ser
1 5 10

<210> 60
<211> 16
<212> PRT
<213> Homo sapiens

<220>

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<221> MISC_FEATURE
<222> (1)..(16)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Heavy Chain Variable Domain CDRH2

<400> 60

Ile Asn Trp Gln Gly Gly Ser Thr Gly Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 61
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(12)
<223> Human Anti-Human DR5 Antibody (Drozitumab; "DR5 mAb 3") Heavy Chain Variable Domain CDRH2

<400> 61

Ile Leu Gly Ala Gly Arg Gly Trp Tyr Phe Asp Tyr
1 5 10

<210> 62
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> Human Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Light Chain Variable Domain

<400> 62

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Ile Ser Arg Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ser Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Gly Ser Ser Pro
                85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  63
<211>  12
<212>  PRT
<213>  Homo sapiens

<220>
<221>  MISC_FEATURE
<222>  (1)..(12)
<223>   Human Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4")
Light
       Chain Variable Domain CDRL1

<400>  63

Arg Ala Ser Gln Gly Ile Ser Arg Ser Tyr Leu Ala
1               5                   10


<210>  64
<211>  7
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<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Huamn Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Light
Chain Variable Domain CDRL2

<400> 64

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 65
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Human Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Light
Chain Variable Domain CDRL3

<400> 65

Gln Gln Phe Gly Ser Ser Pro Trp Thr
1 5

<210> 66
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(122)
<223> Huamn Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Heavy
Chain Variable Domain

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<400> 66

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30

Asp Tyr Phe Trp Ser Trp Ile Arg Gln Leu Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly His Ile His Asn Ser Gly Thr Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Lys Gln Phe
65                  70                  75                  80

Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Asp Arg Gly Gly Asp Tyr Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 67
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(12)
<223> Huamn Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Heavy

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Chain Variable Domain CDRH1

<400> 67

Gly Gly Ser Ile Ser Ser Gly Asp Tyr Phe Trp Ser
1 5 10

<210> 68
<211> 16
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(16)
<223> Human Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Heavy
Chain Variable Domain CDRH2

<400> 68

His Ile His Asn Ser Gly Thr Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 69
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(12)
<223> Human Anti-Human DR5 Antibody (Conatumumab; "DR5 mAb 4") Heavy
Chain Variable Domain CDRH3

<400> 69

Asp Arg Gly Gly Asp Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 70

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<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Light Chain Variable Domain

<400> 70

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Arg Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 71
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")

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Light Chain Variable Domain CDRL1

<400> 71

Lys Ala Ser Gln Asp Val Gly Thr Ala Val Ala
1 5 10

<210> 72
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Light Chain Variable Domain CDRL2

<400> 72

Trp Ala Ser Thr Arg His Thr
1 5

<210> 73
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Light Chain Variable Domain CDRL3

<400> 73

Gln Gln Tyr Ser Ser Tyr Arg Thr
1 5

<210> 74
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")

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Heavy Chain Variable Domain

<400> 74

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Val Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gly Asp Ser Met Ile Thr Thr Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
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<210> 75
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Heavy Chain Variable Domain CDRH1

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<400> 75

Gly Phe Thr Phe Ser Ser Tyr Val Met Ser
1 5 10

<210> 76
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Heavy Chain Variable Domain CDRH2

<400> 76

Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val Lys
1 5 10 15

Gly

<210> 77
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human DR5 Antibody (Tigatumumab; "DR5 mAb 5")
Heavy Chain Variable Domain CDRH3

<400> 77

Arg Gly Asp Ser Met Ile Thr Thr Asp Tyr
1 5 10

<210> 78
<211> 109
<212> PRT
<213> Mus musculus

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<220>
<221> MISC_FEATURE
<222> (1)..(109)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Light Chain Variable Domain

<400> 78

Asp Ile Ala Met Thr Gln Ser His Lys Phe Met Ser Thr Leu Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Ile Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Tyr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Met Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala
100 105

<210> 79
<211> 8
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(8)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Light

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Chain Variable Domain CDRL1

<400> 79

Gln Asp Val Asn Thr Ala Ile Ala
1 5

<210> 80
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Light Chain Variable Domain CDRL2

<400> 80

Trp Ala Ser Thr Arg His Thr
1 5

<210> 81
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Light Chain Variable Domain CDRL3

<400> 81

Gln Gln Trp Ser Ser Asn Pro Leu Thr
1 5

<210> 82
<211> 118
<212> PRT

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<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Heavy Chain Variable Domain

<400> 82

Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Thr Ile His Trp Val Lys Gln Arg Ser Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Phe Tyr Pro Gly Gly Gly Tyr Ile Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Glu Gly Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg His Glu Glu Gly Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 83
<211> 10
<212> PRT

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<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Heavy Chain Variable Domain CDRH1

<400> 83

Gly Tyr Thr Phe Thr Asp Tyr Thr Ile His
1 5 10

<210> 84
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Heavy Chain Variable Domain CDRH2

<400> 84

Trp Phe Tyr Pro Gly Gly Gly Tyr Ile Lys Tyr Asn Glu Lys Phe Lys
1 5 10 15

Asp

<210> 85
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human DR5 Antibody (LBY135-1; "DR5 mAb 6") Heavy Chain Variable Domain CDRH3

<400> 85

His Glu Glu Gly Ile Tyr Phe Asp Tyr
1 5

<210> 86
<211> 104
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(104)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Light Chain Variable Domain

<400> 86

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Ile Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu

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<210> 87
<211> 11
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Light Chain Variable Domain CDRL1

<400> 87

Lys Ala Ser Gln Asp Val Asn Thr Ala Ile Ala
1 5 10

<210> 88
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Light Chain Variable Domain CDRL2

<400> 88

Trp Ala Ser Thr Arg His Thr
1 5

<210> 89
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)

<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Light Chain Variable Domain CDRL3

<400> 89

Gln Gln His Tyr Thr Thr Pro Phe Thr
1 5

<210> 90
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Heavy Chain Variable Domain

<400> 90

Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Thr Ile His Trp Val Lys Gln Arg Ser Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Phe Tyr Pro Gly Gly Gly Tyr Ile Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Ser Asn Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

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Ala Arg His Glu Glu Gly Ile Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 91
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Heavy Chain Variable Domain CDRH1

<400> 91

Gly Tyr Thr Phe Thr Asp Tyr Thr Ile His
1 5 10

<210> 92
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Heavy Chain Variable Domain CDRH2

<400> 92

Trp Phe Tyr Pro Gly Gly Gly Tyr Ile Lys Tyr Asn Glu Lys Phe Lys
1 5 10 15

Asp

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<210> 93
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human DR5 Antibody (LBY135-2; "DR5 mAb 7") Heavy Chain Variable Domain CDRH3

<400> 93

His Glu Glu Gly Ile Tyr Phe Asp Tyr
1 5

<210> 94
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Light Chain Variable Domain

<400> 94

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

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Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 95
<211> 11
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Light Chain
Variable Domain CDRL1

<400> 95

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala
1 5 10

<210> 96
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Light Chain
Variable Domain CDRL2

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<400> 96

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 97
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Light Chain
Variable Domain CDRL3

<400> 97

Gln Gln Arg Ser Asn Trp Pro Leu Thr
1 5

<210> 98
<211> 126
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(126)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Heavy Chain
Variable Domain

<400> 98

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Met Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

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```
Lys Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Met Asn Pro Asp Thr Asp Ser Thr Gly Tyr Pro Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Tyr Gly Ser Gly Ser Tyr Tyr Arg Asp Tyr Tyr Tyr Gly
            100                 105                 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  99
<211>  10
<212>  PRT
<213>  Mus musculus

<220>
<221>  MISC_FEATURE
<222>  (1)..(10)
<223>  Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Heavy
Chain
       Variable Domain CDRH1

<400>  99

Gly Tyr Thr Phe Thr Asn Tyr Lys Ile Asn
1               5                   10


<210>  100
```

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<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Heavy Chain
Variable Domain CDRH2

<400> 100

Trp Met Asn Pro Asp Thr Asp Ser Thr Gly Tyr Pro Gln Lys Phe Gln
1 5 10 15

Gly

<210> 101
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human DR5 Antibody (KMTR2; "DR5 mAb 8") Heavy Chain
Variable Domain CDRH3

<400> 101

Ser Tyr Gly Ser Gly Ser Tyr Tyr Arg Asp Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 102
<211> 112

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<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(112)
<223> Murine Anti-Human CD2 Antibody (Lo-CD2A mAb) Light Chain Variable Domain

<400> 102

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Asp Val Val Leu Thr Gln Thr Pro Pro Thr Leu Leu Ala Thr Ile Gly
1               5                  10                  15

Gln Ser Val Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Ser Gly Asn Thr Tyr Leu Asn Trp Leu Leu Gln Arg Thr Gly Gln Ser
        35                  40                  45

Pro Gln Pro Leu Ile Tyr Leu Val Ser Lys Leu Glu Ser Gly Val Pro
    50                  55                  60

Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Met Gln Phe
                85                  90                  95

Thr His Tyr Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110
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<210> 103
<211> 118
<212> PRT
<213> Mus musculus

<220>

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<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human CD2 Antibody (Lo-CD2A mAb) Heavy Chain Variable Domain

<400> 103

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Gln Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Glu Tyr
20 25 30

Tyr Met Tyr Trp Val Lys Gln Arg Pro Lys Gln Gly Leu Glu Leu Val
35 40 45

Gly Arg Ile Asp Pro Glu Asp Gly Ser Ile Asp Tyr Val Glu Lys Phe
50 55 60

Lys Lys Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Gly Lys Phe Asn Tyr Arg Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 104
<211> 110
<212> PRT
<213> Artificial Sequence

<220>

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<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Light Chain Variable Domain

<400> 104

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 105
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Light Chain Variable Domain CDRL1

<400> 105

Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn

1 5 10

<210> 106
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Light Chain Variable Domain CDRL2

<400> 106

Gly Thr Asn Lys Arg Ala Pro
1 5

<210> 107
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Light Chain Variable Domain CDRL3

<400> 107

Ala Leu Trp Tyr Ser Asn Leu Trp Val
1 5

<210> 108
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Heavy Chain Variable Domain

<400> 108

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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```
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
            20                  25                  30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  109
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Heavy Chain
       Variable Domain CDRH1

<400>  109

Thr Tyr Ala Met Asn
1               5
```

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<210> 110
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Heavy Chain Variable Domain CDRH2

<400> 110

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Asp

<210> 111
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Heavy Chain Variable Domain CDRH3

<400> 111

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr
1 5 10

<210> 112
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanize Anti-Human CD3 Antibody ("CD3 mAb 2") Variant Heavy Chain Variable Domain Containing a D65G (Kabat Numbering; D68G
in Sequence Relative to SEQ ID NO:108)

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<400> 112

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 113
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH2 of Humanized Anti-Human CD3 Antibody ("CD3 mAb 2") Variant
Heavy Chain Variable Domain Containing a D65G (Kabat Numbering;

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D68G in Sequence Relative to SEQ ID NO:108)

<400> 113

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

<210> 114
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Murine Anti-Human CD3 Antibody (OKT3) Light Chain Variable Domain

<400> 114

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
65 70 75 80

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Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> 115
<211> 119
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(119)
<223> Murine Anti-Human CD3 Antibody (OKT3) Heavy Chain Variable Domain

<400> 115

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
20 25 30

Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 116
<211> 111
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(111)
<223> Murine Anti-Human CD16 Antibody (3G8) Light Chain Variable Domain

<400> 116

Asp Thr Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Phe Asp
20 25 30

Gly Asp Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Thr Thr Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

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Glu Asp Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 117
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human CD16 Antibody (3G8) Heavy Chain Variable Domain

<400> 117

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Arg Thr Ser
20 25 30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ala
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Ala Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Gln Ile Asn Pro Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

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Leu Val Thr Val Ser Ala
115

<210> 118
<211> 111
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(111)
<223> Murine Anti-Human CD16 Antibody (A9) Light Chain Variable Domain

<400> 118

Asp Ile Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser Pro
1 5 10 15

Gly Glu Thr Val Thr Leu Thr Cys Arg Ser Asn Thr Gly Thr Val Thr
20 25 30

Thr Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe
35 40 45

Thr Gly Leu Ile Gly His Thr Asn Asn Arg Ala Pro Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr
65 70 75 80

Gly Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp Tyr
85 90 95

Asn Asn His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

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<210> 119
<211> 117
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(117)
<223> Murine Anti-Human CD16 Antibody (A9) Heavy Chain Variable Domain

<400> 119

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Tyr Pro Gly Gly Gly Tyr Thr Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Val Thr Ala Asp Thr Ser Ser Arg Thr Ala Tyr
65 70 75 80

Val Gln Val Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Ala Ser Trp Tyr Phe Asp Val Trp Gly Ala Arg Thr Thr
100 105 110

Val Thr Val Ser Ser
115

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<210> 120
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> Murine Anti-Human CD19 Antibody (HD37) Light Chain Variable Domain

<400> 120

Asp Ile Leu Ile Thr Gln Ser Pro Lys Ser Met Ser Met Ser Val Gly
1 5 10 15

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Glu Asn Val Val Thr Tyr
20 25 30

Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Asp Tyr His Cys Gly Gln Gly Tyr Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 121
<211> 124
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(124)
<223> Murine Anti-Human CD19 Antibody (HD37) Heavy Chain Variable Domain

<400> 121

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1               5                  10                  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

<210> 122
<211> 107
<212> PRT
<213> Artificial Sequence

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<220>
<223> Chimeric Anti-Human CD20 Antibody (Rituximab) Light Chain Variable Domain

<400> 122

Gln Ile Val Leu Ser Gln Ser Pro Ala Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

Ala Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 123
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric Anti-Human CD20 Antibody (Rituximab) Heavy Chain Variable Domain

<400> 123

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```
Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Asn Met His Trp Val Lys Gln Thr Pro Gly Arg Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
            100                 105                 110

Ala Gly Thr Thr Val Thr Val Ser Ala
        115                 120
```

<210> 124
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD22 Antibody (Epratuzumab) Light Chain Variable Domain

<400> 124

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

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```
1               5                   10                  15

Asp Arg Val Thr Met Ser Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
            20                  25                  30

Ala Asn His Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
        35                  40                  45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys His Gln
                85                  90                  95

Tyr Leu Ser Ser Trp Thr Phe Gly Gly Gly Thr Lys Val Gln Ile Lys
            100                 105                 110

Arg
```

<210> 125
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD22 Antibody (Epratuzumab) Heavy Chain Variable Domain

<400> 125

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15
```

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asn Pro Arg Asn Asp Tyr Thr Glu Tyr Asn Gln Asn Phe
    50                  55                  60

Lys Asp Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Phe Cys
                85                  90                  95

Ala Arg Arg Asp Ile Thr Thr Phe Tyr Trp Gly Gln Gly Thr Thr Val
            100                 105                 110

Thr Val Ser Ser
        115
```

<210> 126
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> HumanizedAnti-Human CD32B Antibody ("CD32B mAb 1") Light Chain
Variable Domain

<400> 126

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Leu Ala Ala Leu Gly
1               5                   10                  15
```

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Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Glu Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Phe Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 127
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD32B Antibody ("CD32B mAb 1") Heavy Chain
Variable Domain

<400> 127

Glu Val Lys Leu Glu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Met Lys Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

Trp Met Asp Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val

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35 40 45

Ala Glu Ile Arg Asn Lys Ala Lys Asn His Ala Thr Tyr Tyr Ala Glu
50 55 60

Ser Val Ile Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65 70 75 80

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Gly Ile Tyr
85 90 95

Tyr Cys Gly Ala Leu Gly Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 128
<211> 109
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(109)
<223> Murine Anti-Human CD64 Antibody ("CD64 mAb 1") Light Chain Variable Domain

<400> 128

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

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35 40 45

Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Gly Gly
50 55 60

Ser Gly Ser Gly Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Leu Arg Ser Asn Trp Pro
85 90 95

Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 129
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human CD64 Antibody ("CD64 mAb 1") Heavy Chain Variable Domain

<400> 129

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Gly Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val

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50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Gly Asp Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 130
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD79 Antibody ("CD794 mAb 1") Light Chain
Variable Domain

<400> 130

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Asn Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Thr
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gln Gly Ser
35 40 45

Pro Asn Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 131
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CD79 Antibody ("CD794 mAb 1") Heavy Chain
Variable Domain

<400> 131

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Met Val Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Met Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Met Gly Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser
100 105 110

Ser

<210> 132
<211> 106
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(106)
<223> Murine Anti-Human TCR Antibody (BMA 031) Light Chain Variable Domain

<400> 132

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ser Ala Thr Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 133
<211> 120
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(120)
<223> Murine Anti-Human TCR Antibody (BMA 031) Heavy Chain Variable Domain

<400> 133

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Val His Tyr Cys
85 90 95

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Ala Arg Gly Ser Tyr Tyr Asp Tyr Asp Gly Phe Val Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 134
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> Murine Anti-Human NKG2D Antibody (KYK-1.0) Light Chain Variable
Domain

<400> 134

Gln Pro Val Leu Thr Gln Pro Ser Ser Val Ser Val Ala Pro Gly Glu
1 5 10 15

Thr Ala Arg Ile Pro Cys Gly Gly Asp Asp Ile Glu Thr Lys Ser Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Asp Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Phe Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Ser Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Asp Asn Asn Asp Glu
85 90 95

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2015266797

Trp Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu
100 105

<210> 135
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human NKG2D Antibody (KYK-1.0) Heavy Chain Variable
Domain

<400> 135

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Lys Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Phe Gly Tyr Tyr Leu Asp Tyr Trp Gly Gln Gly Thr

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100 105 110

Leu Val Thr Val Ser Ser
115

<210> 136
<211> 110
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(110)
<223> Murine Anti-Human NKG2D Antibody (KYK-2.0) Light Chain Variable
Domain

<400> 136

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

Ala Val Asn Trp Tyr Gln Gln Leu Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Asp Leu Leu Pro Ser Gly Val Ser Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Phe Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

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Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 137
<211> 121
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(121)
<223> Murine Anti-Human NKG2D Antibody (KYK-2.0) Heavy Chain Variable
Domain

<400> 137

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Arg Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Gly Leu Gly Asp Gly Thr Tyr Phe Asp Tyr Trp Gly
100 105 110

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Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 138
<211> 112
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(112)
<223> Murine Anti-Fluorescein Antibody 4-4-20 Light Chain Variable Domain

<400> 138

Asp Val Val Met Thr Gln Thr Pro Phe Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Arg Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

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<210> 139
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Fluorescein Antibody 4-4-20 Heavy Chain Variable Domain

<400> 139

```
Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                  10                  15

Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
                85                  90                  95

Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser
        115
```

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<210> 140
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "DR5 mAb 1 x CD3 mAb 2 Diabody"

<400> 140

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly
115 120 125

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
130 135 140

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Gly Phe Thr Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro
145 150 155 160

Gly Lys Gly Leu Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn
165 170 175

Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
180 185 190

Arg Asp Asp Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys
195 200 205

Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly
210 215 220

Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
225 230 235 240

Thr Val Ser Ser Ala Ser Thr Lys Gly Glu Val Ala Ala Cys Glu Lys
245 250 255

Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val
260 265 270

Ala Ala Leu Glu Lys
275

<210> 141
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "DR5 mAb 1 x

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CD3 mAb 2 Diabody"

<400> 141
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc
60

atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac
120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct
180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat
240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg
300

acgttcggtg gaggcaccaa gctggaaatc aaaggaggcg gatccggcgg cggaggcgag
360

gtgcagctgg tggagtctgg gggaggcttg gtccagcctg gagggtccct gagactctcc
420

tgtgcagcct ctggattcac cttcagcaca tacgctatga attgggtccg ccaggctcca
480

gggaaggggc tggagtgggt tggaaggatc aggtccaagt acaacaatta tgcaacctac
540

tatgccgact ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg
600

tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg tgtgagacac
660

ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt ggggacaggg gacactggtg
720

actgtgtctt ccgcctccac caagggcgaa gtggccgcat gtgagaaaga ggttgctgct
780

ttggagaagg aggtcgctgc acttgaaaag gaggtcgcag ccctggagaa a
831

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<210> 142
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "DR5 mAb 1 x CD3 mAb 2 Diabody"

<400> 142

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                  10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Glu Val Lys Phe Leu Glu Ser Gly Gly Gly
        115                 120                 125

Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Val Ala Ser Gly
    130                 135                 140
```

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```
Phe Asp Phe Ser Arg Tyr Trp Met Ser Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile
                165                 170                 175

Asn Tyr Thr Pro Ser Leu Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn
            180                 185                 190

Ala Lys Asn Thr Leu Tyr Leu Gln Met Thr Lys Val Arg Ser Glu Asp
        195                 200                 205

Thr Ala Leu Tyr Tyr Cys Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala
225                 230                 235                 240

Ser Thr Lys Gly Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala Leu
                245                 250                 255

Lys Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 143
<211> 816
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "DR5 mAb 1 x
CD3 mAb 2 Diabody"

<400> 143

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caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg
60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag
120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc
180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca
240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
300

gggggtggca caaaactgac tgtgctggga ggtggtggat ccggcggcgg aggcgaggtg
360

aagtttctcg agtctggagg tggcctggtg cagcctggag gatccctgaa actctcctgt
420

gtagcctcag gattcgattt tagtagatac tggatgagtt gggtccggca ggctccaggg
480

aaagggctag aatggattgg agaaattaat ccagatagca atacgataaa ctatacgcca
540

tctctaaagg ataaattcat catctccaga gacaacgcca aaaatacgct gtatctgcaa
600

atgaccaaag tgagatctga ggacacagcc ctttattatt gtacaagaag ggcctactat
660

ggtaacccgg cctggtttgc ttactggggc caagggactc tggtcactgt ctctgcagcc
720

tccaccaagg gcaaagtggc cgcatgtaag gagaaagttg ctgctttgaa agagaaggtc
780

gccgcactta aggaaaaggt cgcagccctg aaagag
816

<210> 144
<211> 273

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<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "DR5 mAb 2 x CD3 mAb 2 Diabody"

<400> 144

```
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1               5                  10                  15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Lys Ser Val Gln Ala
65                  70                  75                  80

Glu Asp Leu Thr Leu Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
        115                 120                 125

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
    130                 135                 140

Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
```

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```
145                 150                 155                 160

Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr
                165                 170                 175

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
            180                 185                 190

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr
        195                 200                 205

Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val
    210                 215                 220

Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240

Ala Ser Thr Lys Gly Glu Val Ala Ala Cys Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys
```

<210> 145
<211> 819
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "DR5 mAb 2 x
CD3 mAb 2 Diabody"

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<400> 145
gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga cagggtcagc
60

atcacctgca aggccagtca ggatgtgaat actgctgtag cctggtatca acaaaaacca
120

gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat
180

cgcttcacag gcagtggatc tgggacagat tatacactca ccatcaaaag tgtgcaggct
240

gaagacctga cactttatta ctgtcagcaa cactatatca ctccgtggac gttcggtgga
300

ggcaccaagc tggaaatcaa aggaggcgga tccggcggcg gaggcgaggt gcagctggtg
360

gagtctgggg gaggcttggt ccagcctgga gggtccctga gactctcctg tgcagcctct
420

ggattcacct tcagcacata cgctatgaat tgggtccgcc aggctccagg gaaggggctg
480

gagtgggttg gaaggatcag gtccaagtac aacaattatg caacctacta tgccgactct
540

gtgaagggta gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg
600

aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg taacttcggc
660

aattcttacg tgtcttggtt tgcttattgg ggacagggga cactggtgac tgtgtcttcc
720

gcctccacca agggcgaagt ggccgcatgt gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaa
819

<210> 146

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<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "DR5 mAb 2 x CD3 mAb 2 Diabody"

<400> 146

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                  10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Lys Val Gln Leu Gln Gln Ser Gly Ala Glu
        115                 120                 125

Leu Val Lys Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly
    130                 135                 140
```

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```
Tyr Thr Phe Thr Glu Tyr Ile Leu His Trp Val Lys Gln Lys Ser Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Trp Phe Tyr Pro Gly Asn Asn Asn Ile
                165                 170                 175

Lys Tyr Asn Glu Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys
            180                 185                 190

Ser Ser Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp
        195                 200                 205

Ser Ala Val Tyr Phe Cys Ala Arg His Glu Gln Gly Pro Gly Tyr Phe
    210                 215                 220

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
225                 230                 235                 240

Lys Gly Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala Leu Lys Glu
                245                 250                 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 147
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "DR5 mAb 2 x
CD3 mAb 2 Diabody"

<400> 147
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

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acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag
120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc
180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca
240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggcgg aggcaaggtc
360

cagctgcagc agtctggagc tgaactggtg aaacccgggg catcagtgaa gctgtcctgc
420

aaggcttctg ggtacacctt cactgagtat attttacact gggtaaagca gaagtctgga
480

cagggtcttg agtggattgg gtggttttat cctggaaata ataatataaa gtacaatgag
540

aaattcaagg acaaggccac actgactgcg gacaaatcct ccagcacagt ctatatggaa
600

cttagtagat tgacatctga agactctgcg gtctatttct gtgcaagaca cgaacaagga
660

ccaggttact ttgactactg gggccaaggc accactctca cagtctcctc cgcctccacc
720

aagggcaaag tggccgcatg taaggagaaa gttgctgctt tgaaagagaa ggtcgccgca
780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g
810

<210> 148
<211> 274
<212> PRT
<213> Artificial Sequence

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2015266797

<220>
<223> First Polypeptide Chain of "DR5 mAb 3 x CD3 mAb 2 Diabody"

<400> 148

Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr
1 5 10 15

Val Arg Ile Thr Cys Ser Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
20 25 30

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly
35 40 45

Ala Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
50 55 60

Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp
65 70 75 80

Glu Ala Asp Tyr Tyr Cys Asn Ser Ala Asp Ser Ser Gly Asn His Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
115 120 125

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
130 135 140

Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
145 150 155 160

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```
Leu Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr
                165                 170                 175

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp
            180                 185                 190

Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr
    210                 215                 220

Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
225                 230                 235                 240

Ser Ala Ser Thr Lys Gly Glu Val Ala Ala Cys Glu Lys Glu Val Ala
                245                 250                 255

Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu
            260                 265                 270

Glu Lys
```

<210> 149
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "DR5 mAb 3 x CD3 mAb 2 Diabody"

<400> 149

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15
```

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```
Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Gln Ser Gly Gly Gly
        115                 120                 125

Val Glu Arg Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
    130                 135                 140

Phe Thr Phe Asp Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Lys Gly Leu Glu Trp Val Ser Gly Ile Asn Trp Gln Gly Gly Ser Thr
                165                 170                 175

Gly Tyr Ala Asp Ser Val Lys Gly Arg Val Thr Ile Ser Arg Asp Asn
            180                 185                 190
```

```
Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Lys Ile Leu Gly Ala Gly Arg Gly Trp
    210                 215                 220

Tyr Phe Asp Tyr Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser Ala
225                 230                 235                 240

Ser Thr Lys Gly Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala Leu
                245                 250                 255

Lys Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 150
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "DR5 mAb 4 x CD3 mAb 2 Diabody"

<400> 150

```
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Ile Ser Arg Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ser Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
```

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```
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Gly Ser Ser Pro
                85                  90                  95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
        115                 120                 125

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
    130                 135                 140

Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
145                 150                 155                 160

Leu Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr
                165                 170                 175

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp
            180                 185                 190

Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr
    210                 215                 220

Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
225                 230                 235                 240
```

Ser Ala Ser Thr Lys Gly Glu Val Ala Ala Cys Glu Lys Glu Val Ala
245 250 255

Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu
260 265 270

Glu Lys

<210> 151
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "DR5 mAb 4 x CD3 mAb 2 Diabody"

<400> 151

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

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```
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Gln Glu Ser Gly Pro Gly
        115                 120                 125

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly
    130                 135                 140

Gly Ser Ile Ser Ser Gly Asp Tyr Phe Trp Ser Trp Ile Arg Gln Leu
145                 150                 155                 160

Pro Gly Lys Gly Leu Glu Trp Ile Gly His Ile His Asn Ser Gly Thr
                165                 170                 175

Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp
            180                 185                 190

Thr Ser Lys Lys Gln Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala
        195                 200                 205

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Gly Gly Asp Tyr Tyr
    210                 215                 220

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
225                 230                 235                 240

Ala Ser Thr Lys Gly Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala
                245                 250                 255

Leu Lys Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
            260                 265                 270
```

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Glu

<210> 152
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 152

Ala Pro Ser Ser Ser
1 5

<210> 153
<211> 106
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(106)
<223> Murine Anti-Human EphA2 Antibody EphA2 mAb 1") Light Chain Variable Domain

<400> 153

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Ile Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly

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50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Tyr Thr Leu Tyr Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 154
<211> 11
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Light Chain Variable Domain CDRL1

<400> 154

Arg Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 155
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Light Chain Variable Domain CDRL2

<400> 155

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Tyr Thr Ser Arg Leu His Ser
1 5

<210> 156
<211> 8
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(8)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Light Chain Variable Domain CDRL3

<400> 156

Gln Gln Gly Tyr Thr Leu Tyr Thr
1 5

<210> 157
<211> 318
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(318)
<223> Polynucleotide Encoding Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Light Chain Variable Domain CDRL1

<400> 157
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagaatcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
300

a c c a a g c t g g a a a t a a a a
318

<210> 158
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Heavy Chain Variable Domain

<400> 158

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Arg Tyr
20 25 30

Ser Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Met Ile Trp Gly Gly Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

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Arg Lys His Gly Asn Tyr Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Ser Val Thr Val Ser Ser
115

<210> 159
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Heavy Chain Variable Domain CDRH1

<400> 159

Gly Phe Ser Leu Ser Arg Tyr Ser Val His
1 5 10

<210> 160
<211> 16
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(16)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Heavy Chain Variable Domain CDRH2

<400> 160

Met Ile Trp Gly Gly Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys Ser
1 5 10 15

<210> 161
<211> 10
<212> PRT

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<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Heavy Chain Variable Domain CDRH3

<400> 161

Lys His Gly Asn Tyr Tyr Thr Met Asp Tyr
1 5 10

<210> 162
<211> 354
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(354)
<223> Polynucleotide Encoding Murine Anti-Human EphA2 Antibody ("EphA2 mAb 1") Heavy Chain Variable Domain

<400> 162
caggtgcagc tgaaggagtc aggacctggc ctggtggcac cctcacagag cctgtccatc 60

acatgcactg tctctgggtt ctcattatcc agatatagtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggaatg atatggggtg gtggaagcac agactataat 180

tcagctctca aatccagact gagtatcagc aaggacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag aaaacatggt 300

aactactata ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcc 354

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<210> 163
<211> 111
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(111)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Light Chain Variable Domain

<400> 163

```
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                  10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 164
<211> 16
<212> PRT

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2015266797

<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(16)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Light Chain Variable Domain CDRL1

<400> 164

Arg Ser Ser Gln Ser Leu Val His Ser Ser Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 165
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Light Chain Variable Domain CDRL2

<400> 165

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 166
<211> 8
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(8)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Light Chain Variable Domain CDRL3

<400> 166

Ser Gln Ser Thr His Val Pro Thr

1 5

<210> 167
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Heavy Chain Variable Domain

<400> 167

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Met Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Glu Leu Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser

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<210> 168
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Heavy Chain Variable Domain CDRH1

<400> 168

Gly Phe Thr Phe Thr Asn Tyr Gly Met Asn
1 5 10

<210> 169
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Heavy Chain Variable Domain CDRH2

<400> 169

Trp Ile Asn Thr Tyr Ile Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 170
<211> 9
<212> PRT
<213> Mus musculus

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<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Heavy Chain Variable Domain CDRH3

<400> 170

Glu Leu Gly Pro Tyr Tyr Phe Asp Tyr
1 5

<210> 171
<211> 354
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(354)
<223> Polynucleotide Encoding Murine Anti-Human EphA2 Antibody ("EphA2 mAb 2") Heavy Chain Variable Domain

<400> 171
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggtt taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacct atattggaga gccgacatat 180

gctgatgact tcaagggacg gtttgtcttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac atggccacat atttctgtgc aagagaactg 300

ggaccatact actttgacta ctggggccaa ggcaccactc tcacagtctc ctcc 354

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<210> 172
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Light Chain Variable Domain

<400> 172

Asp Ile Val Leu Thr Gln Ser His Arg Ser Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Asn Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Phe Trp Ala Ser Thr Arg His Ala Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Gly Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 173
<211> 11
<212> PRT
<213> Mus musculus

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<220>
<221> MISC_FEATURE
<222> (1)..(11)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Light Chain Variable Domain CDRL1

<400> 173

Lys Ala Ser Gln Asp Val Thr Thr Ala Val Ala
1 5 10

<210> 174
<211> 7
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(7)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Light Chain Variable Domain CDRL2

<400> 174

Trp Ala Ser Thr Arg His Ala
1 5

<210> 175
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Light Chain Variable Domain CDRL3

<400> 175

Gln Gln His Tyr Ser Thr Pro Tyr Thr
1 5

<210> 176
<211> 321
<212> DNA
<213> Mus musculus

<220>
<221> misc_feature
<222> (1)..(321)
<223> Polynucleotide Encoding Murine Anti-Human EphA2 Antibody ("EphA2
mAb 3") Light Chain Variable Domain

<400> 176
gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga cagggtcaac
60

atcacctgca aggccagtca ggatgtgact actgctgtag cctggtatca acaaaaacca
120

gggcaatctc ctaaattact gattttctgg gcatccaccc ggcacgctgg agtccctgat
180

cgcttcacag gcagtggatc tgggacagat tttactctca ccatcagcag tgtgcaggct
240

ggagacctgg cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg
300

g g g a c c a a g c t g g a a a t a a a a
321

<210> 177
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Heavy Chain
Variable Domain

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<400> 177

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Lys Pro Gly Gly
1               5                  10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp His
            20                  25                  30

Tyr Met Tyr Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Asp Gly Gly Ser Phe Thr Ser Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ala Lys Asn Asn Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Thr Arg Asp Glu Ser Asp Arg Pro Phe Pro Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> 178
<211> 10
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(10)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Heavy Chain Variable Domain CDRH1

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<400> 178

Gly Phe Thr Phe Thr Asp His Tyr Met Tyr
1 5 10

<210> 179
<211> 17
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(17)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Heavy Chain Variable Domain CDRH2

<400> 179

Thr Ile Ser Asp Gly Gly Ser Phe Thr Ser Tyr Pro Asp Ser Val Lys
1 5 10 15

Gly

<210> 180
<211> 9
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(9)
<223> Murine Anti-Human EphA2 Antibody ("EphA2 mAb 3") Heavy Chain Variable Domain CDRH3

<400> 180

Asp Glu Ser Asp Arg Pro Phe Pro Tyr
1 5

<210> 181

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<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Light Chain
Variable Domain

<400> 181

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 182
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

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<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Light Chain
Variable Domain CDRL1

<400> 182

Ser Ala Arg Ser Ser Ile Ser Phe Met Tyr
1 5 10

<210> 183
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> HumanizedAnti-Human gpA33 Antibody ("gpA33 mAb 1") Light Chain
Variable Domain CDRL2

<400> 183

Asp Thr Ser Asn Leu Ala Ser
1 5

<210> 184
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Light Chain
Variable Domain CDRL3

<400> 184

Gln Gln Trp Ser Ser Tyr Pro Leu Thr
1 5

<210> 185
<211> 318
<212> DNA

12 Dec 2018
2015266797

<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Light Chain Variable Domain

<400> 185
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

a c t a a a c t g g a a a t c a a g 318

<210> 186
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Heavy Chain
Variable Domain

<400> 186

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Ser
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr Asn Tyr Asn Gly Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
115

<210> 187
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Heavy Chain
Variable Domain CDRH1

<400> 187

Gly Tyr Thr Phe Thr Gly Ser Trp Met Asn
1 5 10

<210> 188
<211> 17
<212> PRT
<213> Artificial Sequence

12 Dec 2018
2015266797

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Heavy Chain
Variable Domain CDRH2

<400> 188

Arg Ile Tyr Pro Gly Asp Gly Glu Thr Asn Tyr Asn Gly Lys Phe Lys
1 5 10 15

Asp

<210> 189
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Heavy Chain
Variable Domain CDRH3

<400> 189

Ile Tyr Gly Asn Asn Val Tyr Phe Asp Val
1 5 10

<210> 190
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucelotide Encoding Humanized Anti-Human gpA33 Antibody ("gpA33 mAb 1") Heavy Chain Variable Domain

<400> 190
caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag cgtgaaggtc
60

tcctgcaaag catcaggcta tacatttaca ggcagctgga tgaactgggt gaggcaggct
120

ccaggacagg gactggagtg gatcgggcgc atctaccctg gagacggcga aactaactat
180

aatggaaagt tcaaagaccg agtgaccatc acagccgata agtctactag taccgcctac
240

atggagctga gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac
300

ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt ctcctcc
357

<210> 191
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric Anti-Human Her2 Antibody ("Her2 mAb 1") Light Chain Variable Domain

<400> 191

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> 192
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric Anti-Human Her2 Antibody ("Her2 mAb 1") Heavy Chain Variable Domain

<400> 192

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Asp Pro Lys Phe
50 55 60

Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Val Ser Arg Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Ala Ser Val Thr Val Ser Ser
115 120

<210> 193
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human Her2 Antibody (Trastuzumab) Light Chain Variable Domain

<400> 193

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

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<210> 194
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human Her2 Antibody (Trastuzumab) Heavy Chain Variable Domain

<400> 194

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

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<210> 195
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 1") Light Chain Variable Domain

<400> 195

```
Asp Ile Ala Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Asp Thr Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Phe
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 196
<211> 122
<212> PRT
<213> Mus musculus

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<220>
<221> MISC_FEATURE
<222> (1)..(122)
<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 1") Heavy Chain Variable Domain

<400> 196

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Tyr Ile Ser Ser Asp Ser Ser Ala Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Phe
65                  70                  75                  80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Gly Arg Gly Arg Glu Asn Ile Tyr Tyr Gly Ser Arg Leu Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
        115                 120
```

<210> 197
<211> 107
<212> PRT
<213> Mus musculus

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<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 2") Light Chain Variable Domain

<400> 197

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Asp Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Pro
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 198
<211> 120
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(120)

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<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 2") Heavy Chain Variable Domain

<400> 198

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                   10                  15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Thr Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Gly Ile Pro Arg Leu Trp Tyr Phe Asp Val Trp Gly Ala
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 199
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(108)

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<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 3") Light Chain Variable Domain

<400> 199

```
Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Val Ser Val Gly
1               5                  10                  15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Ile Tyr Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
        35                  40                  45

Tyr Asn Thr Lys Thr Leu Pro Glu Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Gln Phe Ser Leu Lys Ile Asn Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Gly Arg Tyr Tyr Cys Gln His His Tyr Gly Thr Pro Pro
                85                  90                  95

Trp Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys
            100                 105
```

<210> 200
<211> 117
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(117)
<223> Murine Anti-Human B7-H3 Antibody ("B7-H3 mAb 3") Heavy Chain Variable Domain

<400> 200

```
Glu Val Gln Gln Val Glu Ser Gly Gly Asp Leu Val Lys Pro Gly Gly
1               5                  10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Asn Ser Gly Gly Ser Asn Thr Tyr Tyr Pro Asp Ser Leu
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Arg Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Asp Gly Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 201
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric Anti-Human EGFR Antibody (Cetuximab) Light Chain Variable Domain

<400> 201

```
Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
```

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1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
100 105

<210> 202
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Chimeric Anti-Human EGFR Antibody (Cetuximab) Heavy Chain Variable Domain

<400> 202

Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 203
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human VEGF Antibody (Bevacizumab) Light Chain Variable Domain

<400> 203

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile

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35 40 45

Tyr Phe Thr Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Val Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 204
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human VEGF Antibody (Bevacizumab) Heavy Chain Variable Domain

<400> 204

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe
50 55 60

Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 205
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-CD52 Antibody (Alemtuzumab) Light Chain Variable
Domain

<400> 205

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Ile Asp Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asn Thr Asn Asn Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln His Ile Ser Arg Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 206
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-CD52 Antibody (Alemtuzumab) Heavy Chain Variable
Domain

<400> 206

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Thr Asp Phe
20 25 30

Tyr Met Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Phe Ile Arg Asp Lys Ala Lys Gly Tyr Thr Thr Glu Tyr Asn Pro
50 55 60

Ser Val Lys Gly Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln
65 70 75 80

Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr

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85 90 95

Tyr Cys Ala Arg Glu Gly His Thr Ala Ala Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Ser Leu Val Thr Val Ser Ser
115 120

<210> 207
<211> 98
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(98)
<223> Human IgG1 CH1 Domain

<400> 207

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

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Lys Val

<210> 208
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> Variant Human IgG1 CH1 Domain

<400> 208

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
```

Arg Val

<210> 209

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<211> 15
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(15)
<223> Human IgG1 Hinge Domain

<400> 209

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
1 5 10 15

<210> 210
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Human IgG1 CL Kappa Domain

<400> 210

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

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Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 211
<211> 104
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (1)..(104)
<223> human IgG2 CL Lambda2 Domain

<400> 211

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
1 5 10 15

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
20 25 30

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
35 40 45

Lys Ala Gly Val Glu Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
50 55 60

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
65 70 75 80

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
85 90 95

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Thr Val Ala Pro Thr Glu Cys Ser
100

<210> 212
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 212

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
100 105 110

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```
Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
```

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```
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
                405                 410                 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            420                 425                 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        435                 440                 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    450                 455                 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465                 470                 475                 480
```

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 213
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 213
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca gctggtggag 360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga 420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag 480

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tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 214
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 214

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

```
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175

Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
            180                 185                 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
    210                 215                 220

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Cys
225                 230                 235                 240

Gly Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
                245                 250                 255

Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

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<210> 215
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 215
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc 360

cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc 420

aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga 480

cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga 540

aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag 600

ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac 660

aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt 720

ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc
780

gcacttaagg aaaaggtcgc agccctgaaa gag
813

<210> 216
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 216

Glu Val Lys Phe Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr Trp Gly

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```
                100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285
```

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```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        435                 440                 445

Pro Gly Lys
    450
```

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<210> 217
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 217
gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc 60

tcctgtgtag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

ccagggaaag ggctagaatg gattggagaa attaatccag atagcaatac gataaactat 180

acgccatctc taaaggataa attcatcatc tccagagaca acgccaaaaa tacgctgtat 240

ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc 300

tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt cactgtctct 360

tccgcctcca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct 420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc 540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag 600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag 660

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cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg 720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 780

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac 900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc 960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc 1020

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1080

gagatgacca agaaccaggt cagcctgagt tgcgcagtca aaggcttcta tcccagcgac 1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1200

gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga caagagcagg 1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac 1320

acgcagaaga gcctctccct gtctccgggt aaa 1353

<210> 218
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 1"

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Tri-Specific Binding Molecule

<400> 218

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1               5                  10                  15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
            20                  25                  30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95

Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
```

165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 219
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 219
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc 60

atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct 180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg 300

acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

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aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 220
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2"
Tri-Specific Binding Molecule

<400> 220

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

```
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255
```

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```
Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
                405                 410                 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            420                 425                 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
```

435 440 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 221
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x DR5 mAb 2" Tri-Specific Binding Molecule

<400> 221
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

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actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca gctggtggag
360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga
420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag
480

tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 222
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2"
Tri-Specific Binding Molecule

<400> 222

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

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```
Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175

Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
            180                 185                 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
    210                 215                 220

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Cys
225                 230                 235                 240
```

Gly Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
245 250 255

Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 223
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x DR5 mAb 2" Tri-Specific Binding Molecule

<400> 223
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc 360

cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc 420

aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga 480

cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga 540

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aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag 600

ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac 660

aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt 720

ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc 780

gcacttaagg aaaaggtcgc agccctgaaa gag 813

<210> 224
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2"
Tri-Specific Binding Molecule

<400> 224

Lys Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Glu Tyr
20 25 30

Ile Leu His Trp Val Lys Gln Lys Ser Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Phe Tyr Pro Gly Asn Asn Asn Ile Lys Tyr Asn Glu Lys Phe
50 55 60

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```
Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg His Glu Gln Gly Pro Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
```

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245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
355 360 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 225
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x DR5 mAb 2" Tri-Specific Binding Molecule

<400> 225
aaggtccagc tgcagcagtc tggagctgaa ctggtgaaac ccggggcatc agtgaagctg 60

tcctgcaagg cttctgggta caccttcact gagtatattt tacactgggt aaagcagaag 120

tctggacagg gtcttgagtg gattgggtgg ttttatcctg gaaataataa tataaagtac 180

aatgagaaat tcaaggacaa ggccacactg actgcggaca aatcctccag cacagtctat 240

atggaactta gtagattgac atctgaagac tctgcggtct atttctgtgc aagacacgaa 300

caaggaccag gttactttga ctactggggc caaggcacca ctctcacagt ctcctccgcc 360

tccaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc 420

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga
540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
600

atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt tgagcccaaa
660

tcttgtgaca aaactcacac atgcccaccg tgcccagcac ctgaagccgc ggggggaccg
720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag
780

gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac
840

gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
900

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag
960

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa
1020

gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg
1080

accaagaacc aggtcagcct gagttgcgca gtcaaaggct tctatcccag cgacatcgcc
1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
1200

gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag caggtggcag
1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaaccg ctacacgcag
1320

a a g a g c c t c t c c c t g t c t c c g g g t a a a
1347

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<210> 226
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x DR5 mAb 2"
Tri-Specific Binding Molecule

<400> 226

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Lys Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Thr Leu Tyr Tyr Cys Gln Gln His Tyr Ile Thr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

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Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 227
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x DR5 mAb 2" Tri-Specific Binding Molecule

<400> 227
gacattgtga tgacccagtc tcacaaattc atgtccactt cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgaat actgctgtag cctggtatca acaaaaacca 120

gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat tatacactca ccatcaaaag tgtgcaggct 240

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gaagacctga cactttatta ctgtcagcaa cactatatca ctccgtggac gttcggtgga
300

ggcaccaagc tggaaatcaa acgtacggtg gctgcaccat cggtcttcat cttcccgcca
360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat
420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag
480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg
540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc
600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt
642

<210> 228
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 228

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Ile Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

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```
Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Tyr Thr Leu Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220
```

```
Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400
```

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Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
405 410 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
420 425 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
435 440 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 229
<211> 1508
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 1 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 229
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagaatcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

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gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca
180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa
240

gaagatattg ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
300

accaagctgg aaataaaagg tggaggatcc ggcggcggag gcgaggtgca gctggtggag
360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga
420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag
480

tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggga cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a
1508

<210> 230
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 230

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser

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```
                20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Lys Glu Ser Gly Pro Gly
        115                 120                 125

Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
    130                 135                 140

Phe Ser Leu Ser Arg Tyr Ser Val His Trp Val Arg Gln Pro Pro Gly
145                 150                 155                 160

Lys Gly Leu Glu Trp Leu Gly Met Ile Trp Gly Gly Gly Ser Thr Asp
                165                 170                 175

Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
            180                 185                 190

Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr
        195                 200                 205
```

Ala Met Tyr Tyr Cys Ala Arg Lys His Gly Asn Tyr Tyr Thr Met Asp
210 215 220

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Cys Gly
225 230 235 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
245 250 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 231
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 1
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 231
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtg 360

cagctgaagg agtcaggacc tggcctggtg gcaccctcac agagcctgtc catcacatgc
420

actgtctctg ggttctcatt atccagatat agtgtacact gggttcgcca gcctccagga
480

aagggtctgg agtggctggg aatgatatgg ggtggtggaa gcacagacta taattcagct
540

ctcaaatcca gactgagtat cagcaaggac aactccaaga gccaagtttt cttaaaaatg
600

aacagtctgc aaactgatga cacagccatg tactactgtg ccagaaaaca tggtaactac
660

tatactatgg actactgggg tcaaggaacc tcagtcaccg tctcctccgg aggatgtggc
720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca
780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g
810

<210> 232
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 232

Glu Val Lys Phe Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

```
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Thr Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205
```

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```
Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
        355                 360                 365

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    370                 375                 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
```

385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 233
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 1 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 233
gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc 60

tcctgtgtag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

ccagggaaag ggctagaatg gattggagaa attaatccag atagcaatac gataaactat 180

acgccatctc taaaggataa attcatcatc tccagagaca acgccaaaaa tacgctgtat 240

ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc 300

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tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt cactgtctct
360

tccgcctcca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct
420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg
480

tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc
540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag
660

cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg
720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc
780

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac
840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc
960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag cccccatcga gaaaaccatc
1020

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag
1080

gagatgacca agaaccaggt cagcctgagt tgcgcagtca aaggcttcta tcccagcgac
1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
1200

gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga caagagcagg
1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac
1320

acgcagaaga gcctctccct gtctccgggt aaa
1353

<210> 234
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 234

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
85 90 95

```
Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 235
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 1
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 235
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc 60

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atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct 180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg 300

acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 236
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 236

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly

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```
1               5                   10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly
        115                 120                 125

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
    130                 135                 140

Gly Phe Thr Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro
145                 150                 155                 160

Gly Lys Gly Leu Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn
                165                 170                 175

Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
            180                 185                 190
```

```
Arg Asp Asp Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys
        195                 200                 205

Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly
    210                 215                 220

Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
225                 230                 235                 240

Thr Val Ser Ser Gly Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu
                245                 250                 255

Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu
            260                 265                 270

Val Ala Ala Leu Glu Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro
        275                 280                 285

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
    290                 295                 300

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                325                 330                 335

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            340                 345                 350

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
        355                 360                 365
```

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```
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                405                 410                 415

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
            420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    450                 455                 460

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            500                 505
```

<210> 237
<211> 1524
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 2 x

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<400> 237
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
60

atctcttgca gatctagtca gagccttgta cacagtagtg gaaacaccta tttacattgg
120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt
180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc
300

acgttcggct cggggacaaa gttggaaata aaaggtggag gatccggcgg cggaggcgag
360

gtgcagctgg tggagtctgg gggaggcttg gtccagcctg gagggtccct gagactctcc
420

tgtgcagcct ctggattcac cttcagcaca tacgctatga attgggtccg ccaggctcca
480

gggaaggggc tggagtgggt tggaaggatc aggtccaagt acaacaatta tgcaacctac
540

tatgccgact ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg
600

tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg tgtgagacac
660

ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt ggggacaggg gacactggtg
720

actgtgtctt ccggaggatg tggcggtgga gaagtggccg cactggagaa agaggttgct
780

gctttggaga aggaggtcgc tgcacttgaa aaggaggtcg cagccctgga gaaaggcggc
840

ggggacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
900

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc
960

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
1020

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
1080

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac
1140

aagtgcaagg tctccaacaa agccctccca gccccatcg agaaaaccat ctccaaagcc
1200

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc
1260

aagaaccagg tcagcctgtg gtgcctggtc aaaggcttct atcccagcga catcgccgtg
1320

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
1380

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag
1440

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
1500

a g c c t c t c c c t g t c t c c g g g t a a a
1524

<210> 238
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1"

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Tri-Specific Binding Molecule

<400> 238

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                  10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
        115                 120                 125

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
    130                 135                 140

Phe Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
145                 150                 155                 160

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro
```

165 170 175

Thr Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val Phe Ser Leu Glu Thr
180 185 190

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp
195 200 205

Met Ala Thr Tyr Phe Cys Ala Arg Glu Leu Gly Pro Tyr Tyr Phe Asp
210 215 220

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Cys Gly
225 230 235 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
245 250 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 239
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 2
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 239
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

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cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca
240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacagatc
360

cagttggtgc agtctggacc tgagctgaag aagcctggag agacagtcaa gatctcctgc
420

aaggcttctg ggtttacctt cacaaactat ggaatgaact gggtgaagca ggctccagga
480

aagggtttaa agtggatggg ctggataaac acctatattg gagagccgac atatgctgat
540

gacttcaagg gacggtttgt cttctctttg gaaacctctg ccagcactgc ctatttgcag
600

atcaacaacc tcaaaaatga ggacatggcc acatatttct gtgcaagaga actgggacca
660

tactactttg actactgggg ccaaggcacc actctcacag tctcctccgg aggatgtggc
720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca
780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g
810

<210> 240
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

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2015266797

<400> 240

```
Glu Val Lys Phe Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Arg Tyr
            20                  25                  30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu
    50                  55                  60

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Thr Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175
```

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```
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305                 310                 315                 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                325                 330                 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            340                 345                 350
```

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Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 241
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 2 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 241
gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc 60

tcctgtgtag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

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2015266797

ccagggaaag ggctagaatg gattggagaa attaatccag atagcaatac gataaactat
180

acgccatctc taaaggataa attcatcatc tccagagaca acgccaaaaa tacgctgtat
240

ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc
300

tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt cactgtctct
360

tccgcctcca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct
420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg
480

tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc
540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag
600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag
660

cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg
720

ggaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc
780

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac
840

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc
960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag cccccatcga gaaaaccatc
1020

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag
1080

gagatgacca agaaccaggt cagcctgagt tgcgcagtca aaggcttcta tcccagcgac
1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
1200

gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga caagagcagg
1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac
1320

acgcagaaga gcctctccct gtctccgggt aaa
1353

<210> 242
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 242

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
20 25 30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
50 55 60

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```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95

Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
        195                 200                 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 243
<211> 654
<212> DNA

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<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 2
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 243
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc 60

atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct 180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg 300

acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 244
<211> 504
<212> PRT

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<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 244

Asp Ile Val Leu Thr Gln Ser His Arg Ser Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Asn Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Phe Trp Ala Ser Thr Arg His Ala Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Gly Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
115 120 125

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
130 135 140

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```
Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
145                 150                 155                 160

Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr
                165                 170                 175

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
            180                 185                 190

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr
        195                 200                 205

Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val
    210                 215                 220

Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240

Gly Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala
                245                 250                 255

Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu
            260                 265                 270

Glu Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        275                 280                 285

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    290                 295                 300

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
305                 310                 315                 320

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
```

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325 330 335

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
340 345 350

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
355 360 365

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
370 375 380

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
385 390 395 400

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
405 410 415

Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser
420 425 430

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
435 440 445

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
450 455 460

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
465 470 475 480

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
485 490 495

Ser Leu Ser Leu Ser Pro Gly Lys
500

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<210> 245
<211> 1512
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 3 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 245
gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga cagggtcaac 60

atcacctgca aggccagtca ggatgtgact actgctgtag cctggtatca acaaaaacca 120

gggcaatctc ctaaattact gattttctgg gcatccaccc ggcacgctgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat tttactctca ccatcagcag tgtgcaggct 240

ggagacctgg cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg 300

gggaccaagc tggaaataaa aggtggagga tccggcggcg gaggcgaggt gcagctggtg 360

gagtctgggg gaggcttggt ccagcctgga gggtccctga gactctcctg tgcagcctct 420

ggattcacct tcagcacata cgctatgaat tgggtccgcc aggctccagg gaaggggctg 480

gagtgggttg gaaggatcag gtccaagtac aacaattatg caacctacta tgccgactct 540

gtgaagggta gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg 600

aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg taacttcggc 660

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aattcttacg tgtcttggtt tgcttattgg ggacagggga cactggtgac tgtgtcttcc
720

ggaggatgtg gcggtggaga agtggccgca ctggagaaag aggttgctgc tttggagaag
780

gaggtcgctg cacttgaaaa ggaggtcgca gccctggaga aaggcggcgg ggacaaaact
840

cacacatgcc caccgtgccc agcacctgaa gccgcggggg gaccgtcagt cttcctcttc
900

cccccaaaac ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg
960

gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag
1020

gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc
1080

agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc
1140

tccaacaaag ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc
1200

cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc
1260

agcctgtggt gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc
1320

aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc
1380

ttcttcctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc
1440

tcatgctccg tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg
1500

t c t c c g g g t a a a
1512

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<210> 246
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 246

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
100 105 110

Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
115 120 125

```
Ser Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
    130                 135                 140

Phe Thr Phe Thr Asp His Tyr Met Tyr Trp Val Arg Gln Thr Pro Glu
145                 150                 155                 160

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Asp Gly Gly Ser Phe Thr
                165                 170                 175

Ser Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile
            180                 185                 190

Ala Lys Asn Asn Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp
        195                 200                 205

Thr Ala Met Tyr Tyr Cys Thr Arg Asp Glu Ser Asp Arg Pro Phe Pro
    210                 215                 220

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Cys Gly
225                 230                 235                 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
                245                 250                 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 247
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 3

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<400> 247

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggagaagtg 360

cagctggtgg agtctggggg aggctcagtg aagcctggag ggtccctgaa actctcctgt 420

gcagcctctg gattcacttt cactgaccat tacatgtatt gggttcgcca gactccggaa 480

aagaggctgg agtgggtcgc aaccattagt gatggcggta gtttcacctc ctatccagac 540

agtgtgaagg ggcgattcac catctccaga gacattgcca agaacaacct gtacctccaa 600

atgagcagtc tgaagtctga ggacacagcc atgtattact gtacaagaga tgagagcgat 660

aggccgtttc cttactgggg ccaagggact ctggtcactg tctcctccgg aggatgtggc 720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca 780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g 810

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<210> 248
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 248

Glu Val Lys Phe Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Asp Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Asp Ser Asn Thr Ile Asn Tyr Thr Pro Ser Leu
50 55 60

Lys Asp Lys Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Lys Val Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Thr Arg Arg Ala Tyr Tyr Gly Asn Pro Ala Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

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```
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
    210                 215                 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                245                 250                 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            260                 265                 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        275                 280                 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    290                 295                 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
```

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305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 249
<211> 1353
<212> DNA
<213> Artificial Sequence

<220>

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<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 3 x
CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 249

gaggtgaagt ttctcgagtc tggaggtggc ctggtgcagc ctggaggatc cctgaaactc 60

tcctgtgtag cctcaggatt cgattttagt agatactgga tgagttgggt ccggcaggct 120

ccagggaaag ggctagaatg gattggagaa attaatccag atagcaatac gataaactat 180

acgccatctc taaaggataa attcatcatc tccagagaca acgccaaaaa tacgctgtat 240

ctgcaaatga ccaaagtgag atctgaggac acagcccttt attattgtac aagaagggcc 300

tactatggta acccggcctg gtttgcttac tggggccaag ggactctggt cactgtctct 360

tccgcctcca ccaagggccc atcggtcttc cccctggcac cctcctccaa gagcacctct 420

gggggcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 480

tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc 540

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag 600

acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag 660

cccaaatctt gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agccgcgggg 720

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 780

cctgaggtca catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac 840

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tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac
900

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc
960

aaggagtaca agtgcaaggt ctccaacaaa gccctcccag ccccccatcga gaaaaccatc
1020

tccaaagcca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag
1080

gagatgacca agaaccaggt cagcctgagt tgcgcagtca aaggcttcta tcccagcgac
1140

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc
1200

gtgctggact ccgacggctc cttcttcctc gtcagcaagc tcaccgtgga caagagcagg
1260

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccgctac
1320

acgcagaaga gcctctccct gtctccgggt aaa
1353

<210> 250
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x DR5 mAb 1"
Tri-Specific Binding Molecule

<400> 250

Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

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```
Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Lys Ser Val Ser Ser Ser
            20                  25                  30

Gly Tyr Ser Tyr Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
        35                  40                  45

Lys Val Leu Ile Phe Leu Ser Ser Asn Leu Asp Ser Gly Val Pro Ala
    50                  55                  60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65                  70                  75                  80

Pro Val Glu Asp Gly Asp Ala Ala Thr Tyr Tyr Cys Gln His Ser Arg
                85                  90                  95

Asp Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
            180                 185                 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
```

195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 251
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 3
x CD3 mAb 2 x DR5 mAb 1" Tri-Specific Binding Molecule

<400> 251
gacattgtgc tgacacagtc tcctgcttcc ttagctgtat ctctcgggca gagggccacc 60

atctcatgca gggccagcaa aagtgtcagt tcctctggct atagttatat gcactggtac 120

caacagaaac caggacagcc acccaaagtc ctcatctttc tttcatccaa cctagattct 180

ggggtccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg atggggatgc tgcaacctat tactgtcagc acagtaggga tcttcctccg 300

acgttcggtg gaggcaccaa gctggaaatc aaacgtacgg tggctgcacc atcggtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 252
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
1" Tri-Specific Binding Molecule

<400> 252

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
100 105 110

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```
Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285
```

```
Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
                405                 410                 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            420                 425                 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        435                 440                 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    450                 455                 460
```

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 253
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 1" Tri-Specific Binding Molecule

<400> 253
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca gctggtggag 360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga 420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag 480

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tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggga cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 254
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
1" Tri-Specific Binding Molecule

<400> 254

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

```
Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175

Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
            180                 185                 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
    210                 215                 220

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Cys
225                 230                 235                 240

Gly Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
                245                 250                 255

Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

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<210> 255
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 1" Tri-Specific Binding Molecule

<400> 255
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc 360

cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc 420

aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga 480

cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga 540

aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag 600

ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac 660

aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt
720

ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc
780

gcacttaagg aaaaggtcgc agccctgaaa gag
813

<210> 256
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
1" Tri-Specific Binding Molecule

<400> 256

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Arg Tyr
20 25 30

Ser Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Met Ile Trp Gly Gly Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

```
Arg Lys His Gly Asn Tyr Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270
```

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```
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys
        355                 360                 365

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445

<210>  257
```

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<211> 1344
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 1" Tri-Specific Binding Molecule

<400> 257
caggtgcagc tgaaggagtc aggacctggc ctggtggcac cctcacagag cctgtccatc 60

acatgcactg tctctgggtt ctcattatcc agatatagtg tacactgggt tcgccagcct 120

ccaggaaagg gtctggagtg gctgggaatg atatggggtg gtggaagcac agactataat 180

tcagctctca aatccagact gagtatcagc aaggacaact ccaagagcca agttttctta 240

aaaatgaaca gtctgcaaac tgatgacaca gccatgtact actgtgccag aaaacatggt 300

aactactata ctatggacta ctggggtcaa ggaacctcag tcaccgtctc ctccgcctcc 360

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca 420

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 480

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 540

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc 600

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct 660

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca 720

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gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc
780

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
840

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
900

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac
960

aagtgcaagg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc
1020

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc
1080

aagaaccagg tcagcctgag ttgcgcagtc aaaggcttct atcccagcga catcgccgtg
1140

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
1200

tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag gtggcagcag
1260

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccgcta cacgcagaag
1320

a g c c t c t c c c t g t c t c c g g g t a a a
1344

<210> 258
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
1" Tri-Specific Binding Molecule

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<400> 258

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                  10                  15

Asp Arg Ile Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Tyr Thr Leu Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175
```

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 259
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 1" Tri-Specific Binding Molecule

<400> 259
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagaatcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca 180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa 240

gaagatattg ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg 300

accaagctgg aaataaaacg tacggtggct gcaccatcgg tcttcatctt cccgccatct 360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 260
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
2" Tri-Specific Binding Molecule

<400> 260

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

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```
Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
```

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```
                260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
                405                 410                 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            420                 425                 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        435                 440                 445
```

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 261
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 2" Tri-Specific Binding Molecule

<400> 261
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca gctggtggag 360

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tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga
420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag
480

tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggggac cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gccccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 262
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
2" Tri-Specific Binding Molecule

<400> 262

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

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```
Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175

Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
            180                 185                 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
    210                 215                 220

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Cys
225                 230                 235                 240

Gly Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
```

245 250 255

Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 263
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 2" Tri-Specific Binding Molecule

<400> 263
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc 360

cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc 420

aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga 480

cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga 540

aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
600

ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac
660

aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt
720

ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc
780

gcacttaagg aaaaggtcgc agccctgaaa gag
813

<210> 264
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
2" Tri-Specific Binding Molecule

<400> 264

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr

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65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Met Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Glu Leu Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

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```
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys
        355                 360                 365

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430
```

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Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 265
<211> 1344
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 2" Tri-Specific Binding Molecule

<400> 265
cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggtt taccttcaca aactatggaa tgaactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacct atattggaga gccgacatat 180

gctgatgact tcaagggacg gtttgtcttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac atggccacat atttctgtgc aagagaactg 300

ggaccatact actttgacta ctggggccaa ggcaccactc tcacagtctc ctccgcctcc 360

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca 420

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 480

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 540

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc 600

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct
660

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
720

gtcttcctct tcccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc
780

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
840

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
900

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac
960

aagtgcaagg tctccaacaa agccctccca gccccatcg agaaaaccat ctccaaagcc
1020

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc
1080

aagaaccagg tcagcctgag ttgcgcagtc aaaggcttct atcccagcga catcgccgtg
1140

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
1200

tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag gtggcagcag
1260

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccgcta cacgcagaag
1320

a g c c t c t c c c t g t c t c c g g g t a a a
1344

<210> 266
<211> 218
<212> PRT
<213> Artificial Sequence

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<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb 2" Tri-Specific Binding Molecule

<400> 266

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 267
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 2" Tri-Specific Binding Molecule

<400> 267
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagccttgta cacagtagtg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc 300

acgttcggct cggggacaaa gttggaaata aaacgtacgg tggctgcacc atcggtcttc
360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg
420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg
480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc
540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc
600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt
654

<210> 268
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2
mAb
3" Tri-Specific Binding Molecule

<400> 268

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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```
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240
```

```
Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
                405                 410                 415
```

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
420 425 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
435 440 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 269
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 3" Tri-Specific Binding Molecule

<400> 269
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

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gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
300

actaaactgg aaatcaaggg tggaggatcc ggcggcggag gcgaggtgca gctggtggag
360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga
420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag
480

tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggga cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

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aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 270
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
3" Tri-Specific Binding Molecule

<400> 270

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

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```
Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175

Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
            180                 185                 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
        195                 200                 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
    210                 215                 220
```

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Cys
225 230 235 240

Gly Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys
245 250 255

Glu Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 271
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 3" Tri-Specific Binding Molecule

<400> 271
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtc 360

cagctggtcc agagcggggc cgaagtcaaa aaacccggag caagcgtgaa ggtctcctgc 420

aaagcatcag gctatacatt tacaggcagc tggatgaact gggtgaggca ggctccagga
480

cagggactgg agtggatcgg gcgcatctac cctggagacg gcgaaactaa ctataatgga
540

aagttcaaag accgagtgac catcacagcc gataagtcta ctagtaccgc ctacatggag
600

ctgagctccc tgcggtctga agataccgcc gtctactatt gcgctagaat ttacggaaac
660

aatgtctatt ttgacgtgtg ggggcaggga acaactgtga ctgtctcctc cggaggatgt
720

ggcggtggaa aagtggccgc actgaaggag aaagttgctg ctttgaaaga gaaggtcgcc
780

gcacttaagg aaaaggtcgc agccctgaaa gag
813

<210> 272
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
3" Tri-Specific Binding Molecule

<400> 272

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp His
20 25 30

Tyr Met Tyr Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

```
Ala Thr Ile Ser Asp Gly Gly Ser Phe Thr Ser Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ala Lys Asn Asn Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Thr Arg Asp Glu Ser Asp Arg Pro Phe Pro Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220
```

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```
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser Cys
        355                 360                 365

Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser
```

405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 273
<211> 1344
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "gpA33 mAb 1 x
CD3 mAb 2 x EphA2 mAb 3" Tri-Specific Binding Molecule

<400> 273
gaagtgcagc tggtggagtc tgggggaggc tcagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcact gaccattaca tgtattgggt tcgccagact 120

ccggaaaaga ggctggagtg ggtcgcaacc attagtgatg gcggtagttt cacctcctat 180

ccagacagtg tgaaggggcg attcaccatc tccagagaca ttgccaagaa caacctgtac 240

ctccaaatga gcagtctgaa gtctgaggac acagccatgt attactgtac aagagatgag 300

agcgataggc cgtttcctta ctggggccaa gggactctgg tcactgtctc ctccgcctcc 360

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca 420

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 480

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tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc
540

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc
600

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct
660

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
720

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc
780

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
840

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
900

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac
960

aagtgcaagg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc
1020

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc
1080

aagaaccagg tcagcctgag ttgcgcagtc aaaggcttct atcccagcga catcgccgtg
1140

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
1200

tccgacggct ccttcttcct cgtcagcaag ctcaccgtgg acaagagcag gtggcagcag
1260

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccgcta cacgcagaag
1320

a g c c t c t c c c t g t c t c c g g g t a a a
1344

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<210> 274
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "gpA33 mAb 1 x CD3 mAb 2 x EphA2 mAb
3" Tri-Specific Binding Molecule

<400> 274

Asp Ile Val Leu Thr Gln Ser His Arg Ser Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Asn Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
35 40 45

Phe Trp Ala Ser Thr Arg His Ala Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Gly Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 275
<211> 642
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "gpA33 mAb 1
x CD3 mAb 2 x EphA2 mAb 3" Tri-Specific Binding Molecule

<400> 275
gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga cagggtcaac 60

atcacctgca aggccagtca ggatgtgact actgctgtag cctggtatca acaaaaacca 120

gggcaatctc ctaaattact gattttctgg gcatccaccc ggcacgctgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat tttactctca ccatcagcag tgtgcaggct 240

ggagacctgg cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg 300

gggaccaagc tggaaataaa acgtacggtg gctgcaccat cggtcttcat cttcccgcca 360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 642

<210> 276
<211> 503
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 276

Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Ile Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30

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```
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Tyr Thr Leu Tyr Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
            100                 105                 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
        115                 120                 125

Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
```

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```
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
225                 230                 235                 240

Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala
                245                 250                 255

Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu
            260                 265                 270

Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400
```

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Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
405 410 415

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
420 425 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
435 440 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
450 455 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465 470 475 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
485 490 495

Leu Ser Leu Ser Pro Gly Lys
500

<210> 277
<211> 1509
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 1 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 277
gatatccaga tgacacagac tacatcctcc ctgtctgcct ctctgggaga cagaatcacc 60

atcagttgca gggcaagtca ggacattagc aattatttaa actggtatca gcagaaacca 120

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gatggaactg ttaaactcct gatctactac acatcaagat tacactcagg agtcccatca
180

aggttcagtg gcagtgggtc tggaacagat tattctctca ccattagcaa cctggagcaa
240

gaagatattg ccacttactt ttgccaacag ggttatacgc tgtacacgtt cggaggggg
300

accaagctgg aaataaaagg tggaggatcc ggcggcggag gcgaggtgca gctggtggag
360

tctgggggag gcttggtcca gcctggaggg tccctgagac tctcctgtgc agcctctgga
420

ttcaccttca gcacatacgc tatgaattgg gtccgccagg ctccagggaa ggggctggag
480

tgggttggaa ggatcaggtc caagtacaac aattatgcaa cctactatgc cgactctgtg
540

aagggtagat tcaccatctc aagagatgat tcaaagaact cactgtatct gcaaatgaac
600

agcctgaaaa ccgaggacac ggccgtgtat tactgtgtga gacacggtaa cttcggcaat
660

tcttacgtgt cttggtttgc ttattgggga caggggacac tggtgactgt gtcttccgga
720

ggatgtggcg gtggagaagt ggccgcactg gagaaagagg ttgctgcttt ggagaaggag
780

gtcgctgcac ttgaaaagga ggtcgcagcc ctggagaaag gcggcgggga caaaactcac
840

acatgcccac cgtgcccagc acctgaagcc gcgggggga cgtcagtctt cctcttcccc
900

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg
960

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg
1020

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cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc
1080

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc
1140

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga
1200

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc
1260

ctgtggtgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat
1320

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc
1380

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca
1440

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct
1500

c c g g g t a a a
1509

<210> 278
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 278

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

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```
Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Lys Glu Ser Gly Pro Gly
        115                 120                 125

Leu Val Ala Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
    130                 135                 140

Phe Ser Leu Ser Arg Tyr Ser Val His Trp Val Arg Gln Pro Pro Gly
145                 150                 155                 160

Lys Gly Leu Glu Trp Leu Gly Met Ile Trp Gly Gly Gly Ser Thr Asp
                165                 170                 175

Tyr Asn Ser Ala Leu Lys Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser
            180                 185                 190

Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln Thr Asp Asp Thr
```

195 200 205

Ala Met Tyr Tyr Cys Ala Arg Lys His Gly Asn Tyr Tyr Thr Met Asp
210 215 220

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Cys Gly
225 230 235 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
245 250 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 279
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 1
x CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 279
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

ggggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacaggtg
360

cagctgaagg agtcaggacc tggcctggtg gcaccctcac agagcctgtc catcacatgc
420

actgtctctg ggttctcatt atccagatat agtgtacact gggttcgcca gcctccagga
480

aagggtctgg agtggctggg aatgatatgg ggtggtggaa gcacagacta taattcagct
540

ctcaaatcca gactgagtat cagcaaggac aactccaaga gccaagtttt cttaaaaatg
600

aacagtctgc aaactgatga cacagccatg tactactgtg ccagaaaaca tggtaactac
660

tatactatgg actactgggg tcaaggaacc tcagtcaccg tctcctccgg aggatgtggc
720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca
780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g
810

<210> 280
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 280

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Ser

```
                20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe Asp Val Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205
```

```
Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
        355                 360                 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380
```

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 281
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 1 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 281
caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag cgtgaaggtc 60

tcctgcaaag catcaggcta tacatttaca ggcagctgga tgaactgggt gaggcaggct 120

ccaggacagg gactggagtg gatcgggcgc atctaccctg gagacggcga aactaactat 180

aatggaaagt tcaaagaccg agtgaccatc acagccgata agtctactag taccgcctac 240

atggagctga gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac 300

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ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt ctcctccgcc
360

tccaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc
420

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg
480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga
540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
600

atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt tgagcccaaa
660

tcttgtgaca aaactcacac atgcccaccg tgcccagcac ctgaagccgc ggggggaccg
720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag
780

gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac
840

gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
900

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag
960

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa
1020

gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg
1080

accaagaacc aggtcagcct gagttgcgca gtcaaaggct tctatcccag cgacatcgcc
1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
1200

gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag caggtggcag
1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaaccg ctacacgcag
1320

a a g a g c c t c t c c c t g t c t c c g g g t a a a
1347

<210> 282
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 1 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 282

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
85 90 95

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```
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210
```

<210> 283
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 1
x CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 283

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gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt cccgccatct 360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 284
<211> 508
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 284

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```
Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                  10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
                85                  90                  95

Thr His Val Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly
        115                 120                 125

Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
    130                 135                 140

Gly Phe Thr Phe Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro
145                 150                 155                 160

Gly Lys Gly Leu Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn
                165                 170                 175
```

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```
Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
            180                 185                 190

Arg Asp Asp Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys
        195                 200                 205

Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly
    210                 215                 220

Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val
225                 230                 235                 240

Thr Val Ser Ser Gly Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu
                245                 250                 255

Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu
            260                 265                 270

Val Ala Ala Leu Glu Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro
        275                 280                 285

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
    290                 295                 300

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
305                 310                 315                 320

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                325                 330                 335

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            340                 345                 350

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
```

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```
        355                 360                 365

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    370                 375                 380

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
385                 390                 395                 400

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                405                 410                 415

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
            420                 425                 430

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        435                 440                 445

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    450                 455                 460

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
465                 470                 475                 480

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                485                 490                 495

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            500                 505
```

<210> 285
<211> 1524
<212> DNA
<213> Artificial Sequence

<220>

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<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 2 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 285
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagccttgta cacagtagtg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc 300

acgttcggct cggggacaaa gttggaaata aaaggtggag gatccggcgg cggaggcgag 360

gtgcagctgg tggagtctgg gggaggcttg gtccagcctg gagggtccct gagactctcc 420

tgtgcagcct ctggattcac cttcagcaca tacgctatga attgggtccg ccaggctcca 480

gggaaggggc tggagtgggt tggaaggatc aggtccaagt acaacaatta tgcaacctac 540

tatgccgact ctgtgaaggg tagattcacc atctcaagag atgattcaaa gaactcactg 600

tatctgcaaa tgaacagcct gaaaaccgag gacacggccg tgtattactg tgtgagacac 660

ggtaacttcg gcaattctta cgtgtcttgg tttgcttatt ggggacaggg gacactggtg 720

actgtgtctt ccggaggatg tggcggtgga gaagtggccg cactggagaa agaggttgct 780

gctttggaga aggaggtcgc tgcacttgaa aaggaggtcg cagccctgga gaaaggcggc 840

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ggggacaaaa ctcacacatg cccaccgtgc ccagcacctg aagccgcggg gggaccgtca
900

gtcttcctct tcccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc
960

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg
1020

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta caacagcacg
1080

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac
1140

aagtgcaagg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc
1200

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc
1260

aagaaccagg tcagcctgtg gtgcctggtc aaaggcttct atcccagcga catcgccgtg
1320

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
1380

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag
1440

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
1500

a g c c t c t c c c t g t c t c c g g g t a a a
1524

<210> 286
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb

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1" Tri-Specific Binding Molecule

<400> 286

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                  10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
        115                 120                 125

Leu Lys Lys Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly
    130                 135                 140

Phe Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly
145                 150                 155                 160

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro
```

165 170 175

Thr Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val Phe Ser Leu Glu Thr
180 185 190

Ser Ala Ser Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp
195 200 205

Met Ala Thr Tyr Phe Cys Ala Arg Glu Leu Gly Pro Tyr Tyr Phe Asp
210 215 220

Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Cys Gly
225 230 235 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
245 250 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

<210> 287
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 2
x CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 287
caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

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cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca
240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc
300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggacagatc
360

cagttggtgc agtctggacc tgagctgaag aagcctggag agacagtcaa gatctcctgc
420

aaggcttctg ggtttacctt cacaaactat ggaatgaact gggtgaagca ggctccagga
480

aagggtttaa agtggatggg ctggataaac acctatattg gagagccgac atatgctgat
540

gacttcaagg gacggtttgt cttctctttg gaaacctctg ccagcactgc ctatttgcag
600

atcaacaacc tcaaaaatga ggacatggcc acatatttct gtgcaagaga actgggacca
660

tactactttg actactgggg ccaaggcacc actctcacag tctcctccgg aggatgtggc
720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca
780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g
810

<210> 288
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

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<400> 288

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Ser
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe Asp Val Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175
```

```
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350
```

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Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
355 360 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 289
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 2 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 289
caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag cgtgaaggtc 60

tcctgcaaag catcaggcta tacatttaca ggcagctgga tgaactgggt gaggcaggct 120

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ccaggacagg gactggagtg gatcgggcgc atctaccctg gagacggcga aactaactat
180

aatggaaagt tcaaagaccg agtgaccatc acagccgata agtctactag taccgcctac
240

atggagctga gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac
300

ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt ctcctccgcc
360

tccaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc
420

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg
480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga
540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac
600

atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt tgagcccaaa
660

tcttgtgaca aaactcacac atgcccaccg tgcccagcac ctgaagccgc ggggggaccg
720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag
780

gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac
840

gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
900

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag
960

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa
1020

gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg
1080

accaagaacc aggtcagcct gagttgcgca gtcaaaggct tctatcccag cgacatcgcc
1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
1200

gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag caggtggcag
1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaaccg ctacacgcag
1320

a a g a g c c t c t c c c t g t c t c c g g g t a a a
1347

<210> 290
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 2 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 290

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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```
Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210
```

<210> 291
<211> 639
<212> DNA

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<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 2
x CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 291
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact
60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc
120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg
180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa
240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg
300

actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt cccgccatct
360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc
420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag
480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg
540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg
600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt
639

<210> 292
<211> 504
<212> PRT

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<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 292

```
Asp Ile Val Leu Thr Gln Ser His Arg Ser Met Ser Thr Ser Val Gly
1               5                  10                  15

Asp Arg Val Asn Ile Thr Cys Lys Ala Ser Gln Asp Val Thr Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Phe Trp Ala Ser Thr Arg His Ala Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

Gly Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Ser Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
        115                 120                 125

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
    130                 135                 140
```

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```
Ser Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
145                 150                 155                 160

Glu Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr
                165                 170                 175

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
            180                 185                 190

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr
        195                 200                 205

Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val
    210                 215                 220

Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240

Gly Gly Cys Gly Gly Gly Glu Val Ala Ala Leu Glu Lys Glu Val Ala
                245                 250                 255

Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu
            260                 265                 270

Glu Lys Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        275                 280                 285

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    290                 295                 300

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
305                 310                 315                 320

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
```

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```
                325                 330                 335

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            340                 345                 350

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        355                 360                 365

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
    370                 375                 380

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
385                 390                 395                 400

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
                405                 410                 415

Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser
            420                 425                 430

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        435                 440                 445

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    450                 455                 460

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
465                 470                 475                 480

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                485                 490                 495

Ser Leu Ser Leu Ser Pro Gly Lys
            500
```

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<210> 293
<211> 1512
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding First Polypeptide Chain of "EphA2 mAb 3 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 293
gacattgtgc tgacccagtc tcacagatcc atgtccacat cagtaggaga cagggtcaac 60

atcacctgca aggccagtca ggatgtgact actgctgtag cctggtatca acaaaaacca 120

gggcaatctc ctaaattact gattttctgg gcatccaccc ggcacgctgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat tttactctca ccatcagcag tgtgcaggct 240

ggagacctgg cactttatta ctgtcaacaa cattatagca caccgtacac attcggaggg 300

gggaccaagc tggaaataaa aggtggagga tccggcggcg gaggcgaggt gcagctggtg 360

gagtctgggg gaggcttggt ccagcctgga gggtccctga gactctcctg tgcagcctct 420

ggattcacct tcagcacata cgctatgaat tgggtccgcc aggctccagg gaaggggctg 480

gagtgggttg gaaggatcag gtccaagtac aacaattatg caacctacta tgccgactct 540

gtgaagggta gattcaccat ctcaagagat gattcaaaga actcactgta tctgcaaatg 600

aacagcctga aaaccgagga cacggccgtg tattactgtg tgagacacgg taacttcggc 660

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aattcttacg tgtcttggtt tgcttattgg ggacagggga cactggtgac tgtgtcttcc
720

ggaggatgtg gcggtggaga agtggccgca ctggagaaag aggttgctgc tttggagaag
780

gaggtcgctg cacttgaaaa ggaggtcgca gccctggaga aaggcggcgg ggacaaaact
840

cacacatgcc caccgtgccc agcacctgaa gccgcggggg gaccgtcagt cttcctcttc
900

cccccaaaac ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg
960

gtggacgtga gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag
1020

gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc
1080

agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc
1140

tccaacaaag ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc
1200

cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc
1260

agcctgtggt gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc
1320

aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc
1380

ttcttcctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc
1440

tcatgctccg tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg
1500

t c t c c g g g t a a a
1512

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<210> 294
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 294

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
100 105 110

Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly
115 120 125

```
Ser Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly
    130                 135                 140

Phe Thr Phe Thr Asp His Tyr Met Tyr Trp Val Arg Gln Thr Pro Glu
145                 150                 155                 160

Lys Arg Leu Glu Trp Val Ala Thr Ile Ser Asp Gly Gly Ser Phe Thr
                165                 170                 175

Ser Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile
            180                 185                 190

Ala Lys Asn Asn Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp
        195                 200                 205

Thr Ala Met Tyr Tyr Cys Thr Arg Asp Glu Ser Asp Arg Pro Phe Pro
    210                 215                 220

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Cys Gly
225                 230                 235                 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
                245                 250                 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 295
<211> 810
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Second Polypeptide Chain of "EphA2 mAb 3

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<400> 295

caggctgtgg tgactcagga gccttcactg accgtgtccc caggcggaac tgtgaccctg 60

acatgcagat ccagcacagg cgcagtgacc acatctaact acgccaattg ggtgcagcag 120

aagccaggac aggcaccaag gggcctgatc gggggtacaa acaaaagggc tccctggacc 180

cctgcacggt tttctggaag tctgctgggc ggaaaggccg ctctgactat taccggggca 240

caggccgagg acgaagccga ttactattgt gctctgtggt atagcaatct gtgggtgttc 300

gggggtggca caaaactgac tgtgctggga gggggtggat ccggcggagg tggagaagtg 360

cagctggtgg agtctggggg aggctcagtg aagcctggag ggtccctgaa actctcctgt 420

gcagcctctg gattcacttt cactgaccat tacatgtatt gggttcgcca gactccggaa 480

aagaggctgg agtgggtcgc aaccattagt gatggcggta gtttcacctc ctatccagac 540

agtgtgaagg ggcgattcac catctccaga gacattgcca agaacaacct gtacctccaa 600

atgagcagtc tgaagtctga ggacacagcc atgtattact gtacaagaga tgagagcgat 660

aggccgtttc cttactgggg ccaagggact ctggtcactg tctcctccgg aggatgtggc 720

ggtggaaaag tggccgcact gaaggagaaa gttgctgctt tgaaagagaa ggtcgccgca 780

c t t a a g g a a a a g g t c g c a g c c c t g a a a g a g 810

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2015266797

<210> 296
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Third Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 296

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Ser
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr Asn Tyr Asn Gly Lys Phe
50 55 60

Lys Asp Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

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```
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
```

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305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Ser
355 360 365

Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn Arg Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 297
<211> 1347
<212> DNA
<213> Artificial Sequence

<220>

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<223> Polynucleotide Encoding Third Polypeptide Chain of "EphA2 mAb 3 x
CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 297
caggtccagc tggtccagag cggggccgaa gtcaaaaaac ccggagcaag cgtgaaggtc 60

tcctgcaaag catcaggcta tacatttaca ggcagctgga tgaactgggt gaggcaggct 120

ccaggacagg gactggagtg gatcgggcgc atctaccctg gagacggcga aactaactat 180

aatggaaagt tcaaagaccg agtgaccatc acagccgata agtctactag taccgcctac 240

atggagctga gctccctgcg gtctgaagat accgccgtct actattgcgc tagaatttac 300

ggaaacaatg tctattttga cgtgtggggg cagggaacaa ctgtgactgt ctcctccgcc 360

tccaccaagg gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc 420

acagcggccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg 480

aactcaggcg ccctgaccag cggcgtgcac accttcccgg ctgtcctaca gtcctcagga 540

ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac 600

atctgcaacg tgaatcacaa gcccagcaac accaaggtgg acaagagagt tgagcccaaa 660

tcttgtgaca aaactcacac atgcccaccg tgcccagcac ctgaagccgc ggggggaccg 720

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 780

gtcacatgcg tggtggtgga cgtgagccac gaagaccctg aggtcaagtt caactggtac 840

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gtggacggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gtacaacagc
900

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag
960

tacaagtgca aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa
1020

gccaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg
1080

accaagaacc aggtcagcct gagttgcgca gtcaaaggct tctatcccag cgacatcgcc
1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
1200

gactccgacg gctccttctt cctcgtcagc aagctcaccg tggacaagag caggtggcag
1260

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaaccg ctacacgcag
1320

a a g a g c c t c t c c c t g t c t c c g g g t a a a
1347

<210> 298
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Fourth Polypeptide Chain of "EphA2 mAb 3 x CD3 mAb 2 x gpA33 mAb
1" Tri-Specific Binding Molecule

<400> 298

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

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```
Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
```

195 200 205

Asn Arg Gly Glu Cys
210

<210> 299
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Polynucleotide Encoding Fourth Polypeptide Chain of "EphA2 mAb 3
x CD3 mAb 2 x gpA33 mAb 1" Tri-Specific Binding Molecule

<400> 299
gacattcagc tgactcagtc cccctctttt ctgtccgcat ccgtcggaga tcgagtgact 60

attacttgct ctgctaggtc ctcaatcagc ttcatgtact ggtatcagca gaagcccggc 120

aaagcaccta agctgctgat ctacgacaca agcaacctgg cctccggggt gccatctcgg 180

ttctctggca gtgggtcagg aactgagttt accctgacaa ttagctccct ggaggctgaa 240

gatgccgcta cctactattg ccagcagtgg agcagctatc ctctgacctt cggacagggg 300

actaaactgg aaatcaagcg tacggtggct gcaccatcgg tcttcatctt cccgccatct 360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 300
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "4-4-20 x CD3 mAb 2" Diabody

<400> 300

Asp Val Val Met Thr Gln Thr Pro Phe Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Arg Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Glu Val Gln Leu Val Glu Ser Gly
115 120 125

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
130 135 140

Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg Gln Ala
145 150 155 160

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn
165 170 175

Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile
180 185 190

Ser Arg Asp Asp Ser Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu
195 200 205

Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe
210 215 220

Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu
225 230 235 240

Val Thr Val Ser Ser Gly Gly Cys Gly Gly Gly Glu Val Ala Ala Leu
245 250 255

Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys
260 265 270

Glu Val Ala Ala Leu Glu Lys
275

<210> 301

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<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "4-4-20 x CD3 mAb 2" Diabody

<400> 301

Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
100 105 110

Gly Ser Gly Gly Gly Gly Glu Val Lys Leu Asp Glu Thr Gly Gly Gly
115 120 125

Leu Val Gln Pro Gly Arg Pro Met Lys Leu Ser Cys Val Ala Ser Gly
130 135 140

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```
Phe Thr Phe Ser Asp Tyr Trp Met Asn Trp Val Arg Gln Ser Pro Glu
145                 150                 155                 160

Lys Gly Leu Glu Trp Val Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr
                165                 170                 175

Glu Thr Tyr Tyr Ser Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
            180                 185                 190

Asp Asp Ser Lys Ser Ser Val Tyr Leu Gln Met Asn Asn Leu Arg Val
        195                 200                 205

Glu Asp Met Gly Ile Tyr Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp
    210                 215                 220

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Gly Gly Cys Gly
225                 230                 235                 240

Gly Gly Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
                245                 250                 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
            260                 265                 270
```

<210> 302
<211> 108
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(108)
<223> Murine Anti-Human CD317 Antibody ("HM1.24 mAb 1") Light Chain Variable Domain

<400> 302

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```
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1               5                  10                  15

Asp Arg Val Ser Ile Thr Cys Lys Lys Ala Ser Gln Asp Val Asn Thr
            20                  25                  30

Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Ser Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Ile Thr
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln
65                  70                  75                  80

Ala Glu Asp Leu Ala Leu Thr Thr Cys Gln Gln His Tyr Ser Thr Pro
                85                  90                  95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 303
<211> 120
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(120)
<223> Murine Anti-Human CD317 Antibody ("HM1.24 mAb 1") Heavy Chain Variable Domain

<400> 303

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala
1               5                  10                  15
```

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Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Pro Tyr
20 25 30

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ser Ile Phe Pro Gly Asp Gly Asp Thr Arg Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ile Leu Ala Phe Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Arg Arg Gly Gly Tyr Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 304
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Murine Anti-Human CEACAM5 / CEACAM6 Antibody (16C3; EP 2585476)
Light Chain Variable Domain

<400> 304

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gly Ala Ser Glu Asn Ile Tyr Gly Ala
20 25 30

Leu Asn Trp Tyr Gln Arg Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile
35 40 45

Trp Gly Ala Ser Asn Leu Ala Asp Gly Met Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Gln Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Asn Val Leu Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 305
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CEACAM5 / CEACAM6 Antibody (16C3; EP 2585476) Heavy Chain Variable Domain

<400> 305

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Val Val Arg Pro Gly Val
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Met His Trp Val Lys Gln Ser His Ala Lys Ser Leu Glu Trp Ile

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35 40 45

Gly Leu Ile Ser Thr Tyr Ser Gly Asp Thr Lys Tyr Asn Gln Asn Phe
50 55 60

Lys Gly Lys Ala Thr Met Thr Val Asp Lys Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Tyr Ser Gly Ser Arg Tyr Trp Phe Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 306
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CEACAM5 / CEACAM6 Antibody (hMN15; WO 2011/034660) Light Chain Variable Domain

<400> 306

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Arg Val Ser Tyr Ile
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr
35 40 45

Gly Thr Ser Thr Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu
65 70 75 80

Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Tyr Asn Pro Pro Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 307
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human CEACAM5 / CEACAM6 Antibody (hMN15; WO 2011/034660) Heavy Chain Variable Domain

<400> 307

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ser Ser Gly Phe Ala Leu Thr Asp Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Phe Ile Ala Asn Lys Ala Asn Gly His Thr Thr Asp Tyr Ser Pro
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr

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65 70 75 80

Leu Phe Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr
85 90 95

Phe Cys Ala Arg Asp Met Gly Ile Arg Trp Asn Phe Asp Val Trp Gly
100 105 110

Gln Gly Thr Pro Val Thr Val Ser Ser
115 120

<210> 308
<211> 107
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(107)
<223> Murine Anti-Human 5T4 Antibody ("5T4 mAb 1") Light Chain Variable
Domain

<400> 308

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asp Phe Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 309
<211> 118
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(118)
<223> Murine Anti-Human 5T4 Antibody ("5T4 mAb 1") Heavy Chain Variable
Domain

<400> 309

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Phe
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Asn Arg Gly Gly Thr Glu Tyr Asn Glu Lys Ala
50 55 60

Lys Ser Arg Val Thr Met Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Gly Asn Pro Tyr Tyr Pro Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> 310
<211> 112
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(112)
<223> Murine Anti-Human 5T4 Antibody ("5T4 mAb 2") Light Chain Variable
Domain

<400> 310

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val Tyr Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

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Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 311
<211> 127
<212> PRT
<213> Mus musculus

<220>
<221> MISC_FEATURE
<222> (1)..(127)
<223> Murine Anti-Human 5T4 Antibody ("5T4 mAb 2") Heavy Chain Variable
Domain

<400> 311

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Ile Thr Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Tyr Pro Gly Ser Gly Arg Ala Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Asn Cys

85 90 95

Ala Arg Tyr Gly Pro Leu Phe Thr Thr Val Val Asp Pro Asn Ser Tyr
100 105 110

Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120 125

<210> 312
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human ITGB6 Antibody (Derived from Antibody 3G9,
PCT Publication No. WO 2007/008712) Light Chain Variable Domain

<400> 312

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
20 25 30

Tyr Leu Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Ser Thr Ser Asn Leu Ala Ser Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Trp Ser Thr Tyr Pro

85 90 95

Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 313
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human ITGB6 Antibody (Derived from Antibody 3G9,
PCT Publication No. WO 2007/008712) Heavy Chain Variable Domain

<400> 313

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Gly Gly Arg Met Tyr Tyr Pro Phe Thr Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Ser Ile Tyr Asp Gly Tyr Tyr Val Phe Pro Tyr Trp Gly Gln

100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 314
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human ITGB6 Antibody (Derived from Antibody 8G6;
PCT Publication No. WO 2007/008712) Light Chain Variable Domain

<400> 314

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Thr Ser
20 25 30

Ser Tyr Ser Tyr Met Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Tyr Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Asn Trp
85 90 95

Glu Ile Pro Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105 110

<210> 315
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized Anti-Human ITGB6 Antibody (Derived from Antibody 8G6;
PCT Publication No. WO 2007/008712) Heavy Chain Variable Domain

<400> 315

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Ser Thr Tyr Tyr Gly Asn Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Leu Arg Arg Gly Asp Arg Pro Ser Leu Gln Tyr Ala
100 105 110

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

115 120 125

<210> 316
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> First Polypeptide Chain of "gpA33 x CD3 mAb 2" Diabody

<400> 316

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Ile Ser Phe Met
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Asp Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Tyr Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
115 120 125

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```
Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
    130                 135                 140

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
145                 150                 155                 160

Trp Val Gly Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
                165                 170                 175

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys
            180                 185                 190

Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala
        195                 200                 205

Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
    210                 215                 220

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
225                 230                 235                 240

Ser Thr Lys Gly Glu Val Ala Ala Cys Glu Lys Glu Val Ala Ala Leu
                245                 250                 255

Glu Lys Glu Val Ala Ala Leu Glu Lys Glu Val Ala Ala Leu Glu Lys
            260                 265                 270
```

<210> 317
<211> 270
<212> PRT
<213> Artificial Sequence

<220>
<223> Second Polypeptide Chain of "gpA33 x CD3 mAb 2" Diabody

<400> 317

```
Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                  10                  15

Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser
            20                  25                  30

Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Trp Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Ile Thr Gly Ala
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly Gly
            100                 105                 110

Gly Ser Gly Gly Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu
        115                 120                 125

Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
    130                 135                 140

Tyr Thr Phe Thr Gly Ser Trp Met Asn Trp Val Arg Gln Ala Pro Gly
145                 150                 155                 160

Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly Asp Gly Glu Thr
                165                 170                 175
```

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Asn Tyr Asn Gly Lys Phe Lys Asp Arg Val Thr Ile Thr Ala Asp Lys
180 185 190

Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
195 200 205

Thr Ala Val Tyr Tyr Cys Ala Arg Ile Tyr Gly Asn Asn Val Tyr Phe
210 215 220

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
225 230 235 240

Lys Gly Lys Val Ala Ala Cys Lys Glu Lys Val Ala Ala Leu Lys Glu
245 250 255

Lys Val Ala Ala Leu Lys Glu Lys Val Ala Ala Leu Lys Glu
260 265 270

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mAb 2") Light Chain Variable Domain (SEQ ID NO:163)

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tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

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tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccc
300

acgttcggct cggggacaaa gttggaaata aaa
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120

ccggaaaaga ggctggagtg ggtcgcaacc attagtgatg gcggtagttt cacctcctat
180

ccagacagtg tgaaggggcg attcaccatc tccagagaca ttgccaagaa caacctgtac
240

ctccaaatga gcagtctgaa gtctgaggac acagccatgt attactgtac aagagatgag
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Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala
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<212> PRT
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<220>
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<400> 321

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Ser Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Ser Ala Pro Trp
85 90 95

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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 322
<211> 122
<212> PRT
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<220>
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<400> 322

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Asn
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Val Ser Ser Gly Gly Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Gly Thr Thr Ala Leu Ala Thr Arg Phe Phe Asp Val Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser

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