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Description

TECHNICAL FIELD

[0001] This invention relates to therapeutic compositions related to human subjects.

BACKGROUND

[0002] Human subjects exposed to a condition or disease offer a source of antibodies with therapeutic potential and general methods for obtaining such antibodies are known in the art. However, methods for specifically obtaining antibodies with therapeutic potential are generally limited by the low frequency, slow proliferation rate, and low antibody secretion levels of B cells that express such antibodies. For example, memory B cells with defined specificity typically account for only one cell per million peripheral blood mononuclear cells or approximately one milliliter of blood (Lanzavecchia et al., Curr. Opin. Immunol., 21:298-304 (2009): Yoshida et al., Immunol. Rev., 237:117-139 (2010)). The frequency of antibodies with therapeutic potential is likely to be even lower in cancer patients, necessitating the development of novel approaches that enable isolation of such cells with high sensitivity and efficiency.

[0003] Conventional methods generally rely on conversion of memory B cells into antibody secreting cells by in vitro culture and/or use of immunized animal models (e.g., mice) (Crotty et al., J. Immunol., 171:4969-4973 (2003): Fecteau et al., Immunology, 128:e353-e365 (2009): Buisman et al., Vaccine, 28:179-186 (2009): Corti et al., PLoS One, 5:e8805 (2010)). For example, following in vitro culture for up to one week, antibodies can be measured in culture supernatants and frequencies of antibody secreting cells assessing using enzyme-linked immunosorbent spot (ELISPOT) assay. Limitations of such methods are reported (Henn et al., J. Immunol., 183:31777-3187 (2009): Cao et al., J. Immunol., Methods, 358:56-65 (2010)). For instances, in vitro culture of memory B cells alters the memory B cell phenotype to resemble plasma cells with distinct functional properties (Jiang et al., Eur. J. Immunol., 37:2205-2213 (2007): Huggins et al., Blood, 109:1611-1619 (2007): Jourdan et al., Blood, 114:5173-5181 (2009)). Limitations for fluorescent antigen-based methods are also reported (Hofer et al., Immunol. Rev., 211:295-302 (2006): Odendahl et al., Blood, 105:1614-1621 (2005); Kunkel et al., Nat. Rev. Immunol., 3:822-829 (2003): Scheid et al., Nature, 458:636-640 (2009): Wu et al., Science, 329:856-861 (2010)).

[0004] Improved methods for specifically obtaining or targeting antibodies with therapeutic potential are required.

[0005] MICA is a ligand for NKG2D, a C-type lectin-like, type II transmembrane receptor expressed on most human NK cells, $\gamma\delta$ T cells, and CD8+ T cells. Upon ligation, NKG2D signals through the adaptor protein DAP10 to evoke perforin dependent cytolysis and to provide co-stimulation. In humans, the NKG2D ligands include MHC class I chain-related protein A (MICA), the closely related MICB, UL-16 binding proteins (ULBP) 1-4, and RAE-1G While NKG2D ligands are not usually found on healthy tissues, various forms of cellular stress, including DNA damage, may upregulate ligand expression, resulting in their frequent detection in multiple solid and hematologic malignancies, including melanoma. NKG2D activation through ligand positive transformed cells contributes to extrinsic tumor suppression, since NKG2D deficient and wild type mice treated with anti-NKG2D blocking antibodies manifest enhanced tumor susceptibility. Immune escape may be achieved in patients, however, by the shedding of NKG2D ligands from tumor cells, which triggers internalization of surface NKG2D and impaired function of cytotoxic lymphocytes. Soluble NKG2D ligands may also stimulate the expansion of regulatory NKG2D+CD4+Foxp3- T cells that may antagonize antitumor cytotoxicity through Fas ligand, IL-10, and TGF-β. MICA is a NKG2D ligand shed from tumor cells, i.e., released from the cell surface into the surrounding medium, and sera from cancer patients typically contain elevated levels of the soluble form (sMICA). MICA shedding is accomplished in part through interactions with the protein disulfide isomerase ERp5, which forms a disulfide bond with a critical cysteine that results in unfolding of the α3 domain, rendering it susceptible to proteolysis by ADAM-10/17 and MMP14. MICA polypeptides and antibodies binding to MICA are described in WO 03/089616.

[0006] Angiogenesis is the process of forming new capillaries from preexisting blood vessels and has been implicated as a critical part of tumor growth and dissemination. Tumors stimulate angiogenesis to meet increasing oxygen and nutrient requirements that exceed those that can be met by diffusion alone. Consequently, tumors recruit, remodel and expand existing vascular to meet their metabolic demand. The dependence of growing tumors on new blood vessel formation has made angiogenesis an appealing target for anti-cancer therapies. Many cytokines have been are believed to play a role in the regulation of angiogenesis, including vascular endothelial growth factor (VEGF) family members and the angiopoietins. The angiopioetins were discovered as ligands for the Ties, a family of tyrosine kinases that is selectively expressed in the vascular endothelium. There are four know angiopoietins: angiopoietin-1 ("Ang-1") through angiopoietin-4 ("Ang-4"). Studies have suggested that angiopoietins (e.g., Ang-1 and Ang-2) may be involved and tumor angiogenesis. With this information, angiopoietins have been identified as potential targets of immune-based cancer therapy.

[0007] There is a need to identify new agents that specifically recognize and bind targets of immune-based cancer therapy, such as MICA and angiopoietins. Such agents would be useful for diagnostic screening and therapeutic intervention in disease states that are associated with tumor development.

SUMMARY

[0008] Compositions and methods related to antibodies with therapeutic potential are described herein.

[0009] The present invention provides compositions comprising an antibody or antibody fragment that immunospecifically binds to MHC class I polypeptide-related sequence A (MICA), or an epitope thereon. Said antibody or antibody fragment comprises a heavy chain variable region (V_H) and a light chain variable region (V_L) and complementarity determining region (CDR) 3 of the V_H set forth in SEQ ID NO:212 of antibody ID 9; or and complementarity determining region (CDR) 3 of the V_H set forth in SEQ ID NO:158 of antibody ID 6. Further, compositions are described herein comprising peptides which include complementarity determining region (CDR) 3 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, and CDR3 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions. Such peptides may further include complementarity determining region (CDR) 3 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1, and CDR3 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1. Peptides described herein may further include CDR2 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or CDR2 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or both. Such peptides may include complementarity determining region CDR2 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1, or CDR2 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1, or both. Peptides described herein may further include CDR1 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or CDR1 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or both. Such peptides may include complementarity determining region CDR1 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1, or CDR1 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1, or both.

[0010] Peptides described herein may be antibodies or antibody fragments that include: a V_H chain with identity to SEQ ID NO:2, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 1 shown in table 1 having 5 or fewer conservative amino acid substitutions, and regions within SEQ ID NO:2 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 1 shown in table 1; and a V_L chain with identity to SEQ ID NO:11, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 1 shown in table 1 having 5 or fewer conservative amino acid substitutions, and regions within SEQ ID NO:11 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 1 shown in table 1. Peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:2 and a V_L chain comprising SEQ ID NO:11. In addition to the peptides, compositions described herein may further include one or more (e.g., 1 2, 3, 4, 5, 6, 7, 8, 9, 10, or less than 20) anti-cancer therapeutics. Compositions described herein may be formulated as pharmaceutical compositions (e.g., for administration to a subject).

[0011] Peptides described herein may be antibodies or antibody fragments that include: a V_H chain with identity to SEQ ID NO:149, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 6 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:149 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 6 shown in table 1; and a V_L chain with identity to SEQ ID NO:151, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 6 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:151 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 6 shown in table 1. In some aspects, the antibody or antibody fragment useful in the present invention comprises a V_H chain comprising SEQ ID NO:149 and a V_L chain comprising SEQ ID NO:151. In some aspects, in addition to the antibody or antibody fragment, the compositions further include one or more (e.g., 1 2, 3, 4, 5, 6, 7, 8, 9, 10, or less than 20) anti-cancer therapeutics. In some aspects, the compositions are formulated as pharmaceutical compositions (e.g., for administration to a subject).

[0012] Peptides described herein may be antibodies or antibody fragments that include: a V_H chain with identity to SEQ ID NO:168, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 7 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:168 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 7 shown in table 1; and a V_L chain with identity to SEQ ID NO:170, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 7 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID

NO:170 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 7 shown in table 1. Peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:168 and a V_L chain comprising SEQ ID NO:170. In addition to the peptides, compositions described herein may further include one or more (e.g., 1 2, 3, 4, 5, 6, 7, 8, 9, 10, or less than 20) anti-cancer therapeutics. Compositions described herein may be formulated as pharmaceutical compositions (e.g., for administration to a subject).

[0013] Peptides described herein may be antibodies or antibody fragments that include: a V_H chain with identity to SEQ ID NO:186, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 8 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:186 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 8 shown in table 1; and a V_L chain with identity to SEQ ID NO:188, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 8 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:188 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 8 shown in table 1. Peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:186 and a V_L chain comprising SEQ ID NO:188. In addition to the peptides, compositions described herein may further include one or more (e.g., 1 2, 3, 4, 5, 6, 7, 8, 9, 10, or less than 20) anti-cancer therapeutics. Compositions described herein may be formulated as pharmaceutical compositions (e.g., for administration to a subject).

[0014] Peptides described herein may be antibodies or antibody fragments that include: a V_H chain with identity to SEQ ID NO:204 wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 9 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:204 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 9 shown in table 1; and a V_L chain with identity to SEQ ID NO:206, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 9 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:206 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 9 shown in table 1. In some aspects, the antibody or antibody fragment useful in the present invention comprises a V_H chain comprising SEQ ID NO:204 and a V_L chain comprising SEQ ID NO:206. In some aspects, in addition to the antibody or antibody fragment, the compositions further include one or more (e.g., 1 2, 3, 4, 5, 6, 7, 8, 9, 10, or less than 20) anti-cancer therapeutics. In some aspects, the compositions are formulated as pharmaceutical compositions (e.g., for administration to a subject).

[0015] Further, compositions are described herein that include one or more peptides that bind to angiopoietin or an epitope thereon. Peptides of the compositions described herein may include complementarity determining region (CDR) 3 of the V_H of antibody ID 2, 3, 4, 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions, and CDR3 of the V_L of antibody ID 2, 3, 4 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions. Peptides described herein can include complementarity determining region (CDR) 3 of the V_H of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1, and CDR3 of the V_L of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1. Peptides described herein can further include CDR2 of the V_H of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or CDR2 of the V_L of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or both. Such peptides can include complementarity determining region CDR2 of the V_H of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1, or CDR2 of the V_L of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1, or both. Peptides described herein can further include CDR1 of the V_H of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or CDR1 of the V_L of antibody ID 2, 3, 4, or 5 shown in Table 1 having 5 or fewer conservative amino acid substitutions, or both. Such peptides can include complementarity determining region CDR1 of the V_H of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1, or CDR1 of the V_L of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1, or both.

[0016] Peptides described herein may include an antibody or antibody fragment comprising: a V_H chain with identity to SEQ ID NO:20, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 2 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:20 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 2 shown in table 1; and a V_L chain with identity to SEQ ID NO:29, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 2 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:29 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 2 shown in table 1. The peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:20 and a V_L chain comprising SEQ ID NO:29.

[0017] The peptides described herein may be antibodies or antibody fragments comprising: a V_H chain with identity to SEQ ID NO:38, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 3 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:38 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 3 shown in table 1; and a V_L chain with identity to SEQ ID NO:47, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 3 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:47 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 3 shown in table 1. Peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:38 and a V_L chain comprising SEQ ID NO:47.

[0018] Peptides described herein may include an antibody or antibody fragment comprising: a V_H chain with identity to SEQ ID NO:56, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 4 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:56 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 4 shown in table 1; and a V_L chain with identity to SEQ ID NO:65, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 4 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:65 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 4 shown in table 1. Peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:56 and a V_L chain comprising SEQ ID NO:65.

[0019] Peptides described herein may include an antibody or antibody fragment comprising: a V_H chain with identity to SEQ ID NO:74, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 5 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:74 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 5 shown in table 1; and a V_L chain with identity to SEQ ID NO:83, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 5 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:83 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 5 shown in table 1. The peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:74 and all chain comprising SEQ ID NO:83. The peptides described herein may immunospecifically bind to at least angiopoietin-2. The compositions described herein may further include one or more anti-cancer therapeutics. The compositions described herein may be formulated as a pharmaceutical composition.

[0020] Peptides described herein may include an antibody or antibody fragment comprising: a V_H chain with identity to SEQ ID NO:222, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_H of antibody ID 10 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:222 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_H of antibody ID 10 shown in table 1; and a V_L chain with identity to SEQ ID NO:224, wherein regions corresponding to CDR1, CDR2, and CDR3 comprise CDR1, CDR2, and CDR3 of the V_L of antibody ID 10 shown in table 1 having 5 or fewer conservative amino acid substitutions within the CDR1, CDR2, and CDR3 regions, and regions within SEQ ID NO:224 corresponding to FR1, FR2, FR3, FR4, comprise amino acid sequences with at least 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, or 100% identity to FR1, FR2, FR3, FR4 of the V_L of antibody ID 10 shown in table 1. The peptides described herein may include an antibody or antibody fragment comprising a V_H chain comprising SEQ ID NO:222 and a V_L chain comprising SEQ ID NO:224. The peptides described herein may immunospecifically bind to at least angiopoietin-2. The compositions described herein may further include one or more anti-cancer therapeutics. The compositions described herein may be formulated as a pharmaceutical composition.

[0021] Further, methods of treating cancer in a subject are described herein. The methods may include administering to a subject a composition described herein.

[0022] Also described herein are methods of isolating human antibodies from cancer patients following immunotherapy.

[0023] A method of obtaining immune cells directed against a self antigen from a subject is described herein, the method comprising identifying a subject exhibiting a positive immune response towards the self antigen, providing a multimeric form of the self antigen, contacting the multimeric form of the self antigen with a sample from the subject exhibiting a positive immune response towards the self antigen, and obtaining immune cells bound to the multimeric form of the self antigen.

[0024] In some embodiments, the disclosure includes method of obtaining immune cells from a cancer patient directed against a self antigen, the method comprising identifying a subject exhibiting a positive immune response towards the self antigen; providing a multimeric form of the self antigen; contacting the multimeric form of the self antigen with a sample from the subject exhibiting a positive immune response towards the self antigen; and obtaining immune cells bound to the multimeric form of the self antigen.

[0025] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0026] Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

[0027]

FIG. 1 | Nucleic acid sequence of the variable heavy (V_H) chain of antibody ID 1 (anti-MHC class I polypeptide-related sequence A (MICA) antibody) (SEQ ID NO:1).
FIG. 2 | Amino acid sequence of V_H chain of antibody ID 1 (anti-MICA antibody) (SEQ ID NO:2).
FIG 3 | Nucleic acid sequence of the variable light (V_L) chain of antibody ID 1 (anti-MICA antibody) (SEQ ID NO:10).
FIG. 4 | Amino acid sequence of V_L chain of antibody ID 1 (anti-MICA antibody) (SEQ ID NO:11).
FIG. 5 | Nucleic acid sequence of the V_H chain of antibody ID 2 (anti-angiopoietin-2 antibody) (SEQ ID NO:19).
FIG. 6 | Amino acid sequence of V_H chain of antibody ID 2 (anti- angiopoietin-2 antibody) (SEQ ID NO:20).
FIG. 7 | Nucleic acid sequence of the V_L chain of antibody ID 2 (anti-angiopoietin-2 antibody) (SEQ ID NO:28).
FIG. 8 | Amino acid sequence of V_L chain of antibody ID 2 (anti- angiopoietin-2 antibody) (SEQ ID NO:29).
FIG. 9 | Nucleic acid sequence of the V_H chain of antibody ID 3 (anti-angiopoietin-2 antibody) (SEQ ID NO:37).
FIG. 10 | Amino acid sequence of V_H chain of antibody ID 3 (anti- angiopoietin-2 antibody) (SEQ ID NO:38).
FIG. 11 | Nucleic acid sequence of the V_L chain of antibody ID 3 (anti-angiopoietin-2 antibody) (SEQ ID NO:46).
FIG. 12 | Amino acid sequence of V_L chain of antibody ID 3 (anti- angiopoietin-2 antibody) (SEQ ID NO:47).
FIG. 13 | Nucleic acid sequence of the V_H chain of antibody ID 4 (anti-angiopoietin-2 antibody) (SEQ ID NO:55).
FIG. 14 | Amino acid sequence of V_H chain of antibody ID 4 (anti- angiopoietin-2 antibody) (SEQ ID NO:56).
FIG. 15 Nucleic acid sequence of the V_L chain of antibody ID 4 (anti-angiopoietin-2 antibody) (SEQ ID NO:64).
FIG. 16 | Amino acid sequence of V_L chain of antibody ID 4 (anti- angiopoietin-2 antibody) (SEQ ID NO:65).
FIG. 17 | Nucleic acid sequence of the V_H chain of antibody ID 5 (anti-angiopoietin-2 antibody) (SEQ ID NO:73).
FIG. 18 | Amino acid sequence of V_H chain of antibody ID 5 (anti- angiopoietin-2 antibody) (SEQ ID NO:74).
FIG. 19 | Nucleic acid sequence of the V_L chain of antibody ID 5 (anti-angiopoietin-2 antibody) (SEQ ID NO:82).
FIG. 20 | Amino acid sequence of V_L chain of antibody ID 5 (anti- angiopoietin-2 antibody) (SEQ ID NO:83).
FIG. 21A-21F | Illustrates exemplary methods for making antibodies from B-cells. (A) Antigen is expressed with a BirA tag for site-specific biotinylation and tetramerization with fluorescently-labeled streptavidin. (B) B cells are stained with tetramer and a panel of monoclonal antibodies. Tetramer$^+$, class-switched memory B cells are single-cell sorted into PCR strips. (C) mRNA amplification is performed with T7 RNA polymerase. (D) Sequencing of PCR products is carried out using 300-400bp PCR products. (E) Overlap PCR is used for construction of full-length IgG1 heavy chain and kappa/lambda light sequences which are cloned into separate vectors. Vectors are transiently transfected into CHO-S cells for expression of fully human recombinant antibodies. (F) Antibodies are tested for antigen binding and assessed for potential therapeutic properties.
FIGs. 22A-22B | Graphs showing comparison of monomeric and tetrameric antigen for identification of memory B cells. (A) Mono-biotinylated TTCF or CD80 antigens were directly labeled with Alexa-488 fluorophore; tetramers were generated with unlabeled streptavidin. Enriched B cells from each donor were split into three fractions and stained with control CD80 tetramer, TTCF monomer, or TTCF tetramer at the same total antigen concentration of 0.125 μg/mL. FACS plots depict CD19$^+$ CD27$^+$ IgM$^-$class-switched memory B cells; numbers adjacent to the gate represent the percentage of the parental gate. (B) Frequencies of tetramer$^+$ memory B cells detected in three different

donors. Numbers are calculated as tetramer$^+$ cells per 1x10^6 CD19$^+$ memory B cells.

FIGs. 23A-23B | Line graphs showing high affinity binding of TTCF by antibodies generated from plasmablasts and memory B cells. Saturation binding experiments were carried out to determine the affinities of recombinant antibodies. TTCF antigen was labeled with europium, which emits a strong fluorescent signal at 615nm upon incubation with a chelating reagent. Antibodies were immobilized in a 96-well plate and incubated with TTCF-europium (100nM to 4pM) for two hours at 37°C. Fluorescent counts at 615nm were recorded and K_D calculated using non-linear regression analysis. Control antibody (clone 8.18.C5) that was also produced in CHO-S cells was included in all experiments. (A) Recombinant TTCF Abs 1 and 2 were generated from TTCF tetramer$^+$ plasmablasts (donor 1). (B) TTCF antibodies 3, 4, and 5 originated from TTCF tetramer$^+$ memory B cells of three different donors.

FIG. 24 | Bar chart showing binding of anti-MICA antibodies to MICA-coated luminex beads.

FIGs. 25A-25O | Line graphs showing binding of anti-MICA antibodies to MICA-coated beads.

FIGs 26A-26D | Bar graphs showing binding of four human angiopoietin 2 specific antibodies as well as a control antibody to three human angiopoietins (angiopoietin-1, 2 and 4) and ang-like-3. Recombinant angiopoietins were immobilized in an ELISA plate and binding of human recombinant antibodies was detected with europium-labeled streptavidin.

FIGs. 27A-27C | Show graphs and a gel relating to isolation of angiopoietin-specific antibodies from a lung cancer patient. (A) Angiopoietin-2 reactivity of lung cancer patient (L19) serum (diluted 1:1000) determined by ELISA. (B) FACS plot showing PBMC sample (timepoint- 10/98) gated on CD19$^+$, CD27$^+$ IgM-B cells with CD 19 on the X-axis and fluorescently-tagged angiopoietin-2 on the Y-axis. (C) Heavy, light chain, and hinge region PCR products from 10 angiopoietin-2 reactive memory B-cells isolated from patient L19. The 500 base pair marker is indicated on the left.

FIG. 28 | Nucleic acid sequence of the variable heavy (V_H) chain of antibody ID 6 (anti-MHC class I polypeptide-related sequence A (MICA) antibody) (SEQ ID NO:148).

FIG. 29 | Amino acid sequence of V_H chain of antibody 6 (anti-MICA antibody) (SEQ ID NO:149).

FIG. 30 | Nucleic acid sequence of the variable light (V_L) chain of antibody ID 6 (anti-MICA antibody) (SEQ ID NO:150).

FIG. 31 | Amino acid sequence of V_L chain of antibody ID 6 (anti-MICA antibody) (SEQ ID NO: 151).

FIG. 32 | Nucleic acid sequence of the variable heavy (V_H) chain of antibody ID 7 (anti-MHC class I polypeptide-related sequence A (MICA) antibody) (SEQ ID NO:167).

FIG. 33 | Amino acid sequence of V_H chain of antibody ID 7 (anti-MICA antibody) (SEQ ID NO:168).

FIG. 34 | Nucleic acid sequence of the variable light (V_L) chain of antibody ID 7 (anti-MICA antibody) (SEQ ID NO:169).

FIG. 35 | Amino acid sequence of V_L chain of antibody ID 7 (anti-MICA antibody) (SEQ ID NO: 170).

FIG. 36 | Nucleic acid sequence of the variable heavy (VH) chain of antibody ID 8 (anti-MHC class I polypeptide-related sequence A (MICA) antibody) (SEQ ID NO:185).

FIG. 37 | Amino acid sequence of VH chain of antibody ID 8 (anti-MICA antibody) (SEQ ID NO:186).

FIG. 38 | Nucleic acid sequence of the variable light (VL) chain of antibody ID 8 (anti-MICA antibody) (SEQ ID NO:187).

FIG. 39 | Amino acid sequence of VL chain of antibody ID 8 (anti-MICA antibody) (SEQ ID NO: 188).

FIG. 40 | Nucleic acid sequence of the variable heavy (V_H) chain of antibody ID 9 (anti-MHC class I polypeptide-related sequence A (MICA) antibody) (SEQ ID NO:203).

FIG. 41 | Amino acid sequence of V_H chain of antibody ID 9 (anti-MICA antibody) (SEQ ID NO:204).

FIG. 42 | Nucleic acid sequence of the variable light (V_L) chain of antibody ID 9 (anti-MICA antibody) (SEQ ID NO:205).

FIG. 43 | Amino acid sequence of V_L chain of antibody ID 9 (anti-MICA antibody) (SEQ ID NO: 206).

FIG. 44 | Nucleic acid sequence of the V_H chain of antibody ID 10 (anti-angiopoietin-2 antibody) (SEQ ID NO:221).

FIG. 45 | Amino acid sequence of V_H chain of antibody ID 10 (anti- angiopoietin-2 antibody) (SEQ ID NO:222).

FIG. 46 | Nucleic acid sequence of the V_L chain of antibody ID 10 (anti-angiopoietin-2 antibody) (SEQ ID NO:223).

FIG. 47 | Amino acid sequence of V_L chain of antibody ID 10 (anti- angiopoietin-2 antibody) (SEQ ID NO:224).

FIGs. 48A-G | Line graphs showing assessment of MICA allele-specific binding by recombinant anti-MICA antibodies.

FIG. 49 | Line graph showing labeling of autologous tumor cells by anti-MICA antibody CM24002 Ab2.

FIG. 50 | A series of FACS plot showing regulation of NKG2D by serum MICA. Human NK cells were incubated with control serum from patient CM24002 and a 1:10 dilution for 48 hours. Indicated antibodies were added at the start of the incubation at a concentration of 10 μg/ml. NKG2D expression was assessed on CD56+ NK cells by flow cytometry.

FIG. 51 | A series of FACS plot showing regulation of NKG2D by recombinant MICA. Human NK cells were incubated with recombinant MICA at a concentration of 2 ng/ml for 48 hours. Indicated antibodies were added at the start of the incubation at a concentration of 10 μg/ml. After 48 hours, NKG2D expression was assessed on CD56+ NK cells by flow cytometry.

FIG. 52 | Line graph demonstrating enhancement of cell-mediated toxicity by anti-MICA antibody CM24002 Ab2. Human NK cells were incubated with recombinant MICA (2ng/ml) for 48 hours in the presence of indicated antibodies at 10 μg/ml. The ability of NK cells (effectors) to kill K562 target cells was assessed by measuring LDH release following 4 hour incubation at the indicated ratios.

FIG. 53 | Bar graph demonstration cell-mediated toxicity by anti-MICA antibodies CM24002 Ab2 and CM33322 Ab29. Human NK cells were incubated with recombinant MICA (2ng/ml) for 48 hours in the presence of indicated antibodies at 10 μg/ml. The ability of NK cells (effectors) to kill K562 target cells was assessed by measuring LDH release following 4 hour incubation. NKG2D blocking antibody or Fc blocking antibody was added during the 4 hr incubation of effector and target cells to assess the contribution of Fc receptor and NKG2D to cell-mediated toxicity.

FIG. 54 | A series of line graphs showing binding of MICA alpha 3 domain by recombinant anti-MICA antibodies. Recombinant MICA alpha 3 domains were biotinylated and captured on the surface of streptavidin-coated beads. Indicated antibodies were incubated at 10μg/ml with the beads coated with the individual recombinant protein for 1hr. Beads were subsequently washed and incubated with FITC-conjugated anti-human IgG secondary antibody. FITC fluorescence was quantified by flow cytometry.

FIG. 55 | Line graphs demonstrating labeling of tumor cells by anti-MICA antibodies CM24002 Ab2 and CM33322 Ab29. Fluorescence was determined by flow cytometry.

FIG. 56 | Bar graph demonstrating MICA allelic specificity of anti-MICA antibodies CM33322 Ab29 as determined by Luminex assay.

FIG. 57 | Bar graphs showing binding of anti-angiopoietin 2 specific antibody anti-Ang6 Ab2 as well as a control antibody to three human angiopoietins (angiopoietin-1, 2 and 4) and ang-like-3. Recombinant angiopoietins were immobilized in an ELISA plate and binding of human recombinant antibodies was detected with europium-labeled streptavidin.

DETAILED DESCRIPTION

[0028] The present disclosure is based, in part, on the observation that antibodies directed against therapeutic targets important in a disease can be obtained from human subjects exposed to the disease by labeling of B cells with a tetrameric form of the antigen of interest. As described in the background section above, prior methods are limited at least in that they are inefficient at identifying appropriate B cells in human subjects and/or because they induce any captured B cells to undergo phenotypic changes, thus reducing their value. In contrast, methods are described herein that allow capture of rare memory B cells directed against specific disease-related antigens. As described below, the methods require tetramerization of the disease-related antigen, which process, as demonstrated in the Examples below, enhances the identification of appropriate memory B cells. Specifically, methods herein permit more efficient capture of appropriate memory B cells for increased periods of time following initial exposure of a subject to the antigen. Methods herein also include antibodies (and peptides generated from the sequences of such antibodies) generated using genetic material obtained from memory B cells captured using the methods described herein.

[0029] Described herein are human antibodies against MHC class I polypeptide-related sequence A (MICA) and human antibodies targeted against angiopoietin-2. Both types of human antibodies were identified from patients who had received a cell-based cancer vaccine (GM-CSF transduced autologous tumor cells) by methods that entail the use of tetrameric antigens.

[0030] Methods for specifically obtaining or targeting antibodies with therapeutic potential from select human subjects and therapeutic compositions resulting therefrom are described herein. These methods can include: obtaining or targeting immune cells in a human subject, wherein immune cells include but are not limited to, for example, B cells and/or memory B cells, isolating or purifying genetic material (e.g., DNA and/or mRNA) from the obtained or targeted immune cells, and using the isolated or purified genetic material to produce therapeutic compositions, e.g., therapeutic compositions disclosed herein. Further description of the methods is provided under the section entitled "Methods," below.

[0031] Therapeutic compositions (e.g., including therapeutic peptides, including antibodies, antibody fragments, antibody derivatives, and/or antibody conjugates) related to antibodies present in subjects that have or had a condition or disease and that exhibited a positive immune response towards the condition or disease are also described herein.

Therapeutic Compositions

[0032] In some instances, therapeutic compositions herein can interact with (e.g., bind, bind specifically and/or bind immunospecifically) binding partners (e.g., an immunogen(s), antigen(s), and/or epitope(s)) related to a disease or condition, wherein interaction between the therapeutic composition and the binding partners results in a positive immune response towards the condition or disease (e.g., a decrease in the level of disease or symptoms thereof in a subject).

[0033] In some instances, therapeutic compositions can include peptides that include (e.g., comprise, consist essentially of, or consist of) at least one (e.g., one, two, three, four, five, and/or six) complementarity determining region (CDR) of the variable heavy chain (V_H) and/or variable light chain (V_L) of antibody ID 1, 2, 3, 4, or 5, 5, 7, 8, 9 or 10, shown in Table 1.

[0034] In some instances, therapeutic compositions can include peptides that include (e.g., comprise, consist essentially of, or consist of) at least one (e.g., one, two, three, four, five, and/or six) complementarity determining region (CDR) of the variable heavy chain (VH) and/or variable light chain (VL) of antibody ID 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, shown in Table 1, and that interact with (e.g., bind, bind specifically and/or bind immunospecifically) to MHC class I polypeptide-related sequence A (MICA (e.g., UniGene Hs.130838)) (e.g., soluble MICA (sMICA)) and/or angiopoietin-2 (e.g., UniGene Hs.583870), including epitopes thereof.

[0035] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, peptides can include at least two CDRs, wherein the at least two CDRs are CDRs shown in Table 1 for different antibodies.. In other words, CDRs (and FRs and/or AA sequences) shown in Table 1 for antibodies IDs 1, 6, 7, 8 and 9 are interchangeable and can be combined to generate peptides, so long as the peptides bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 1, 6, 7, 8 and/or 9 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9 shown in Table 1. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 1, 6, 7, 8 and/or 9, shown in Table 1. In some instances, such peptides include one of SEQ ID NO:2, 149, 168, 186 or 204 and/or one of SEQ ID NO:11, 151, 170, 188, or 206. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, the affinity of binding between the peptides and MICA can be between about 0.1nM to 1μM, for example, about 10nM.

[0036] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 6 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 6 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 6 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 6 shown in Table 1. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 6. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 6 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 6, shown in Table 1. In some instances, such peptides include SEQ ID NO:149 and/or SEQ ID NO:151. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, the affinity of binding between the peptides and MICA can be between about 0.1nM to 1μM, for example, about 10nM.

[0037] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 7 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 7 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 7 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 7 shown in Table 1. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 7. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 7 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 7, shown in Table 1. In some instances, such peptides include SEQ ID NO:168 and/or SEQ ID NO:170. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, the affinity of binding between the peptides and MICA can be between about 0.1nM to 1μM, for example, about 10nM.

[0038] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 8 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 8 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 8 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 8 shown in Table 1. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 8. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 8 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 8, shown in Table 1. In some instances, such peptides include SEQ ID NO:186 and/or SEQ ID NO:188. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, the affinity of binding between the peptides and MICA can be between about 0.1nM to 1μM, for example, about 10nM.

[0039] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 9 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 9 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 9 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 9 shown in Table 1. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 9. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 9 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 9, shown in Table 1. In some instances, such peptides include SEQ ID NO:204 and/or SEQ ID NO:206. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to MICA (e.g., human MICA (e.g., soluble MICA (sMICA))). In some instances, the affinity of binding between the peptides and MICA can be between about 0.1nM to 1μM, for example, about 10nM.

[0040] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, peptides can include at least two CDRs, wherein the at least two CDRs are CDRs shown in Table 1 for different antibodies. In other words, CDRs (and FRs and/or AA sequences) shown in Table 1 for antibodies IDs 2, 3 4, 5, and 10 are interchangeable and can be combined to generate peptides, so long as the peptides bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 2, 3, 4, 5, and/or 10 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 2, 3, 4, 5, and/or 10 5, shown in Table 1. In some instances, such peptides include one of SEQ ID NO:20, 38, 56, 74, or 222 and/or one of SEQ ID NO:29, 47, 65, 83 or 224. In some instances, peptides include one of SEQ ID NO:20, 38, 56, 74, or 222 and one of SEQ ID NO:29, 47, 65, 83 or 224. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2 (e.g, UniGene Hs.583870)).

[0041] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 2 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 2 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 2 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 2 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 2. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 2 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 2, shown in Table 1. In some instances, such peptides include SEQ ID NO:20 and/or SEQ ID NO:29. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, the affinity of binding between the peptides and angiopoietin-2 can be between about 0.1nM to 1μM, for example, about 10nM.

[0042] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 3 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 3 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 3 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 3 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 3. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 3 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 3, shown in Table 1. In some instances, such peptides include SEQ ID NO:38 and/or SEQ ID NO:47. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, the affinity of binding between the peptides and angiopoietin-2 can be between about 0.1nM to 1μM, for example, about 10nM.

[0043] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 4 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 4 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 4 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 4 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 4. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 4 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 4, shown in Table 1. In some instances, such peptides include SEQ ID NO:56 and/or SEQ ID NO:65. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, the affinity of binding between the peptide and angiopoietin-2 can be between X-Y, for example, X-Y, X-Y. In some instances, the affinity of binding between the peptides and angiopoietin-2 can be between about 0.1nM to 1μM, for example, about 10nM.

[0044] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 5 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 5 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 5 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 5 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 5. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 5 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 5, shown in Table 1. In some instances, such peptides include SEQ ID NO:74 and/or SEQ ID NO:83. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, the affinity of binding between the peptides and angiopoietin-2 can be between about 0.1nM to 1μM, for example, about 10nM.

[0045] In some instances, therapeutic compositions can include peptides that include at least one CDR of the V_H and/or V_L of antibody ID 10 shown in Table 1, wherein the peptide binds (e.g., binds specifically and/or binds immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, such peptides include CDR3 of the V_H and/or V_L of antibody ID 10 shown in Table 1. In some instances, such peptides include CDR3 of the V_H and V_L of antibody ID 10 and CDR1 and/or CDR2 of the V_H and/or V_L of antibody ID 10 shown in Table 1. In some instances, such peptides include CDR1, CDR2, and CDR3 of the V_H and/or V_L of antibody ID 10. In some instances, such peptides include CDR1 CDR2, and CDR3 of the V_H and/or V_L of antibody ID 10 and at least one of FR1 FR2 FR3, and/or FR4 of the V_H and/or V_L of antibody ID 10, shown in Table 1. In some instances, such peptides include SEQ ID NO:222 and/or SEQ ID NO:224. In each instance, the peptide can bind (e.g., bind specifically and/or bind immunospecifically) to angiopoietin-2 (e.g., human angiopoietin-2). In some instances, the affinity of binding between the peptides and angiopoietin-2 can be between about 0.1nM to 1μM, for example, about 10nM.

[0046] In some instances, peptides that bind to angiopoietin-2 can also bind to angiopoietin-1 (e.g., Unigene Hs.369675) and/or angiopoietin-4 (e.g., Unigene Hs.278973). For example, in some instances, peptides that bind to angiopoietin-2 can also bind specifically and/or immunospecifically relative to other antigens (other than angiopoietin-1) to angiopoietin-1. In some instances, peptides that bind to angiopoietin-2 can also bind specifically and/or immunospecifically relative to other antigens (other than angiopoietin-4) to angiopoietin-4.

[0047] In some instances, therapeutic compositions can include peptides that include: SEQ ID NO: 2 and/or SEQ ID NO:11; SEQ ID NO: 149 and/or SEQ ID NO:151; SEQ ID NO: 168 and/or SEQ ID NO:170; SEQ ID NO: 186 and/or SEQ ID NO:188; SEQ ID NO: 204 and/or SEQ ID NO:206; SEQ ID NO:20 and/or SEQ ID NO:29; SEQ ID NO:38 and/or SEQ ID NO:47; SEQ ID NO:56 and/or SEQ ID NO:65; SEQ ID NO:74 and/or SEQ ID NO:83; and SEQ ID NO: 222 and/or SEQ ID NO:224.

TABLE 1

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
1	Human MICA	V_H	QVQLQQ W GAGLLKP SETLALT CAVS (SEQ ID NO: 3)	GGSFTDH Y (SEQ ID NO: 4)	WSWIR QAPGK GLEWIGE (SEQ ID NO: 5)	INHSGVT (SEQ ID NO: 6)	NYNPS LKSRLT ISVDTS KSQFSL RLTSVT AADTA LYYC (SEQ ID NO: 7)	AKTG LYYD DVW GTFR PRGG FDS (SEQ ID NO: 8)	WGQGT LVTVSS (SEQ ID NO: 9)	SEQ ID NO: 2 (see FIG. 2)	SEQ ID NO: 1 (see FIG. 1)
		V_L	DIVMTQS PD SLAVSLG ERATINC KSS (SEQ ID NO: 12)	QSILYSSD NKNY (SEQ ID NO: 13)	LAWYQ HKPGQPP KLLFY (SEQ ID NO: 14)	WAS (SEQ ID NO: 15)	IRESG VPDRF SGGGSGT DFTLT ISSLQA EDVAV YYC (SEQ ID NO: 16)	QQYYSP PCS (SEQ ID NO: 17)	FGQGTK LEIQ (SEQ ID NO: 18)	SEQ ID NO: 11 (see FIG. 4)	SEQ ID NO: 10 (see FIG. 3)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.[#]	Nuc. Acid [##]
6	Human MICA	V_H	QVQLQES GPGLVEP SGTLSLT CTVS (SEQ ID NO: 152)	GGSISRS NW (SEQ ID NO: 153)	WSWVRQ PPGEGLE WIGE (SEQ ID NO: 154)	IHHIGRS (SEQ ID NO: 156)	SYNPSLK SRVTMS VDKSQN QFSLRLT SVTAAD TAVYY (SEQ ID NO: 157)	CAKNGYY AMDVW (SEQ ID NO: 158)	GQGTTVT VSS (SEQ ID NO: 155)	SEQ ID NO: 149 (see FIG. 28)	SEQ ID NO: 148 (see FIG. 29)
		V_L	EIVLTQS PGTLSLS PGERATL SCRAS (SEQ ID NO: 159)	QSVSSDF (SEQ ID NO: 160)	LAWYQQ KPGQAPR LLIY (SEQ ID NO: 161)	ATS (SEQ ID NO: 162)	FRATGIS DRFSGSG SGTDFSL TINRLEP EDFAVYY (SEQ ID NO: 163)	CQHYRSS PPWYTF (SEQ ID NO: 164)	AQGTKL DMRRTV AAPSV (SEQ ID NO: 165)	SEQ ID NO: 151 (see FIG. 31)	SEQ ID NO: 150 (see FIG. 30)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.[#]	Nuc. Acid [##]
7	Human MICA	V_H	QVQLQES GPGLVKP SGTLSLT CAVS (SEQ ID NO: 171)	GASITNG AW (SEQ ID NO: 172)	WSWVRQ PPGKGLE WIGE (SEQ ID NO: 173)	IYLNGNT (SEQ ID NO: 174)	NSNPSLK SRVIISVD KSKNHFS LTLNSVT AADTAV YY (SEQ ID NO: 166)	CAKNAAY NLEFW (SEQ ID NO: 176)	GQGALVT VSS (SEQ ID NO: 177)	SEQ ID NO: 168 (see FIG. 33)	SEQ ID NO: 167 (see FIG. 32)
		V_L	EIVLTQS PGTLSLS PGERATL SCRAS (SEQ ID NO: 178)	QTVSSPY (SEQ ID NO: 179)	VAWYQQ KRGQAP RLLIY (SEQ ID NO: 180)	GAS (SEQ ID NO: 181)	TRATGIP DRFSGSG SGTDFTL TISRLEP EDFAVYY (SEQ ID NO: 182)	CQQYDRS YYYTF (SEQ ID NO: 183)	GQGTKLE IK (SEQ ID NO: 184)	SEQ ID NO: 170 (see FIG. 35)	SEQ ID NO: 169 (see FIG. 34)

(continued)

ID	Target	VH | VL	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
8	Human MICA	V_H	QVQLQESGPGLVKPSENLSLTCTVS (SEQ ID NO: 189)	DASMSDYH (SEQ ID NO: 190)	WSWIRQAAGKGLEWIGR (SEQ ID NO: 191)	MYSTGSP (SEQ ID NO: 192)	YYKPSLKGRVTMSIDTSKNQFSLKLASVTAADTAIYY (SEQ ID NO: 193)	CASGQHIGGWVPPDFW (SEQ ID NO: 194)	GQGTLVTVSS (SEQ ID NO: 195)	SEQ ID NO: 186 (see FIG. 37)	SEQ ID NO: 185 (see FIG. 36)
		V_L	DIVMTQTPLSSPVTLGQPASISCRSS (SEQ ID NO: 196)	EGLVYSDGDTY (SEQ ID NO: 197)	LSWFHQRPGQPPRLLIY (SEQ ID NO: 198)	KIS (SEQ ID NO: 199)	NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYY (SEQ ID NO: 200)	CMQATHFPWTF (SEQ ID NO: 201)	GQGTKVEVKR (SEQ ID NO: 202)	SEQ ID NO: 188 (see FIG. 39)	SEQ ID NO: 187 (see FIG. 38)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
9	Human MICA	V_H	EVQLLES GGGLVQP GGSLRLS CAAS (SEQ ID NO: 207)	GFTFSSY G (SEQ ID NO: 208)	LTWIRQA PGKGLE WVSS (SEQ ID NO: 209)	ISGSGNNT (SEQ ID NO: 210)	YYADSVK GRFTISR DKVKKT LYLQMD SLTVGDT AVYY (SEQ ID NO: 211)	CLGVGQ (SEQ ID NO: 212)	GHGIPVI VSS (SEQ ID NO: 213)	SEQ ID NO: 204 (see FIG. 41)	SEQ ID NO: 203 (see FIG. 40)
		V_L	DIVMTQT PLSSPVT LGQPASI SCRSS (SEQ ID NO: 214)	QSLVHRD GNTY (SEQ ID NO: 215)	LSWFLQ RPGQAPR LLIY (SEQ ID NO: 216)	RIS (SEQ ID NO: 217)	NRFSGVP DRFSGSG AGTDFTL KISRVEA EDVGVY Y (SEQ ID NO: 218)	CMQATQI PNTF (SEQ ID NO: 219)	GQGTKLE IK (SEQ ID NO: 220)	SEQ ID NO: 206 (see FIG. 43)	SEQ ID NO: 205 (see FIG. 42)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
2	Angiopoietin-2	V_H	EVQLVES GGGLVQP GGSLRLS CAAS (SEQ ID NO: 21)	GFTFSSY A (SEQ ID NO: 22)	MSWVRQ APGKGLE WVSG (SEQ ID NO: 23)	IYWSGGS T (SEQ ID NO: 24)	YYADSVK GRFTI SRDISKN TLYLQM NSLRAD D TAVYYC (SEQ ID NO: 25)	ARGDYYG SGAHFDY (SEQ ID NO: 26)	WGQGTL VTVSS (SEQ ID NO: 27)	SEQ ID NO: 20 (see FIG. 6)	SEQ ID NO: 19 (see FIG. 5)
		V_L	DIVMTQT PLSSPVT LGQPASI SCRSS (SEQ ID NO: 30)	QSLVHSD GNTY (SEQ ID NO: 31)	LSWLQQ RPGQPPR LLIY (SEQ ID NO: 32)	QIS (SEQ ID NO: 33)	NRFSGVP DRFSGS GAGTDF TLKISRV EAEDVG V YYC (SEQ ID NO: 34)	MQGTQF PRT (SEQ ID NO: 35)	FGQGTKV EIK (SEQ ID NO: 36)	SEQ ID NO: 29 (see FIG. 8)	SEQ ID NO: 28 (see FIG. 7)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
3	Angiopoietin-2	V_H	EVQLVES GGGLVQP GGSLRLS CAAS (SEQ ID NO: 39)	GFTFSNN W (SEQ ID NO: 40)	MHWVR QAPGKGL EWISE (SEQ ID NO: 41)	IRSDGNF T (SEQ ID NO: 42)	RYADSM KGRFTI SRDNAK STLYLQ MNSLRV ED TGLYYC (SEQ ID NO: 43)	ARDYPYS IDY (SEQ ID NO: 44)	WGQGTL VTVSS (SEQ ID NO: 45)	SEQ ID NO: 38 (see FIG. 10)	SEQ ID NO: 37 (see FIG. 9)
		V_L	DIVMTQT PLSSPVT LGQPASI SCTSS (SEQ ID NO: 48)	QSLVHSN GNTY (SEQ ID NO: 49)	LSWLQQ RPGQPPR LLIY (SEQ ID NO: 50)	EIS (SEQ ID NO: 51)	KRVSGVP DRFSGSG AGTDFTL KISRVEA EDVGVY YC (SEQ ID NO: 52)	MQGKQL RT (SEQ ID NO: 53)	FGQGTKL EIK (SEQ ID NO: 54)	SEQ ID NO: 47 (see FIG. 12)	SEQ ID NO: 46 (see FIG. 11)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
4	Angiopoietin-2	V_H	EVQLVES GGGLVQP GGSVRLS CAAS (SEQ ID NO: 57)	GFILSNF A (SEQ ID NO: 58)	MSWVRQ A PGKGLD WVSG (SEQ ID NO: 59)	NFGGRE NT (SEQ ID NO: 60)	YY ADSVKG RFTI SRDSSKS TLYLQM NNLRAE D TAVYYC (SEQ ID NO: 61)	ARGD YHGSGAH FDY (SEQ ID NO: 62)	WGQGILV TVSS (SEQ ID NO: 63)	SEQ ID NO: 56 (see FIG. 14)	SEQ ID NO: 55 (see FIG. 13)
		V_L	DIVMTQS PLS SPVILGQ PASISCRS S (SEQ ID NO: 66)	QSLL HSDGNT Y (SEQ ID NO: 67)	LSWLHQ RPGQPPR LLIY (SEQ ID NO: 68)	QIS (SEQ ID NO: 69)	NRF SGVPDRF SGS GTGTDF TLKISRV EAEDAGI YYC (SEQ ID NO: 70)	MQGTEFP RT (SEQ ID NO: 71)	FGQGTKV E IK (SEQ ID NO: 72)	SEQ ID NO: 65 (see FIG. 16)	SEQ ID NO: 64 (see FIG. 15)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
5	Angiopoietin-2	V_H	EVQLVES GGG LIQPGGS LRLSCAT S (SEQ ID NO: 75)	GFTFR TSS (SEQ ID NO: 76)	MSWVRR A PGKGLE WVSA (SEQ ID NO: 77)	IGAESHD T (SEQ ID NO: 78)	HY TDSAEG RFTI SKDYSK NTVYLQ MNGLRV DD TAIYYC (SEQ ID NO: 79)	AHHYYYG SRQKPKD WGDAFD M (SEQ ID NO: 80)	WGQ GTMVSVS S (SEQ ID NO: 81)	SEQ ID NO: 74 (see FIG. 18)	SEQ ID NO: 73 (see FIG. 17)
		V_L	DIQMTQS PSS VSASVGD RVTITCR AS (SEQ ID NO: 84)	QDIS TW (SEQ ID NO: 85)	LTWYQQ RAGKAP NLLIY (SEQ ID NO: 86)	GAS (SEQ ID NO: 87)	TLEDGVP S RFSGSGS GTD FTLTIDS LQPDDF ATYYC (SEQ ID NO: 88)	QQ SHSFPYT (SEQ ID NO: 89)	FGQ GTQLGIS (SEQ ID NO: 90)	SEQ ID NO: 83 (see FIG. 20)	SEQ ID NO: 82 (see FIG. 19)

(continued)

ID	Target	V_H | V_L	FR1*	CDR1**	FR2*	CDR2**	FR3*	CDR3**	FR4*	A.A.#	Nuc. Acid ##
10	Angiopoietin-2	V_H	EVQLVES GGGLIQP GGSLRLS CAAS (SEQ ID NO: 225)	GFLISSYF (SEQ ID NO: 226)	MSWVRQ APGKGPE WVSV (SEQ ID NO: 227)	IYSDGST (SEQ ID NO: 228)	YYVDSVK GRFTIST DNSKNT LYLQMN SLRAEDT ARYY (SEQ ID NO: 229)	CATRHLN YDGDHW (SEQ ID NO: 230)	GQGTLVT VSSASTK (SEQ ID NO: 175)	SEQ ID NO: 222 (see FIG. 45)	SEQ ID NO: 221 (see FIG. 44)
		V_L	DVVMTQ SPLSLPV TLGQPAS ISCRSS (SEQ ID NO: 231)	QSLVHSD GNTY (SEQ ID NO: 232)	LNWFHQ RPGQSPR RLIY (SEQ ID NO: 233)	KVS (SEQ ID NO: 234)	KRDSGV PDRFSGS GSGSDFT LKISRVE AEDVGIY Y (SEQ ID NO: 235)	CMQGTH WPTF (SEQ ID NO: 236)	GQGTKVE IKRTVAA (SEQ ID NO: 237)	SEQ ID NO: 224 (see FIG. 47)	SEQ ID NO: 223 (see FIG. 46)

* Sequences include sequences or variants with (e.g., with at least) 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, and/or 100% sequence identity to the sequences shown.
** Sequences can include one, two, three, four, five, less than five, or less than ten conservative amino acid modifications.
# Sequences include sequences or variants with (e.g., with at least) 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, and/or 100% sequence identity to the sequences shown, e.g., within regions corresponding to FR1, FR2, FR3, and/or FR4, and/or one, two, three, four, five, less than 5, or less than ten conservative amino acid modifications within regions corresponding to CDRs 1, 2, and/or 3.
Sequences include sequences or variants with (e.g., with at least) 80%, 85%, 90%, 95%, 96%, 97%, 98, 99%, and/or 100% sequence identity to the sequences shown, wherein the sequences encode the corresponding AA.
A.A.# shows the V_H or V_L amino acid sequence.
Nuc. Acid ## shows the V_H or V_L nucleic acid sequence.

[0048] While CDR and FR regions are shown above, such regions can also be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)). Amino acid numbering of antibodies or antigen binding fragments is also according to that of Kabat.

[0049] In some instances, therapeutic compositions can include peptides, including for example, antibodies, including full length and/or intact antibodies, or antibody fragments. An "antibody" is an immunoglobulin molecule 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 region of the immunoglobulin molecule. As used herein, the term "antibody" encompasses not only intact polyclonal or monoclonal antibodies, but also any antigen binding fragment (i.e., "antigen-binding portion") or single chain thereof, fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site including. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Exemplary antibodies and antibody fragments include, but are not limited to, monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, multispecific antibodies formed from at least two different epitope binding fragments (e.g., bispecific antibodies), camelised antibodies, chimeric antibodies, single-chain Fvs (scFv), single-chain antibodies, single domain antibodies, domain antibodies, Fab fragments, F(ab')2 fragments, antibody fragments that exhibit the desired biological activity (e.g. the antigen binding portion), disulfide-linked Fvs (dsFv), and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies useful in the invention), intrabodies, and epitope-binding fragments of any of the above. Antibodies or antibody fragments can be human or humanized.

[0050] Fragments of antibodies are suitable for use in the methods described herein so long as they retain the desired affinity and specificity of the full-length antibody. Thus, a fragment of an anti- MICA antibody or the anti-Angiopoietin antibody will retain an ability to bind to MICA or angiopoietin, respectively, in the Fv portion and the ability to bind the Fc receptor on dendritic cells in the FC portion. Such fragments are characterized by properties similar to the corresponding full-length anti-MICA antibody or the anti-Angiopoietin antibody, that is, the fragments will specifically bind a human MICA antigen or the angiopoietin antigen, respectively, expressed on the surface of a human cell or the corresponding sMICA antigen that has been shed into the media.

[0051] An Fv fragment is an antibody fragment which contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in tight association, which can be covalent in nature, for example in scFv. It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the VH-VL dimer. Collectively, the six CDRs or a subset thereof confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) can have the ability to recognize and bind antigen, although usually at a lower affinity than the entire binding site.

[0052] Single-chain Fv or (scFv) antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Generally the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains, which enables the scFv to form the desired structure for antigen binding.

[0053] The Fab fragment contains a variable and constant domain of the light chain and a variable domain and the first constant domain (CH1) of the heavy chain. F(ab')2 antibody fragments comprise a pair of Fab fragments which are generally covalently linked near their carboxy termini by hinge cysteines between them. Other chemical couplings of antibody fragments are also known in the art.

[0054] Diabodies are small antibody fragments with two antigen-binding sites, which fragments comprise a V_H connected to a V_L in the same polypeptide chain (V_H and V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites.

[0055] Linear antibodies comprise a pair of tandem Fd segments (V_H-CH1-V_H-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

[0056] Antibodies and antibody fragments useful in the present invention can be modified in the Fc region to provide desired effector functions or serum half-life. In some instances, the Fc region can be conjugated to PEG or albumin to increase the serum half-life, or some other conjugation that results in the desired effect. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, certain other Fc regions may be used.

[0057] Human and humanized antibodies include antibodies having variable and constant regions derived from (or having the same amino acid sequence as those derived from) human germline immunoglobulin sequences. Human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3.

[0058] A "CDR" of a variable domain are amino acid residues within the hypervariable region that are identified in accordance with the definitions of the Kabat, Chothia, the cumulation of both Kabat and Chothia, AbM, contact, and/or conformational definitions or any method of CDR determination well known in the art. Antibody CDRs may be identified as the hypervariable regions originally defined by Kabat et al. See, e.g., Kabat et al., 1992, Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, NIH, Washington D.C. The positions of the CDRs may also be identified as the structural loop structures originally described by Chothia and others. See, e.g., Chothia et al., 1989, Nature 342:877-883. Other approaches to CDR identification include the "AbM definition," which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now Accelrys®), or the "contact definition" of CDRs based on observed antigen contacts, set forth in MacCallum et al., 1996, J. Mol. Biol., 262:732-745. In another approach, referred to herein as the "conformational definition" of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., 2008, Journal of Biological Chemistry, 283:1156-1166. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, AbM, contact, and/or conformational definitions.

[0059] In some instances, amino acid sequences of the peptides disclosed herein can be modified and varied to create peptide variants (e.g., peptides with a defined sequence homology to the peptides disclosed herein), for example, so long as the antigen binding property of the peptide variant is maintained or improved relative to the unmodified peptide (antigen binding properties of any modified peptide can be assessed using the in vitro and/or in vivo assays described herein and/or techniques known in the art).

[0060] While peptide variants are generally observed and discussed at the amino acid level, the actual modifications are typically introduced or performed at the nucleic acid level. For example, variants with 80%, 85%, 90%, 95%, 96%, 97%, 98, or 99% amino acid sequence identity to the peptides shown in Table 1 can be generated by modifying the nucleic acids encoding SEQ ID NOs:1, 10, 19, 28, 37, 46, 55, 64, 73, and/or 82 or portions/fragments thereof, using techniques (e.g., cloning techniques) known in the art and/or that are disclosed herein.

[0061] Amino acid sequence modifications typically fall into one or more of three classes: substitutional, insertional, or deletional modifications. Insertions include amino and/or terminal fusions as well as intra-sequence insertions of single or multiple amino acid residues. Insertions ordinarily will be smaller insertions than those of amino or carboxyl terminal fusions, for example, on the order of one to four residues. Deletions are characterized by the removal of one or more amino acid residues from the protein sequence. Typically, no more than about from 2 to 6 residues are deleted at any one site within the protein molecule. Amino acid substitutions are typically of single residues, but can occur at a number of different locations at once; insertions usually will be on the order of about from 1 to 10 amino acid residues; and deletions will range about from 1 to 30 residues. Deletions or insertions can be made in adjacent pairs, i.e., a deletion of 2 residues or insertion of 2 residues. Substitutions, deletions, insertions or any combination thereof may be combined to arrive at a final construct. The mutations must not place the sequence out of reading frame and preferably will not create complementary regions that could produce secondary mRNA structure. Substitutional modifications are those in which at least one residue has been removed and a different residue inserted in its place. In some instances, substitutions can be conservative amino acid substitutions. In some instances, peptides herein can include one or more conservative amino acid substitutions relative to a peptide shown in Table 1. For example, variants can include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 20-30, 30-40, or 40-50 conservative amino acid substitutions relative to a peptide shown in Table 1. Alternatively, variants can include 50 or fewer, 40 or fewer, 30 or fewer, 20 or fewer, 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, or 2 or fewer conservative amino acid substitutions relative to a peptide shown in Table 1. Such substitutions generally are made in accordance with the following Table 2 and are referred to as conservative substitutions. Methods for predicting tolerance to protein modification are known in the art (see, e.g., Guo et al., Proc. Natl. Acad. Sci., USA, 101(25):9205-9210 (2004)).

Table 2: Conservative Amino Acid Substitutions

Amino Acid	Substitutions (others are known in the art)
Ala	Ser, Gly, Cys
Arg	Lys, Gln, His
Asn	Gln, His, Glu, Asp

(continued)

Amino Acid	Substitutions (others are known in the art)
Asp	Glu, Asn, Gln
Cys	Ser, Met, Thr
Gln	Asn, Lys, Glu, Asp, Arg
Glu	Asp, Asn, Gln
Gly	Pro, Ala, Ser
His	Asn, Gln, Lys
Ile	Leu, Val, Met, Ala
Leu	Ile, Val, Met, Ala
Lys	Arg, Gln, His
Met	Leu, Ile, Val, Ala, Phe
Phe	Met, Leu, Tyr, Trp, His
Ser	Thr, Cys, Ala
Thr	Ser, Val, Ala
Trp	Tyr, Phe
Tyr	Trp, Phe, His
Val	Ile, Leu, Met, Ala, Thr

[0062] In some instances, substitutions are not conservative. For example, an amino acid in a peptide shown in Table 1 can be replaced with an amino acid that can alter some property or aspect of the peptide. In some instances, non-conservative amino acid substitutions can be made, e.g., to change the structure of a peptide, to change the binding properties of a peptide (e.g., to increase or decrease the affinity of binding of the peptide to an antigen and/or to alter increase or decrease the binding specificity of the peptide to the antigen).

[0063] In some instances, peptides and/or peptide variants can include or can be fragments of the peptides shown in Table 1. Such fragments can include, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 50-100, 101-150, fewer amino acids than the CDRs, FRs, and/or AAs shown in Table 1, e.g., so long as the fragments retain at least at portion of the binding properties of the full-length peptide (e.g., at least 50%, 60%, 70%, 80%, 90%, or 100% of the binding properties of the full-length peptide). Truncations can be made at the amino-terminus, the carboxy-terminus, and/or within the peptides herein.

[0064] In some instances, the interacting face of a peptide variant can be the same (e.g., substantially the same) as an unmodified peptide, e.g., to alter (e.g., increase or decrease), preserve, or maintain the binding properties of the peptide variant relative to the unmodified peptide. Methods for identifying the interacting face of a peptide are known in the art (Gong et al., BMC: Bioinformatics, 6:1471-2105 (2007); Andrade and Wei et al., Pure and Appl. Chem., 64(11):1777-1781 (1992); Choi et al., Proteins: Structure, Function, and Bioinformatics, 77(1):14-25 (2009); Park et al., BMC: and Bioinformatics, 10:1471-2105 (2009).

[0065] Those of skill in the art readily understand how to determine the identity of two polypeptides (e.g., an unmodified peptide and a peptide variant). For example, identity can be calculated after aligning the two sequences so that the identity is at its highest level. Another way of calculating identity can be performed by published algorithms. Optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman, Adv. Appl. Math, 2:482 (1981), by the identity alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman, Proc. Natl. Acad. Sci. USA 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection.

[0066] The same types of identity can be obtained for nucleic acids by, for example, the algorithms disclosed in Zuker, Science 244:48-52 (1989); Jaeger et al., Proc. Natl. Acad. Sci. USA 86:7706-10 (1989); Jaeger et al., Methods Enzymol. 183:281-306 (1989). It is understood that any of the methods typically can be used and that in certain instances the results of these various methods may differ, but the skilled artisan understands if identity is found with at least one of these methods, the sequences would be said to have the stated identity and to be disclosed herein.

[0067] In some instances, as described in more detail under the methods section below, therapeutic compositions disclosed herein can be produced using genetic material (e.g., DNA and/or mRNA) isolated and/or purified from immune cells (e.g., B cells, including memory B cells) obtained using the methods disclosed herein. Once such genetic material has been obtained, methods for using it to produce the therapeutic compositions disclosed herein are known in the art and/or are summarized below.

[0068] In some instances, peptides can include a detectable label. As used herein, a "label" refers to a moiety that has at least one element, isotope, or functional group incorporated into the moiety which enables detection of the peptide to which the label is attached. Labels can be directly attached (ie, via a bond) or can be attached by a linker (e.g., such as, for example, a cyclic or acyclic, branched or unbranched, substituted or unsubstituted alkylene; cyclic or acyclic, branched or unbranched, substituted or unsubstituted alkenylene; cyclic or acyclic, branched or unbranched, substituted or unsubstituted alkynylene; cyclic or acyclic, branched or unbranched, substituted or unsubstituted heteroalkylene; cyclic or acyclic, branched or unbranched, substituted or unsubstituted heteroalkenylene; cyclic or acyclic, branched or unbranched, substituted or unsubstituted heteroalkynylene; substituted or unsubstituted arylene; substituted or unsubstituted heteroarylene; or substituted or unsubstituted acylene, or any combination thereof, which can make up a linker). Labels can be attached to a peptide at any position that does not interfere with the biological activity or characteristic of the inventive polypeptide that is being detected.

[0069] Labels can include: labels that contain isotopic moieties, which may be radioactive or heavy isotopes, including, but not limited to, ^{2}H, ^{3}H ^{13}C, ^{14}C, ^{15}N, ^{31}P, ^{32}P, ^{35}S, ^{67}Ga, ^{99m}Tc(Tc-99m), ^{111}In, ^{123}I, ^{125}I, ^{169}Yb, and ^{186}Re; labels that include immune or immunoreactive moieties, which may be antibodies or antigens, which may be bound to enzymes {e.g., such as horseradish peroxidase); labels that are colored, luminescent, phosphorescent, or include fluorescent moieties (e.g., such as the fluorescent label FITC); labels that have one or more photoaffinity moieties; labels that have ligand moieties with one or more known binding partners (such as biotin-streptavidin, FK506-FKBP, etc.).

[0070] In some instances, labels can include one or more photoaffinity moieties for the direct elucidation of intermolecular interactions in biological systems. A variety of known photophores can be employed, most relying on photoconversion of diazo compounds, azides, or diazirines to nitrenes or carbenes (see, e.g., Bayley, H., Photogenerated Reagents in Biochemistry and Molecular Biology (1983), Elsevier, Amsterdam). In certain embodiments of the invention, the photoaffinity labels employed are o-, m- and p-azidobenzoyls, substituted with one or more halogen moieties, including, but not limited to 4-azido-2,3,5,6-tetrafluorobenzoic acid.

[0071] Labels can also be or can serve as imaging agents. Exemplary imaging agents include, but are not limited to, those used in positron emissions tomography (PET), computer assisted tomography (CAT), single photon emission computerized tomography, x-ray, fluoroscopy, and magnetic resonance imaging (MRI); anti-emetics; and contrast agents. Exemplary diagnostic agents include but are not limited to, fluorescent moieties, luminescent moieties, magnetic moieties; gadolinium chelates (e.g., gadolinium chelates with DTPA, DTPA-BMA, DOTA and HP-DO3A), iron chelates, magnesium chelates, manganese chelates, copper chelates, chromium chelates, iodine -based materials useful for CAT and x-ray imaging, and radionuclides. Suitable radionuclides include, but are not limited to, ^{123}I, ^{125}I, ^{130}I, ^{131}I, ^{133}I, ^{135}I, ^{47}Sc, ^{72}As, ^{72}Se, ^{90}Y, ^{88}Y, ^{97}Ru, ^{100}Pd, ^{101}mRh, ^{119}Sb, ^{128}Ba, ^{197}Hg, ^{211}At, ^{212}Bi, ^{212}Pb, ^{109}Pd, ^{111}In, ^{67}Ga, ^{68}Ga, ^{67}Cu, ^{75}Br, ^{77}Br, ^{99}mTc, ^{14}C, ^{13}N, $^{15}0$, ^{32}P, ^{33}P, and ^{18}F.

[0072] Fluorescent and luminescent moieties include, but are not limited to, a variety of different organic or inorganic small molecules commonly referred to as "dyes," "labels," or "indicators." Examples include, but are not limited to, fluorescein, rhodamine, acridine dyes, Alexa dyes, cyanine dyes, etc. Fluorescent and luminescent moieties may include a variety of naturally occurring proteins and derivatives thereof, e.g., genetically engineered variants. For example, fluorescent proteins include green fluorescent protein (GFP), enhanced GFP, red, blue, yellow, cyan, and sapphire fluorescent proteins, reef coral fluorescent protein, etc. Luminescent proteins include luciferase, aequorin and derivatives thereof. Numerous fluorescent and luminescent dyes and proteins are known in the art (see, e.g., U.S. Patent Publication 2004/0067503; Valeur, B., "Molecular Fluorescence: Principles and Applications," John Wiley and Sons, 2002; and Handbook of Fluorescent Probes and Research Products, Molecular Probes, 9th edition, 2002).

[0073] The term "purified" as used herein, refers to other molecules, e.g. polypeptide, nucleic acid molecule that have been identified and separated and/or recovered from a component of its natural environment. Thus, in one embodiment the antibodies useful in the invention are purified antibodies wherein they have been separated from one or more components of their natural environment.

[0074] The term "epitope" as used herein refers to a protein determinant capable of binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0075] Nucleotide sequences corresponding to (e.g., encoding) the disclosed peptides (e.g., disclosed in Table 1) are described herein. These sequences include all degenerate sequences related to the disclosed peptides, i.e., all nucleic acids having a sequence that encodes one particular peptide and variants and derivatives thereof. Thus, while each particular nucleic acid sequence may not be written out herein, it is understood that each and every sequence is in fact disclosed and described herein through the disclosed polypeptide sequences.

[0076] In some instances, nucleic acids of the disclosed can include expression vectors. Examples of suitable vectors include, but are not limited to, plasmids, artificial chromosomes, such as BACs, YACs, or PACs, and viral vectors.

[0077] The vectors described herein also can include, for example, origins of replication and/or markers. A marker gene can confer a selectable phenotype, e.g., antibiotic resistance, on a cell. The marker product is used to determine if the vector has been delivered to the cell and once delivered is being expressed. Examples of selectable markers for mammalian cells are dihydrofolate reductase (DHFR), thymidine kinase, neomycin, neomycin analog G418, hygromycin, puromycin, and blasticidin. When such selectable markers are successfully transferred into a mammalian host cell, the transformed mammalian host cell can survive if placed under selective pressure. Examples of other markers include, for example, the E. coli lacZ gene, green fluorescent protein (GFP), and luciferase. In addition, an expression vector can include a tag sequence designed to facilitate manipulation or detection (e.g., purification or localization) of the expressed polypeptide. Tag sequences, such as GFP, glutathione S-transferase (GST), polyhistidine, c-myc, hemagglutinin, or FLAG™ tag (Kodak; New Haven, CT) sequences typically are expressed as a fusion with the encoded polypeptide. Such tags can be inserted anywhere within the polypeptide including at either the carboxyl or amino terminus.

[0078] Cells are described herein which comprise the nucleic acids (e.g., vectors) and/or peptides disclosed herein. Cells can include, for example, eukaryotic and/or prokaryotic cells. In general, cells that can be used herein are commercially available from, for example, the American Type Culture Collection (ATCC), P.O. Box 1549, Manassas, VA 20108. See also F. Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, NY, (1998). Transformation and transfection methods useful in the generation of the cells disclosed herein are described, e.g., in F. Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York, NY, (1998).

Pharmaceutical Formulations

[0079] In some instances, therapeutic compositions disclosed herein can include other compounds, drugs, and/or agents used for the treatment of cancer. Such compounds, drugs, and/or agents can include, for example, chemotherapy drugs, small molecule drugs or antibodies that stimulate the immune response to a given cancer. In some instances, therapeutic compositions can include, for example, one or more peptides disclosed herein and one or more of an anti-CTLA-4 antibody or peptide, an anti-PD-1 antibody or peptide, and/or an anti-PDL-1 antibody or peptide. For example, in some instances, therapeutic compositions disclosed herein can be combined with one or more (e.g., one, two, three, four, five, or less than ten) compounds.

[0080] In some instances, therapeutic compositions disclosed herein can include other compounds including histone deacetylase inhibitors ("HDAC") inhibitors. Examples of HDAC inhibitors include, for example, hydroxamic acid, Vorinostat (Zolinza); suberoylanilide hydroxamic acid (SAHA)(Merck), Trichostatin A (TSA), LAQ824 (Novartis), Panobinostat (LBH589) (Novartis), Belinostat (PXD101)(CuraGen), ITF2357 Italfarmaco SpA (Cinisello), Cyclic tetrapeptide; Depsipeptide (romidepsin, FK228) (Gloucester Pharmaceuticals), Benzamide; Entinostat (SNDX-275/MS-275)(Syndax Pharmaceuticals), MGCD0103 (Celgene), Short-chain aliphatic acids, Valproic acid, Phenyl butyrate, AN-9, pivanex (Titan Pharmaceutical), CHR-3996 (Chroma Therapeutics), and CHR-2845 (Chroma Therapeutics).

[0081] In some instances, therapeutic compositions disclosed herein can include other compounds including proteasome inhibitors, including, for example, Bortezomib, (Millennium Pharmaceuticals), NPI-0052 (Nereus Pharmaceuticals), Carfilzomib (PR-171)(Onyx Pharmaceuticals), CEP 18770, and MLN9708

[0082] In some instances, the therapeutic compositions disclosed herein can include alkylating agents such as mephalan and topoisomerase inhibitors such as Adriamycin (doxorubicin) have been shown to increase MICA expression, which could enhance efficacy of an anti-MICA monoclonal antibody.

[0083] In some instances, therapeutic compositions disclosed herein can be formulated for use as or in pharmaceutical compositions. Such compositions can be formulated or adapted for administration to a subject via any route, e.g., any route approved by the Food and Drug Administration (FDA). Exemplary methods are described in the FDA's CDER Data Standards Manual, version number 004 (which is available at fda.give/cder/dsm/DRG/drg00301.htm).

[0084] In some instances, pharmaceutical compositions can include an effective amount of one or more peptides. The terms "effective amount" and "effective to treat," as used herein, refer to an amount or a concentration of one or more peptides for a period of time (including acute or chronic administration and periodic or continuous administration) that is effective within the context of its administration for causing an intended effect or physiological outcome.

[0085] In some instances, pharmaceutical compositions can include one or more peptides and any pharmaceutically acceptable carrier, adjuvant and/or vehicle. In some instances, pharmaceuticals can further include one or more additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms.

[0086] The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a peptide described herein, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0087] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-I-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as I-, ϑ-, and K-cyclodextrin, may also be advantageously used to enhance delivery of compounds of the formulae described herein.

[0088] The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra¬articular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0089] Pharmaceutical compositions can be in the form of a solution or powder for inhalation and/or nasal administration. Such compositions may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0090] Pharmaceutical compositions can be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0091] Alternatively or in addition, pharmaceutical compositions can be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0092] Methods are described herein for using any one or more of the peptides or pharmaceutical compositions (indicated below as 'X') disclosed herein in the following methods:

> Substance X for use as a medicament in the treatment of one or more diseases or conditions disclosed herein (e.g., cancer, referred to in the following examples as 'Y'). Use of substance X for the manufacture of a medicament for the treatment of Y; and substance X for use in the treatment of Y.

[0093] In some instances, therapeutic compositions disclosed herein can be formulated for sale in the US, import into the US, and/or export from the US.

Methods

[0094] In some instances, methods can include selection of a human subject who has or had a condition or disease and who exhibits or exhibited a positive immune response towards the condition or disease. In some instances, suitable subjects include, for example, subjects who have or had a condition or disease but that resolved the disease or an aspect thereof, present reduced symptoms of disease (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease), and/or that survive for extended periods of time with the condition or disease (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease), e.g., in an asymptomatic state (e.g., relative to other subjects (e.g., the majority of subjects) with the same condition or disease). In some instances, subjects can be selected if they have been vaccinated (e.g., previously vaccinated and/or vaccinated and re-vaccinated (e.g., received a booster vaccine)) against a condition or disease.

[0095] The term "subject," as used herein, refers to any animal. In some instances, the subject is a mammal. In some instances, the term "subject", as used herein, refers to a human (e.g., a man, a woman, or a child). Samples for use in the methods can include serum samples, e.g., obtained from the selected subject.

[0096] In some instances, subject selection can include obtaining a sample from a subject (e.g., a candidate subject) and testing the sample for an indication that the subject is suitable for selection. In some instances, the subject can be confirmed or identified, e.g. by a health care professional, as having had or having a condition or disease. In some instances, exhibition of a positive immune response towards a condition or disease can be made from patient records, family history, and/or detecting an indication of a positive immune response. In some instances multiple parties can be included in subject selection. For example, a first party can obtain a sample from a candidate subject and a second party can test the sample. In some instances, subjects can be selected and/or referred by a medical practitioner (e.g., a general practitioner). In some instances, subject selection can include obtaining a sample from a selected subject and storing the sample and/or using the in the methods disclosed herein. Samples can include, for example, cells or populations of cells.

[0097] In some instances, obtaining or targeting immune cells can include one or more and/or combinations of, for example: obtaining or providing a tetrameric immunogen that can bind (e.g., bind specifically) to a target immune cell; contacting the tetrameric immunogen with a sample; detecting the tetrameric immunogen; determining whether the tetrameric immunogen is bound to a target immune cell; and, if the tetrameric immunogen is bound to a target immune cell, then obtaining the target immune cell.

[0098] Tetrameric immunogens can include immunogens related to a condition or disease and/or that bind (e.g., bind specifically) to a target immune cell, e.g., wherein the target immune cell is related to a selected condition or disease. Immunogens and target immune cells related to a condition or disease include, for example, immunogens or immune cells present in subjects with a certain condition or disease, but not subjects without the condition or disease; and/or immunogens or immune cells present at altered levels (e.g., increased) in subjects with a certain condition or disease relative to subjects without the condition or disease. In some instances, immunogens or immune cells can be cancer specific. Immunogens can be soluble. Tetrameric immunogen can include tetrameric (including, e.g., tetramerized monomeric, dimeric, and/or trimeric antigen immunogen (e.g., antigen and/or epitope). In some instances, a tetrameric immunogen has increased binding to a cell relative to the level of binding between a non-tetrameric form of the immunogen to the cell under similar conditions. In some instances, a tetrameric antigen includes a detectable moiety, e.g., a streptavidin moiety. Tetramerization methods are known in the art and are disclosed herein.

[0099] Detecting tetrameric immunogen and/or determining whether tetrameric immunogen is bound to a target cell can be performed using methods known in the art and/or disclosed herein. For example, methods can include flow cytometry. Optimization methods for flow cytometry, including sorting and gating methods, are known in the art and/or are disclosed herein. In some instances, methods can include analysis of the level of binding, binding affinity, and/or binding specificity between a tetrameric immunogen bound to a target immune cell. For example, a target immune cell can be obtained if (e.g., only if) a pre-determined level of binding between a tetrameric immunogen and a target immune cell is determined. Pre-determined levels of binding can be specific levels and/or can be relative levels. Obtaining target immune cells can include obtaining, providing, identifying, selecting, purifying, and/or isolating the target immune cells. Such methods can include, for example, cell sorting methods, cell enrichment, and/or background reduction.

[0100] In some instances, obtaining immune cells directed against a self antigen can include one or more and/or combinations of, for example, identifying a subject exhibiting a positive immune response towards the self antigen; obtaining or providing a multimeric form of the self antigen; contacting the multimeric form of the self antigen with a sample from the subject exhibiting a positive immune response towards the self antigen; obtaining immune cells bound to the multimeric form of the self antigen.

[0101] In some instances, methods can include obtaining immune cells directed against a self antigen from a cancer patient, can include one or more and/or combinations of, for example, identifying a subject exhibiting a positive immune response towards the self antigen; providing a multimeric form of the self antigen; contacting the multimeric form of the self antigen with a sample from the subject exhibiting a positive immune response towards the self antigen; and obtaining immune cells bound to the multimeric form of the self antigen.

[0102] Multimeric forms of a self antigen can include self antigens related to a condition or disease and/or that bind (e.g., bind specifically) to a target immune cell, e.g., wherein the target immune cell is related to a selected condition or disease. Self antigens and target immune cells related to a condition or disease include, for example, antigens or immune cells present in subjects with a certain condition or disease, but not subjects without the condition or disease; and/or immunogens or immune cells present at altered levels (e.g., increased) in subjects with a certain condition or disease relative to subjects without the condition or disease. In some instances, the condition or disease can be a cancer. In some embodiments, the cancer is melanoma, lung, breast, kidney, ovarian, prostate, pancreatic, gastric, and colon carcinoma, lymphoma or leukemia. In some instances, the self antigens or immune cells can be cancer specific. The self antigens can be soluble. Multimeric form of the self antigen can include a tetrameric form (including, e.g., tetramerized monomeric, dimeric, and/or trimeric antigen) of the self-antigen (e.g., antigen and/or epitope). In some instances, a multimeric form of the self antigen includes a detectable moiety, e.g., a streptavidin moiety. Multimerization methods are known in the art and are disclosed herein.

[0103] Methods for isolating or purifying genetic material (e.g., DNA and/or mRNA) from the obtained target immune cell are known in the art and are exemplified herein. Once such genetic material has been obtained, methods for using it to produce the therapeutic compositions disclosed herein are known in the art and/or are summarized below. As discussed above, genetic material can be varied, using techniques known in the art to create peptide variants disclosed herein.

[0104] Generating peptides from nucleic acids (e.g., cDNA) contained within or obtained from the target cell can include, for example, analysis, e.g., sequencing of heavy and light chain variable domains from target immune cells (e.g., single or isolated identified target immune cells). In some instances, methods can include generating fully human antibodies, or fragments thereof (e.g., as disclosed above), and humanization of non-human antibodies. DNA can be readily isolated and/or sequenced from the obtained immune cells using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

[0105] Once isolated, DNA can be placed into expression vectors, which are then transfected into host cells such as *Escherichia coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opinion in Immunol., 5:256-262 (1993) and Pluckthun, Immunol. Revs., 130:151-188 (1992).

[0106] Recombinant expression of an antibody or variant thereof generally requires construction of an expression vector containing a polynucleotide that encodes the antibody. Thus, replicable vectors are described herein which comprise a nucleotide sequence encoding an antibody molecule, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a portion thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., US. Patent Nos. 5,981,216; 5,591,639; 5,658,759 and 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[0107] Once the expression vector is transferred to a host cell by conventional techniques, the transfected cells are then cultured by conventional techniques to produce an antibody. Thus, host cells are described herein which containe a polynucleotide encoding an antibody useful in the invention or fragments thereof, or a heavy or light chain thereof, or portion thereof, or a single-chain antibody useful in the invention, operably linked to a heterologous promoter. In certain embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0108] Mammalian cell lines available as hosts for expression of recombinant antibodies are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), human epithelial kidney 293 cells, and a number of other cell lines. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the antibody or portion thereof expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any functional immunoglobulin chains), SP20, CRL7O3O and HsS78Bst cells. In one embodiment, human cell lines developed by immortalizing human lymphocytes can be used to recombinantly produce monoclonal antibodies. In one embodiment, the human cell line PER.C6. (Crucell, Netherlands) can be used to recombinantly produce monoclonal antibodies.

[0109] In some instances, peptides disclosed herein can be generated synthetically. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing peptides described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3d. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

[0110] Peptides can also be made by chemical synthesis methods, which are well known to the ordinarily skilled artisan. See, for example, Fields et al., Chapter 3 in Synthetic Peptides: A User's Guide, ed. Grant, W. H. Freeman & Co., New York, N.Y., 1992, p. 77. Hence, peptides can be synthesized using the automated Merrifield techniques of solid phase synthesis with the α-NH_2 protected by either t-Boc or Fmoc chemistry using side chain protected amino acids on, for example, an Applied Biosystems Peptide Synthesizer Model 430A or 431.

[0111] One manner of making of the peptides described herein is using solid phase peptide synthesis (SPPS). The C-terminal amino acid is attached to a cross-linked polystyrene resin via an acid labile bond with a linker molecule. This resin is insoluble in the solvents used for synthesis, making it relatively simple and fast to wash away excess reagents and by-products. The N-terminus is protected with the Fmoc group, which is stable in acid, but removable by base. Any side chain functional groups are protected with base stable, acid labile groups.

[0112] Longer peptides could be made by conjoining individual synthetic peptides using native chemical ligation. Alternatively, the longer synthetic peptides can be synthesized by well-known recombinant DNA techniques. Such techniques are provided in well-known standard manuals with detailed protocols. To construct a gene encoding a peptide described herein, the amino acid sequence is reverse translated to obtain a nucleic acid sequence encoding the amino acid sequence, preferably with codons that are optimum for the organism in which the gene is to be expressed. Next, a synthetic gene is made, typically by synthesizing oligonucleotides which encode the peptide and any regulatory elements, if necessary. The synthetic gene is inserted in a suitable cloning vector and transfected into a host cell. The peptide is then expressed under suitable conditions appropriate for the selected expression system and host. The peptide is purified and characterized by standard methods.

[0113] The peptides can be made in a high-throughput, combinatorial fashion, e.g., using a high-throughput multiple channel combinatorial synthesizer available from Advanced Chemtech.

[0114] Peptide bonds can be replaced, e.g., to increase physiological stability of the peptide, by: a retro-inverso bonds (C(O)-NH); a reduced amide bond ($NH-CH_2$); a thiomethylene bond ($S-CH_2$ or CH_2-S); an oxomethylene bond ($O-CH_2$ or CH_2-O); an ethylene bond (CH_2-CH_2); a thioamide bond (C(S)-NH); a trans-olefin bond (CH=CH); a fluoro substituted trans-olefin bond (CF=CH); a ketomethylene bond (C(O)-CHR) or CHR-C(O) wherein R is H or CH_3; and a fluoro-ketomethylene bond (C(O)-CFR or CFR-C(O) wherein R is H or F or CH_3.

[0115] Peptides can be further modified by: acetylation, amidation, biotinylation, cinnamoylation, farnesylation, fluoresceination, formylation, myristoylation, palmitoylation, phosphorylation (Ser, Tyr or Thr), stearoylation, succinylation and sulfurylation. As indicated above, peptides can be conjugated to, for example, polyethylene glycol (PEG); alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations thereof.

[0116] In some instances, peptides can be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigens Protein A or Protein G, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies useful in the present invention or fragments thereof may be fused to heterologous polypeptide sequences (refered to herein as "tags") described above or otherwise known in the art to facilitate purification.

[0117] An exemplary, non-limiting, overview of the methods is shown in FIG. 21. Ordering is not implied.

Methods of Use

[0118] Methods of treatment are described herein that include administering to a subject a composition disclosed herein.

[0119] Methods for treating and/or preventing cancer or symptoms of cancer in a subject are described herein which comprise administering to the subject a therapeutically effective amount of a composition comprising a peptide that immunospecifically binds to MHC class I polypeptide-related sequence A (MICA), wherein the peptide comprises complementarity determining region (CDR) 3 of the V_H of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions, and CDR3 of the V_L of antibody ID 1, 6, 7, 8 or 9 shown in Table 1 having 5 or fewer conservative amino acid substitutions. In some embodiments the cancer is a cancer associated with overexpression of MICA. In some embodiments, the cancer is melanoma, lung, breast, kidney, ovarian, prostate, pancreatic, gastric, and colon carcinoma, lymphoma or leukemia. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is a plasma cell malignancy, for example, multiple myeloma (MM) or pre-malignant condition of plasma cells. In some embodiments the subject has been diagnosed as having a cancer or as being predisposed to cancer.

[0120] Methods for treating and/or preventing cancer or symptoms of cancer in a subject are described herein which compris administering to the subject a therapeutically effective amount of a composition comprising an isolated antibody which specifically binds to MHC class I polypeptide-related sequence A (MICA), wherein the antibody comprises a heavy chain variable region (VH) comprising the VH CDR1, VH CDR2, and VH CDR3 as shown in the VH sequence of SEQ ID NO: 11, 149, 168, 186, or 204 and a light chain variable region (VL) sequence of SEQ ID No: 4, 151, 170, 189, or 206.

[0121] Also described herein are methods for treating and/or preventing cancer or symptoms of cancer in a subject comprising administering to the subject a therapeutically effective amount of a peptide that immunospecifically binds to angiopoietin, wherein the peptide comprises complementarity determining region (CDR) 3 of the VH of antibody ID 2, 3, 4 or 5 or 10 shown in Table 1 having 5 or fewer conservative amino acid substitutions, and CDR3 of the VL of antibody ID 2, 3, 4 or 5 shown in Table 1 having 5 or fewer conservative amino acid substitutions. In some embodiments the cancer is a cancer associated with overexpression of MICA. In some embodiments, the cancer is melanoma, lung, breast, kidney, ovarian, prostate, pancreatic, gastric, and colon carcinoma, lymphoma or leukemia. In some embodiments, the cancer is melanoma. In some embodiments, the cancer is a plasma cell malignancy, for example, multiple myeloma (MM) or pre-malignant condition of plasma cells. In some embodiments the subject has been diagnosed as having a cancer or as being predisposed to cancer.

[0122] Methods for treating and/or preventing cancer or symptoms of cancer in a subject are described herein which comprise administering to the subject a therapeutically effective amount of a composition comprising an isolated antibody which specifically binds to angiopoietin (e.g., angiopoietin-2), wherein the antibody comprises a heavy chain variable region (VH) comprising the VH CDR1, VH CDR2, and VH CDR3 as shown in the VH sequence of SEQ ID NO: 20, 38, 56, 74, 222 and a light chain variable region (VL) sequence of SEQ ID No: 29, 47, 65, 83, or 224.

[0123] Symptoms of cancer are well-known to those of skill in the art and include, without limitation, unusual mole features, a change in the appearance of a mole, including asymmetry, border, color and/or diameter, a newly pigmented skin area, an abnormal mole, darkened area under nail, breast lumps, nipple changes, breast cysts, breast pain, death, weight loss, weakness, excessive fatigue, difficulty eating, loss of appetite, chronic cough, worsening breathlessness, coughing up blood, blood in the urine, blood in stool, nausea, vomiting, liver metastases, lung metastases, bone metastases, abdominal fullness, bloating, fluid in peritoneal cavity, vaginal bleeding, constipation, abdominal distension, perforation of colon, acute peritonitis (infection, fever, pain), pain, vomiting blood, heavy sweating, fever, high blood pressure, anemia, diarrhea, jaundice, dizziness, chills, muscle spasms, colon metastases, lung metastases, bladder metastases, liver metastases, bone metastases, kidney metastases, and pancreatic metastases, difficulty swallowing, and the like.

[0124] The methods disclosed herein can be applied to a wide range of species, e.g., humans, non-human primates (e.g., monkeys), horses, cattle, pigs, sheep, deer, elk, goats, dogs, cats, mustelids, rabbits, guinea pigs, hamsters, rats, and mice.

[0125] The terms "treat" or "treating," as used herein, refers to partially or completely alleviating, inhibiting, ameliorating, and/or relieving the disease or condition from which the subject is suffering. In some instances, treatment can result in the continued absence of the disease or condition from which the subject is suffering.

[0126] In general, methods include selecting a subject at risk for or with a condition or disease. In some instances, the subject’s condition or disease can be treated with a pharmaceutical composition disclosed herein. For example, in some instances, methods include selecting a subject with cancer, e.g., wherein the subject’s cancer can be treated by targeting one or both of MICA and/or angiopoetin-2.

[0127] In some instances, treatments methods can include a single administration, multiple administrations, and repeating administration as required for the prophylaxis or treatment of the disease or condition from which the subject is suffering. In some instances treatment methods can include assessing a level of disease in the subject prior to treatment, during treatment, and/or after treatment. In some instances, treatment can continue until a decrease in the level of disease in the subject is detected.

[0128] The terms "administer," "administering," or "administration," as used herein refers to implanting, absorbing, ingesting, injecting, or inhaling, the inventive peptide (i.e. antibody or antibody fragment), regardless of form. In some instances, one or more of the peptides disclosed herein can be administered to a subject topically (e.g., nasally) and/or orally. For example, the methods herein include administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient’s disposition to the disease, condition or symptoms, and the judgment of the treating physician.

[0129] Following administration, the subject can be evaluated to detect, assess, or determine their level of disease. In some instances, treatment can continue until a change (e.g., reduction) in the level of disease in the subject is detected.

[0130] Upon improvement of a patient’s condition (e.g., a change (e.g., decrease) in the level of disease in the subject), a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0131] Methods for detecting immune cells e.g., B cells and/or memory B cells, from a human subject are described herein. Such methods can be used, for example, to monitor the levels of immune cells e.g., B cells and/or memory B cells, in a human subject, e.g., following an event. Exemplary events can include, but are not limited to, detection of diseases, infection; administration of a therapeutic composition disclosed herein, administration of a therapeutic agent or treatment regimen, administration of a vaccine, induction of an immune response. Such methods can be used clinically and/or for research.

EXAMPLES

[0132] The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

[0133] Methods are described herein that allow sensitive, specific, and reliable detection of rare memory B cells, with defined antigen specificity, from limited quantities of peripheral blood. Methods allowed visualization and isolation of memory B cells months to years after antigen had been cleared.

[0134] Proof of principle for the methods disclosed herein was established using tetramers of tetanus toxin C-fragment (TTCF), as reported in detail in Franz et al. (Blood, 118(2):348-357 (2011)).

[0135] TTCF (i.e., the 52 kDa, non-toxic, C-terminal fragment of TTCF) was selected as a model antigen because the majority of individuals have been vaccinated with tetanus toxoid and persistent IgG antibody titers are induced by the vaccine (Amanna et al., N. Engl. J. Med., 357:1903-1915, 2007). Accordingly, use of TTCF afforded a large pool of subjects in which the methods disclosed herein could be verified. One of skill in the art will appreciate, however, that the present methods can be adapted to include any disease-related antigen using routine skill. As demonstrated in the examples below, such adaption has been shown through the acquisition of antibodies directed against MICA and angiopoietin-2, which are cancer-related antigens.

Example 1: Antigen Expression and Tetramer Formation

[0136] As described in further detail below, TTCF was expressed in *Eschericia coli* and a BirA site was attached to the N-terminus for site-specific mono-biotinylation by BirA enzyme. A flexible linker was placed between the protein and the biotinylation site to prevent steric hindrance of antibody binding. TTCF was purified by anion-exchange chromatography, biotinylated with BirA, and separated from free biotin and BirA by gel filtration chromatography. TTCF tetramers were generated by incubating fluorescently tagged streptavidin with biotinylated TTCF antigen at a molar ratio of 1:4. These tetramers were then used along with a panel of mAbs for the identification of tetanus toxoid specific memory B cells.

[0137] TTCF was cloned in pET-15b (Novagen). Protein expression was induced in BL21(DE3) *Eschericia coli* with 1mM isopropyl β-D-1-thiogalactopyranoside (IPTG) for 4 hours at 28°C. Cells were washed, lysed, and resulting supernatant was collected. TTCF was purified using a HIS-Select affinity column (Sigma). The His-tag was removed proteolytically. Murine CD80 membrane proximal domain was produced using similar methods. Proteins were mono-biotinylated. For certain experiments, Alexa-488 dye molecules (Molecular probes) were linked to primary amines on biotinylated TTCF or CD80.

[0138] Antigen tetramers were prepared by incubating biotinyated antigen with premium grade PE labeled streptavidin (Molecular Probes) for at least 20 minutes on ice at a molar ratio of 4:1. Prior to use, tetramer preparations were centrifuged to remove aggregates. In some experiments, tetramers were formed with Alexa-fluor-488 tagged antigens and non-fluorescent streptavidin at a 4:1 ratio.

Example 2: Identification Methods

[0139] Methods were performed as described in Franz et al., Blood, 118(2):348-357 (2011).

[0140] Cells were sorted on a BD FACS Aria II cell sorter. Cells were single-cell sorted. Samples were first gated on $CD19^+$ cells that were negative for a panel of exclusion markers (CD3, CD14, CD16, 7AAD) then gated on plasmablasts, identified by high levels of CD27 and an immediate level of CD 19 expression, and finally on $tetramer^+$ $CD19^+$ cells.

[0141] Due to the low frequency of memory B cells, it was necessary to carefully reduce background as much as possible. B cells were first enriched by negative selection (cocktail of antibodies to CD2, CD3, CD14, CD16, CD56 and glycophorin A) to remove most cells that could non-specifically bind the tetramer. Enriched cells were split evenly and stained with TTCF or a control tetramer followed by labeling with CD19, CD27 and IgM to specifically select class-switched memory B cells. The gating strategy considered expression of CD 19, lack of labeling with a panel of exclusion markers (CD3, CD 14, CD16, 7AAD), expression of the memory marker CD27 and lack of IgM expression as evidence of class switching. Tetramer staining was plotted versus CD27 staining for visualization of memory B cells with the antigen specificity of interest. Tetramer-positive B cells were directly sorted into PCR strips containing 3 μl mRNA extraction buffer.

[0142] Tubes were kept cold during sorting and sorted cells were frozen and stored at-80°C. CD19+ CD27+ IgM- B cells were used as positive controls.

[0143] A previously reported nest PCR protocol was used to amplify heavy and light chain variable segments (Wang et al., J. Immunol. Methods., 244:217-225, 2000). mRNA amplification was carried out under conditions suitable to minimize contamination. Primers used included:

TAATACGACTCACTATAGGTTCGGGGAAGTAGTCCTTGACCAGG (SEQ ID NO: 91);
TAATACGACTCACTATAGGGATAGAAGTTATTCAGCAGGCACAC(SEQ ID NO:92);
TAATACGACTCACTATAGGCGTCAGGCTCAGRTAGCTGCTGGCCGC (SEQ ID NO:93).
Nested RT-PCR was performed as described in Franz et al., Blood, 118(2):348-357(2011).

[0144] Negative controls were included to monitor and guard against contamination. From a total of 35 single cells labeled with the TTCF tetramer, 32 heavy and 30 light chain segments were amplified and directly sequence from gel-purified PCR products, corresponding to an overall PCR efficiency of 89%. Sequence analysis revealed that TTCF tetramer$^+$ cells employed a variety of different $V_H D$-J_H gene segments, without dominance of one particular gene segment. Sequences observed supported that clones represented cells diversified by somatic hypermutation.

[0145] Antibody production and purification included cloning heavy and light variable domain DNA into separate pcDNA3.3 expression vectors containing the bovine prolactin signal peptide sequence as well as full length IgG1 heavy or kappa light chain constant domains. Antibodies were expressed in CHO-S media (Invitrogen) supplemented with 8mM Glutamax (Gibco) in 100ml sinner flasks at 37 °C with 8% CO_2. One day prior to transfection, cells were split to $6x10^5$ cells/ml. On the day of transfection, cells were adjusted, were necessary, to $1x10^6$ cells/ml. 25 μg of heavy and light chain plasmid DNA were co-transfected using MAX transfection reagent (Invitrogen) and transfected cells were cultured for 6-8 days. Protein was obtained using Protein G sepharose beads and antibody was eluted using 100mM glycine pH2.5 and separated from beads using Spin-X centrifuge tubes. Purified antibody was exchanged into phosphate buffered saline (PBS) using Micro Bio-Spin columns (BioRad). Protein concentration was assessed by absorbance at 280nm.

[0146] For saturation binding assay, non-biotinylated, MonoQ purified TTCF was labeled with europium and free europium was removed. 96-well flat bottom plates were coated overnight with 20ng of antibody per well in 100mM $NaHCO_3$ buffer at pH 9.6. Blocking was performed with assay buffer supplemented with bovine serum albumin (BSA) and bovine gamma globulins. TTCF-europium was diluted in assay buffer (100nM to 4pM) and 200μl was added per well in triplicate. Plates were incubated for 2 hours at 37 °C and washed three times with 200 μl wash buffer (50mM Tris pH 8, 150mM NaCl, 20 μM EDTA, 0.05% Tween). 100 μl enhancement solution was added to each well and fluorescence counts measured using a Victor^3 plate reader at 615nm.

[0147] Heavy and light chain variable domain sequences were analyzed using IMGT/V-Quest and JIONSOLVER software. Flow cytometry data were evaluated using FlowJo analysis software. Statistical analyses were carried out using GraphPad Prism 5 software using unpaired t-test. To determine antibody K_D values, saturation binding data were fitted using GraphPad Prism 5 software using non-linear regression analysis.

Example 3: Multimerization Enhances Identification of Memory B Cells

[0148] Tetrameric and monomeric TTCF were compared. TTCF was fluorescently labeled with Alexa-488 and then used in monomeric form or was converted to a tetramer using unlabeled streptavidin (see above). Enriched B cells were then incubated with tetrameric or monomeric TTCF-Alexa-488 at the same concentration. Control protein (CD80 membrane proximal domain) was labeled in the same way and also used as a tetramer.

[0149] As shown in FIGs. 22A and 22B, TTCF labeled some memory B cells, but frequencies identified with tetramer were substantially larger (1.6-7.3 fold) using cells from three donors. In one of the three donors TTCF specific memory B cells could be detected with the tetramer but not with the monomer.

[0150] These results demonstrate that antigen tetramers enable sensitive detection of memory B cells based on the antigen specificity of their BCR, despite such cells being very rare in peripheral blood. Class-switched memory B cells specific for TTCF were brightly labeled by the appropriate tetrameric TTCF antigen, while background labeling with control tetramer was consistently low.

Example 4: Method/Antibody Validation

[0151] Fully human antibodies were generated by joining constant regions of IgG heavy and kappa chains to isolated variable segments via overlap PCR. Antibodies were expressed in a transient, serum free mammalian expression system using CHO-S cells for a period of 6-8 days. Antibodies were purified using protein G and gel filtration chromatography.

[0152] As shown in FIG. 23, antibodies isolated from TTCF-specific plasmablasts showed high binding affinities to TTCF antigen, with a K_D of 2.2 nM (TTCF Ab 1) and 323 pM (TTCF Ab 2)(FIG. 23B. Antibodies isolated from memory B cells also exhibited high binding affinities, with K_D of 382 pM, 228 pM, and 1.4 nM, for other antibodies (TTCF Abs 3, 4, and 5)(FIG. 23B).

[0153] These data support the specificity of the methods disclosed herein. Moreover, the specificity of the methods herein was demonstrated by the construction of five anti-TTCF antibodies from three different donors, all of which bound to TTCF with high affinities.

[0154] Data herein also demonstrate that antigen tetramers enable sensitive detection of memory B cells long after clearance of the antigen from the host.

Example 5: Obtaining Anti-MICA Antibodies

[0155] Antibodies that immunospecifically bind to MICA were developed using the methods herein.

[0156] Briefly, MICA antigen (UniGene Hs.130838) was expressed with a C-terminal BirA tag (GLNDIFEAQKIEWHE (SEQ ID NO: 238)), which enables mono-biotinylation of the antigen. Antigen was tetramerized with streptavidin (SA) labeled with R-Phycoerythrin (PE) at a molar ration of 4 MICA: 1 SA. Peripheral blood mononuclear cells were obtained from advanced stage melanoma patients who had been vaccinated with autologous tumor cells transduced with a GM-CSF expression vector (GVAX) (PNAS 103: 9190, 2006), and subsequently treated with the anti-CTLA-4 monoclonal antibody ipilimumab (YERVOY™ (available from Bristol Myers Squib)) Peripheral blood mononuclear cells were quickly thawed, washed and resuspended at $5x10^6$ in phosphate buffered saline (pH 7.2) supplemented with 2% fetal calf serum and stained with approximately 0.1ug/ml tetramer for 30 minutes on ice. Antibodies were added to identify class-switched, memory B-cells ($CD19^+$, $CD27^+$, and IgM^-). A panel of exclusion antibodies labeling T-cells, natural killer-cells, marcro-phages, and dead cells were included to reduce background tetramer staining (CD3, CD14, CD16, 7-AAD). Single B-cells that bound to the MICA tetramer were sorted into 8-tube-PCR strips using the BD FACS Aria II. The B-cell receptor (BCR) mRNA was amplified using a commercial kit from Epicentre Biotechnologies (catalog number: MBCL90310) using gene specific primers shown below:

mRNA Amplification
IgG-T7: AATACGACTCACTATAGGTTCGGGGAAGTAGTCCTTGACCAGG (SEQ ID NO:94)
Kappa-T7: TAATACGACTCACTATAGGGATAGAAGTTATTCAGCAGGCACAC (SEQ ID NO:95)
Lambda-T7: TAATACGACTCACTATAGGCGTCAGGCTCAGRTAGCTGCTGGCCGC(SEQID NO:96)

PCR One

[0157]

VHL-1: TCACCATGGACTG(C/G)ACCTGGA (SEQ ID NO:97)
VHL-2: CCATGGACACACTTTG(C/T)TCCAC (SEQ ID NO:98)
VHL-3: TCACCATGGAGTTTGGGCTGAGC (SEQ ID NO:99)
VHL-4: AGAACATGAAACA(C/T)CTGTGGTTCTT (SEQ ID NO:100)
VHL-5: ATGGGGTCAACCGCCATCCT (SEQ ID NO:101)
VHL-6: ACAATGTCTGTCTCCTTCCTCAT (SEQ ID NO:102)
VkL-1: GCTCAGCTCCTGGGGCTCCTG (SEQ ID NO:103)
VkL-2: CTGGGGCTGCTAATGCTCTGG (SEQ ID NO:104)
VkL-3: TTCCTCCTGCTACTCTGGCTC (SEQ ID NO:105)
VkL-4: CAGACCCAGGTCTTCATTTCT (SEQ ID NO:106)
V1L-1: CCTCTCCTCCTCACCCTCCT (SEQ ID NO:107)
V1L-2: CTCCTCACTCAGGGCACA (SEQ ID NO:108)
V1L-3: ATGGCCTGGA(T/C)C(C/G)CTCTCC (SEQ ID NO:109)
CgII: GCCAGGGGGAAGAC(C/G)GATG (SEQ ID NO:110)
CkII: TTTCAACTGCTCATCAGATGGCGG (SEQ ID NO:111)
ClII: AGCTCCTCAGAGGAGGG(C/T)GG (SEQ ID NO:112)

PCR Two

[0158]

VH-1: CAGGT(G/C)CAGCTGGT(G/A)CAGTC (SEQ ID NO:113)
VH-2: CAG(A/G)TCACCTTGAAGGAGTC (SEQ ID NO:114)
VH-3: (G/C)AGGTGCAGCTGGTGGAGTC (SEQ ID NO:115)
VH-4: CAGGTGCAGCTGCAGGAGTC (SEQ ID NO:116)
VH-5: GA(G/A)GTGCAGCTGGTGCAGTC (SEQ ID NO:117)
VH-6: CAGGTACAGCTGCAGCAGTC (SEQ ID NO:118)
Vk-1: CG(A/C)CATCC(A/G)G(A/T)TGACCCAGT (SEQ ID NO:119)
Vk-2: CGAT(A/G)TTGTGATGAC(C/T)CAG (SEQ ID NO:120)
Vk-3: CGAAAT(T/A)GTG(T/A)TGAC(G/A)CAGTCT (SEQ ID NO:121)
Vk-4: CGACATCGTGATGACCCAGT (SEQ ID NO:122)
Vl-1: CCAGTCTGTGCTGACTCAGC (SEQ ID NO:123)
Vl-2: CCAGTCTGCCCTGACTCAGC (SEQ ID NO:124)
Vl-3: CTCCTATGAGCTGAC(T/A)CAGC (SEQ ID NO:125)
CgIII: GAC(C/G)GATGGGCCCTTGGTGGA (SEQ ID NO:126)

CkIII: AAGATGAAGACAGATGGTGC (SEQ ID NO:127)
ClIII: GGGAACAGAGTGACCG (SEQ ID NO:128)

[0159] The primers and PCR cycling conditions used in PCR one and PCR two are adapted from Wang and Stollar et al. (journal of immunological methods2000).

[0160] An alternate heavy chain variable region forward primer set was developed to cover heavy chain variable region sequences potentially not adequately covered by the above primer set. The following alternate primers were generated:

PCR One

[0161]

VH1-58: TCACTATGGACTGGATTTGGA (SEQ ID NO:129)
VHL2-5: CCATGGACA(C/T)ACTTTG(C/T)TCCAC (SEQ ID NO:130)
VHL3-7: GTAGGAGACATGCAAATAGGGCC (SEQ ID NO:131)
VHL3-11: AACAAAGCTATGACATATAGATC (SEQ ID NO:132)
VHL3-13.1: ATGGAGTTGGGGCTGAGCTGGGTT (SEQ ID NO:133)
VHL3-13.2: AGTTGTTAAATGTTTATCGCAGA (SEQ ID NO:134)
VHL3-23: AGGTAATTCATGGAGAAATAGAA (SEQ ID NO:135)
VHL4-39: AGAACATGAAGCA(C/T)CTGTGGTTCTT (SEQ ID NO:136)
VHL4-61: ATGGACTGGACCTGGAGCATC (SEQ ID NO:137)
VHL-9: CCTCTGCTGATGAAAACCAGCCC (SEQ ID NO:138)

PCR Two

[0162]

VH1-3/18: CAGGT(C/T)CAGCT(T/G)GTGCAGTC (SEQ ID NO:139)
VH1-45/58: CA(A/G)ATGCAGCTGGTGCAGTC (SEQ ID NO:140)
VH2-5: CAG(A/G)TCACCTTGA(A/G)GGAGTCTGGT (SEQ ID NO:141)
VH3-9/23/43: GA(A/G)GTGCAGCTG(T/G)TGGAGTC (SEQ ID NO:142)
VH3-16: GAGGTACAACTGGTGGAGTC (SEQ ID NO:143)
VH3-47: GAGGATCAGCTGGTGGAGTC (SEQ ID NO:144)
V4-34: CAGGTGCAGCTACAGCAGTG (SEQ ID NO:145)
V4-30-2/ 39: CAGCTGCAGCTGCAGGAGTC (SEQ ID NO:146)
VH7-4-1: CAGGTGCAGCTGGTGCAATC (SEQ ID NO:147)

[0163] Briefly, 2ul cDNA generated via mRNA amplification was used as a template for first-round PCR, with the following cycling conditions: 3 cycles of preamplification (94°C/45 seconds, 45°C/45 seconds, 72°C/105 seconds); 30 cycles of amplification (94°C/45 seconds, 50°C/45 seconds, 72°C/105 seconds); 10 minutes of final extension at 72°C.

[0164] 3ul of first-round PCR product served as a template for the second round of nested PCR. The same cycling conditions were used for the first round of PCR, but the 3 cycles of preamplification were omitted. Both PCR steps were performed by the use of cloned Pfu polymerase AD (Agilent Technologies). PCR products were separated on 1% agarose gels and products of 300-400 nucleotides in size isolated with the use of Zymoclean DNA gel recovery kit (Zymo Research). Sequencing was performed by the use of forward and reverse primers used for the second-round nested PCR. A two-step nested PCR amplifies the BCR variable domains of heavy and light chains (see above). Peripheral blood mononuclear cells were obtained from advanced stage melanoma patients who had been vaccinated with autologous tumor cells transduced with a GM-CSF expression vector (GVAX) (PNAS 103: 9190, 2006). The antibodies were expressed as full-length IgG1 antibodies in a transient CHO-S expression system.

[0165] Validation of anti-MICA antibody binding to MICA was performed using two independent bead-based assays. The first assay used a commercially available solution-based bead assay kit designed for detection of anti-MICA antibodies reactive to a variety of MICA alleles (One Lambda, catalog number LSMICA001). Varying concentrations of the MICA antibody were incubated with beads, then washed, and incubated with an anti-human IgG antibody conjugated with phycoerythrin. Following a second wash step, beads were analyzed on a Luminex machine. A negative control consisted of incubation of beads with anti-human IgG antibody conjugated with phycoerythrin alone (no anti-MICA antibody). A positive control consisted of incubation of beads with a commercially available anti-MICA/MICB monoclonal antibody (clone 6D4) directly conjugated to phycoerythrin (BioLegend catalog #320906). The second assay was developed internally using polystyrene beads conjugated with streptavidin. Beads were coated with monobiotinylated MICA protein, and incubated with varying concentrations of anti-MICA antibody, anti-TTCF antibody (isotype negative control), or BioLegend anti-MICA/MICB antibody directly conjugated to phycoerythrin (positive control). Beads incubated with anti-MICA antibody or anti-TTCF antibody were washed and then incubated with anti-human IgG antibody conjugated with Alexa488. To determine background binding to the beads, the same incubation was performed using streptavidin-conjugated beads not coated with MICA protein for comparison. Beads were analyzed for binding to antibodies on a FACS Caliber flow cytometer.

[0166] As shown in FIGs. 24 and 25, anti-MICA antibodies (MICA-Ab12 and MICA-Ab20) bind with high affinity to MICA. MICA-Ab20 corresponds to the anti-MICA antibody ID-1 described in Table 1.

Example 6: Anti-MICAAntibodies

[0167] Additional anti- MICA antibodies with clinically relevant biological properties were developed using the methods herein. MICA-specific antibodies reactive to common alleles were identified in patients who had received a cellular cancer vaccine (GM-CSF transduced cancer cells, referred to as GVAX) and an antibody that blocks the inhibitory CTLA-4 receptor on T cells ipilimumab (YERVOY™ (available from Bristol Myers Squib)). MICA tetramers were then used to isolate B cells from peripheral blood mononuclear cells of patients with the highest serum MICA reactivity. Heavy and light chain sequences were determined from these B cells by single cell PCR, as outlined in the in Example 5. This effort led to the identification of antibodies that recognize alleles common in the North American population.

[0168] CM24002 Ab2 (anti-MICA antibody ID-6 described in Table 1) is an antibody isolated from a patient with acute myeloid leukemia (AML) who demonstrated a significant clinical response to the GVAX + Ipilimumab combination therapy and whose plasma reacted strongly with MICA. The CM24002 Ab2 light chain (FIGs. 30 and 31) and heavy chain (FIGs. 28 and 29) nucleotide and amino acid sequences are shown, with CDR1, CDR2 and CDR3 sequences underlined. An additional antibody with strong binding was obtained from the same patient and is labeled as CM24002 Ab4 (anti-MICA antibody ID-7 described in Table 1) The CM24002 Ab4 light chain (FIGs. 34 and 35) and heavy chain (FIGs. 23 and 32) nucleotide and amino acid sequences are shown, with CDR1, CDR2 and CDR3 sequences underlined.

[0169] CM33322 Ab11 (anti-MICA antibody ID-8 described in Table 1) and CM33322 Ab29 (anti-MICA antibody ID-9 described in Table 1) are antibodies isolated from a patient with metastatic melanoma who is a long-term responder (>15 years) to the GVAX + Ipilimumab combination therapy. The CM33322 Ab11 light chain ((FIGs. 38 and 39) and heavy chain (FIGs. 36 and 37) nucleotide and amino acid sequences are shown, with CDR1, CDR2 and CDR3 sequences underlined. The CM33322 Ab29 light chain ((FIGs. 42 and 43) and heavy chain (FIGs. 40 and 41) nucleotide and amino acid sequences are shown, with CDR1, CDR2 and CDR3 sequences underlined. Due to the long-term clinical response of this patient, these antibodies are of particular interest.

[0170] After initial identification, cloning, and expression of the antibodies of interest, the specificity of these antibodies for different MICA alleles was determined with a cytometric bead assay. Briefly, soluble, recombinant MICA alleles 002, 008, 009 and MICB with a single BirA biotinylation site were expressed, purified, and captured on streptavidin beads. Indicated anti-MICA antibodies were then incubated with the beads coated with recombinant MICA at different concentrations for one hour, then washed, and incubated with a FITC-labeled anti-human IgG secondary antibody. Following a second wash step, quantification of bead-bound FITC fluorescence was completed by flow cytometry. MICA alleles 002, 008, 009 as well as the related MICB protein were chosen based on their prevalence in the North American population (FIG. 48). MICA alleles 002, 008, 009 as well as the related MICB protein were also chosen based on their generally high prevalence worldwide. Importantly, CM24002 Ab2 and CM33322 Ab29 bound strongly to all MICA alleles as well as to MICB. The other two antibodies bound to a subset of alleles: CM24002 Ab4 bound highly to MICA*009 and MICB, and CM33322 Ab11 bound highly to MICA*002, MICA*008, and MICB. (FIGs. 48A-F) Specificity was documented by use of a negative human control antibody generated with the same technology (specific for tetanus toxoid C-terminal fragment, TTCF) and a positive control antibody to MICA (a commercial murine antibody from BioLegend directed against MICA). These studies identified CM24002 Ab2 and CM33322 Ab29 as potential candidates for clinical application.

Example 7: Binding of Anti-MICA Antibody to Autologous Tumor Cells

[0171] The ability of isolated anti-MICA antibody CM24002 Ab2 to bind to autologous tumor cells was examined by flow cytometry (FIG. 49). Bone marrow obtained from patient CM24002 and tested binding to tumor cells by CM24002 Ab2. Tumor cells were then identified from the bone marrow sample as CD33+ CD34+ cells. The tumor cells were then stained with 10 μg/ml with anti-MICA antibody CM24002 Ab2, positive control commercial MICA antibody (BioLegend) or a negative control antibody (TTCF specific). As shown in FIG. 49, CM24002 Ab2 strongly bound to these cells. CM24002 Ab2 did not display binding to non-tumor cells (CD16+ and CD3+ cells) and only background binding to CD14+ cells, demonstrating anti-tumor specificity (data not shown).

Example 8. Anti-MICA Antibody Inhibition of NKG2D Receptor on NK Cells.

[0172] The ability of isolated anti-MICA antibody CM24002 Ab2 to prevent soluble MICA-mediated down-regulation of is cognate receptor, NKG2D was examined. Serum from patient CM24002 was used at a 1:10 dilution and incubated with human NK cells for a period of 48 hours. CM24002 Ab2 (concentration of 10μg/ml), positive control commercial MICA antibody (BioLegend) or a negative control antibody (TTCF specific) were added to these cultures. NKG2D expression was assessed by flow cytometry at 48hr (FIG. 50). Serum from patient CM24002 strongly down-regulated expression of NKG2D (thus disabling the function of this receptor). CM24002 Ab2 and the positive control MICA antibody partially restored NKG2D surface expression by NK cells. To demonstrate specificity, we repeated the above experiment by incubating cells with recombinant MICA at 2ng/ml instead of patient serum (FIG. 51). CM24002 Ab2 completely prevented MICA-mediated down-regulation of NKG2D expression, while the negative control antibody (specific for TTCF) had no effect (FIG. 51). These data demonstrate that human MICA antibodies can prevent inhibition of the critical NKG2D receptor on human NK cells.

Example 9: Anti-MICAAntibody Cell-Mediated Cytotoxicity

[0173] To determine if CM24002 Ab2 enables cell-mediated cytotoxicity, human NK cells (effector cells) were incubated for 48 hours with recombinant MICA (2ng/ml) in the presence of CM24002 Ab2, a negative control antibody (TTCF specific) or a positive control antibody (BioLegend), all at 10μg/ml. After 48 hours, cells were washed and incubated with K562 tumor cells at 20:1, 10:1, and 5:1 effector:target ratios for 4 hours. Specific lysis of target cells by NK cells was determined by release of a cytosolic protein (LDH) from K562 tumor cells. In the absence of MICA antibodies, there was no killing of K562 tumor cells by NK cells. However, CM24002 Ab2 greatly enhanced NK cell mediated lysis of K562 tumor cells and was more effective than the positive control murine MICA antibody at all effector:target ratios (FIG. 52). It was further demonstrated that killing of K562 tumor cells was indeed mediated by the NKG2D pathway (rather than Fc receptors). The above experiment was repeated, with the addition two experimental groups: a blocking antibody for NKG2D and human Fc block. In addition, CM33322 Ab29 was also tested. The data show that addition of CM24002 Ab2 and CM33322 Ab29 enabled NK cell mediated cytotoxicity. Killing of K562 cells did not occur when a blocking NKG2D antibody was added, while the Fc blocking reagent had little effect (FIG. 53). These data show that CM24002 Ab2 and CM33322 Ab29 restore the anti-tumor function of the NKG2D pathway.

Example 10: Binding of Anti-MICA Antibody to Alpha 3 MICA domain

[0174] The NKG2D receptor binds to the top alpha 1 and alpha 2 domains of MICA, and antibodies that bind to the same site may compete with the NKG2D receptor and thereby block killing of tumor cells by NK cells. Antibodies that bind to the alpha 3 domain are of particular interest because they cannot block NKG2D receptor binding. At the same time, such antibodies can interfere with proteolytic cleavage of MICA from the tumor cell surface. The ability of anti-MICA antibodies to the MICA alpha 3 domain was assessed using the previously described cytometric bead assay. The biotinylated recombinant protein was captured on streptavidin beads. Beads were then incubated with antibodies CM24002 Ab2, CM24002 Ab4, CM33322 Ab11, CM33322 AB29, a negative control antibody (TTCF specific) or a positive control antibody (BioLegend), at 10μg/ml followed by a FITC-labeled anti-human IgG secondary antibody and quantification of bead-bound FITC fluorescence by flow cytometry (FIG. 54). As shown in FIG. 54, CM33322 Ab29 bound to the MICA alpha 3 domain and is therefore of great interest for therapeutic applications.

Example 11: Binding of Anti-MICA Antibody to Tumor Cells

[0175] The potential of CM24002 Ab2 and CM33322 Ab29 to be used to target a broad range of cancers was assessed. A panel of multiple myeloma (RPMI 8226 and Xg-1), ovarian cancer (OVCAR3), acute myeloid leukemia (U937), melanoma (K028), lung cancer (1792 and 827), and breast cancer (MCF7) cells were tested for labeling by CM24002 Ab2 and CM33322 Ab29. The tumor cells were resuspended at a concentration of $1x10^6$ cells/ml in PBS with 1% BSA and stained with the CM24002 Ab2 and CM33322 Ab29, as well as positive and negative controls (murine MICA antibody and TTCF-specific antibody, respectively)(directly conjugated) at a concentration of 10 μg/ml for 1 hour at 4°C. Labeling was assessed by flow cytometry (FIG. 55). CM24002 Ab2 and CM33322 Ab29 both bound every tumor cell type tested, with labeling being greater than the commercial positive control for the majority of tested cell lines.

Example 11a: MICA Allele Specificity of Anti-MICA antibody

[0176] The allelic specificity of CM33322 Ab29 was assessed using a commercially available Luminex assay. The commercial test kit contains recombinant MICA alleles (MICA*001, *002, *007, *012, *017, *018, *027, *004, *009, and

*015) directly conjugated to Luminex beads, each with intrinsic fluorescent properties enabling binding to be assessed in a single sample. Luminex beads coated with the indicated MICA alleles were incubated with CM33322 Ab29, BioLegend positive control, and the negative control (TTCF), at 10 μg/ml for 1 hr, with subsequent incubation with PE-conjugated anti-human IgG secondary antibody. Fluorescence was determined following incubation for 60 minutes with the indicated antibodies and subsequent incubation with anti-human PE-conjugated secondary antibody using a Luminex 200 instrument (FIG. 56). CM33322 Ab29 was able to bind to all alleles present in the commercial assay, indicating that it may be used in patients regardless of MICA genotype.

[0177] These data demonstrate the high biological activity of CM24002 Ab2 and CM33322 Ab29 and their ability to restore NK cell mediated lysis of tumor cells. These data demonstrate that cancer patients who responded to immunotherapies produced MICA antibodies that restored the anti-tumor activity of NK cells. Together, these results highlight the therapeutic potential of anti-MICA antibodies to overcome immune suppression and promote tumor destruction in cancer patients.

Example 12: Obtaining Anti-Angiopoietin-2 Antibodies

[0178] Antibodies that bind to angiopoietin-2 were developed using the methods herein. Briefly, biotinylated angiopoietin-2 (UniGene Hs.583870) was purchased from R&D Systems. Peripheral blood mononuclear cells were quickly thawed, washed and resuspended at $5x10^6$ in phosphate buffered saline (pH 7.2) supplemented with 2% fetal calf serum and stained with approximately 0.5ug/ml angiopoietin-2 for 30 minutes on ice. Cells were washed twice with 4ml PBS/2% FCS. Then antibodies were added to identify class-switched, memory B-cells (CD19+, CD27+, and IgM-) as well as SA-PE to label B-cells with biotinylated angiopoietin on the surface. A panel of exclusion antibodies labeling T-cells, natural killer-cells, marcrophages, and dead cells were included to reduce background tetramer staining (CD3, CD14, CD16, 7-AAD). Single B-cells that bound to angiopoietin-2 were sorted into 8-tube-PCR strips using the BD FACS Aria II. The B-cell receptor (BCR) mRNA was amplified using a commercial kit from Epicentre Biotechnologies (catalog number: MBCL90310) using gene specific primers (see above). A two-step nested PCR amplifies the BCR variable domains of heavy and light chains (see above). Peripheral blood mononuclear cells were obtained from a patient with malignant non-small cell lung carcimonnoma who had been vaccinated with autologous tumor cells transduced with a GM-CSF expression vector (GVAX) (Cancer Res. 70: 10150, 2010). The antibodies were expressed as full-length IgG1 antibodies in a transient CHO-S expression system.

[0179] Validation of anti-angiopoietin-2 antibodies binding to angiopoietin-2 was performed using ELISA assays. Briefly, angiopoietin-2 was coated overnight at 4μg/ml in 100mM sodium bicarbonate buffer pH 9.6 in 96-well flat bottom plates (PerkinElmer) at 4°C. Plates were blocked with assay buffer containing bovine serum albumin and bovine gamma globulins (PerkinElmer) at room temperature for three hours. Antibodies were diluted in assay buffer at 20ug/ml-0.16ug/ml and incubated for 1 hour at 4°C. Plates were washed three times with 200μl wash buffer (50mM Tris pH8, 150mM NaCl, 20mM EDTA, 0.05% Tween). 100μl enhancement solution (PerkinElmer) was added to each well and fluorescence counts measured using a Victor3 plate reader (PerkinElmer) at a wavelength of 615nm. Human angiopoietin-1 and -4 was also tested for binding and showed similar reactivity.

[0180] Relevant data is shown in FIGs. 27A-27C, that provide graphs and a gel relating to isolation of angiopoietin-specific antibodies from a lung cancer patient. (A) Angiopoietin-2 reactivity of lung cancer patient (L19) serum (diluted 1:1000) determined by ELISA. Dates of serum collection are shown on the X-axis. The control protein bovine serum albumin (BSA) was included as a negative control. (B) FACS plot showing PBMC sample (timepoint- 10/98) gated on CD19+, CD27+ IgM-B cells with CD 19 on the X-axis and fluorescently-tagged angiopoietin-2 on the Y-axis. The gate indicates approximately where the sorting cut-off was made. Ten B-cells were sorted from this sample. (C) Heavy, light chain, and hinge region PCR products from 10 angiopoietin-2 reactive memory B-cells isolated from pateitn L19. Heavy (top) and light (bottom) chain PCR products after two rounds of nested PCR of approximately 350 base pairs.

Example 13: Binding of Anti-Angiopoietin-2 Antibodies Against Human

Recombinant Angiopoietin Family Members

[0181] 96 well plates were coated overnight with 4 μg/mL recombinant angiopoietin-1, - 2, and -4 (R&D Systems) in sodium bicarbonate buffer at pH9.6. Plates were subsequently blocked for 3 hours at room temperature with assay buffer (Perkin Elmer) containing bovine serum albumin (BSA) and bovine gamma-globulins. Antibodies ID 2, 3, 4, and 5 (see Table 1), diluted between 20 μg/mL-0.16 μg/mL, were incubated on plates for 1 hour at 4°C with rotation. Plates were subsequently washed before being incubated with anti-human IgG-Europium antibody (Perkin Elmer). Fluorescent counts at 615 nm were obtained via plate reader. A negative control antibody (clone 8.18.C5) was used to determine specificity. Data was determined in duplicate.

[0182] As shown in FIGs. 26A-26C, antibodies ID 2, 3, 4, and 5 (see Table 1)bind with high specificity to angiopoietin-

1 -2, and -4. Antibodies do not bind to Ang-like-3, a structurally-related protein (*see* FIG. 26D).

[0183] An additional anti- angiopoietin antibody, designated anti-Ang2 Ab6 (anti-MICA antibody ID-10 described in Table 1) with clinically relevant biological properties were developed using the methods herein. Binding of anti-Ang2 Ab6 to human recombinant angiopoietin family members was analyzed as described above. Briefly, ELISA plates were coated with 4 μg/ml of angiopoietins Ang-1, Ang-2, Ang4, and Ang-like-3 binding, and detection by anti-Ang2 Ab6 was tested at 20 μg/ml. 4 μg/ml, 0.8 μg/ml, and 0.16 μg/ml. Europium conjugated anti-human IgG secondary was used, with europium counts measured after 45 minutes. As shown in FIG. 57, anti-Ang2 Ab6 binds to all angiopoietins in a dose dependent manner.

SEQUENCE LISTING

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        35                  40                  45

Gly Glu Ile Asn His Ser Gly Val Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Ser Gln Phe Ser Leu
65                  70                  75                  80

Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Leu Tyr Tyr Cys Ala
                85                  90                  95

Lys Thr Gly Leu Tyr Tyr Asp Asp Val Trp Gly Thr Phe Arg Pro Arg
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 10

```
gacatcgtga tgacccagtc tccggactcc ctggctgtgt ctctgggcga gagggccacc    60
atcaactgca agtccagcca gagtatttta tatagctccg acaataagaa ttacttagct   120
tggtaccagc acaagccagg acagcctcct aagctcctct tttactgggc atctatccgg   180
gaatccgggg tccctgaccg attcagtggc ggcgggtctg ggacagattt cactctcacc   240
atcagcagtc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtcct   300
ccttgcagtt ttggccaggg gaccaagctg gagatccaa                           339
```

<210> 11
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 11

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Ile Leu Tyr Ser
            20   25   30

Ser Asp Asn Lys Asn Tyr Leu Ala Trp Tyr Gln His Lys Pro Gly Gln
        35   40   45

Pro Pro Lys Leu Leu Phe Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val
    50   55   60

Pro Asp Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85   90   95

Tyr Tyr Ser Pro Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100   105   110

Gln

<210> 12
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 12

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1   5   10   15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser
            20   25

<210> 13
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 13

Gln Ser Ile Leu Tyr Ser Ser Asp Asn Lys Asn Tyr
1   5   10

<210> 14

<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 14

```
Leu Ala Trp Tyr Gln His Lys Pro Gly Gln Pro Pro Lys Leu Leu Phe
1               5                   10                  15

Tyr
```

<210> 15
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 15

```
Trp Ala Ser
1
```

<210> 16
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16

```
Ile Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Gly Gly Ser Gly
1               5                   10                  15

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
            20                  25                  30

Val Tyr Tyr Cys
        35
```

<210> 17
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 17

Gln Gln Tyr Tyr Ser Pro Pro Cys Ser
1 5

<210> 18
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 18

Phe Gly Gln Gly Thr Lys Leu Glu Ile Gln
1 5 10

<210> 19
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 19

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagt agttatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcaggt atttattgga gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca tatccaagaa cacgctgtat 240
ctgcaaatga acagtctgag agccgacgac acggccgtgt attactgtgc gagaggcgat 300
tactatggtt cgggggctca ctttgactac tggggccagg gaaccctggt caccgtctcc 360
tca 363

<210> 20
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20

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

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Gly Ile Tyr Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Asp Tyr Tyr Gly Ser Gly Ala His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 21
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 21

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
            20   25

<210> 22
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 22

Gly Phe Thr Phe Ser Ser Tyr Ala
1   5

<210> 23
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 23

```
Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
1               5                   10                  15

Gly
```

<210> 24
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 24

```
Ile Tyr Trp Ser Gly Gly Ser Thr
1               5
```

<210> 25
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25

```
Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile
1               5                   10                  15

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp
            20                  25                  30

Thr Ala Val Tyr Tyr Cys
        35
```

<210> 26
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 26

Ala Arg Gly Asp Tyr Tyr Gly Ser Gly Ala His Phe Asp Tyr
1 5 10

<210> 27
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 27

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 28
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 28

gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagcca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctcctaattt atcagatttc taaccggttc 180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcggggtt tactactgca tgcaaggtac acaatttcct 300
cggacgttcg gccaagggac caaggtggaa atcaaa 336

<210> 29
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1   5   10   15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20   25   30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
        35   40   45

Pro Arg Leu Leu Ile Tyr Gln Ile Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85   90   95

Thr Gln Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys

            100   105   110

<210> 30
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 30

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1   5   10   15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
            20   25

<210> 31
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 31

Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr
1   5   10

<210> 32

<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 32

```
Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile
1               5                   10                  15

Tyr
```

<210> 33
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 33
Gln Ile Ser
1

<210> 34
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34

```
Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly
1               5                   10                  15

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            20                  25                  30

Val Tyr Tyr Cys
        35
```

<210> 35
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 35

Met Gln Gly Thr Gln Phe Pro Arg Thr
1 5

<210> 36
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 36

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 37
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 37

gaggtgcagc tggtggagtc cgggggaggc ttagttcagc ctggggggatc cctgagactc 60
tcctgtgcag cctcagggtt cacctttagt aataactgga tgcactgggt ccgccaggct 120
ccagggaagg ggctggagtg gatctcagag attagaagtg atgggaattt cacaaggtac 180
gcggactcca tgaagggccg attcaccatc tccagagaca acgccaagag cacactgtat 240
ttgcaaatga acagtctgag agtcgaggac acgggtctgt attactgtgc aagagactac 300
ccctatagca ttgactactg gggccaggga accctggtca ccgtctcctc a 351

<210> 38
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 38

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 Asn Asn
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Glu Ile Arg Ser Asp Gly Asn Phe Thr Arg Tyr Ala Asp Ser Met
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Gly Leu Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Pro Tyr Ser Ile Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 39
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 39

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
20 25

<210> 40
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 40

Gly Phe Thr Phe Ser Asn Asn Trp
1 5

<210> 41
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 41

```
Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ser
1               5                   10                  15

Glu
```

<210> 42
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 42

```
Ile Arg Ser Asp Gly Asn Phe Thr
1               5
```

<210> 43
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 43

```
Arg Tyr Ala Asp Ser Met Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
1               5                   10                  15

Ala Lys Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Val Glu Asp
            20                  25                  30

Thr Gly Leu Tyr Tyr Cys
        35
```

<210> 44
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 44

Ala Arg Asp Tyr Pro Tyr Ser Ile Asp Tyr
1   5   10

<210> 45
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 45

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 46
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 46

gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc 60

atctcctgca catctagtca aagcctcgta cacagtaatg gaaacaccta cttgagttgg 120

cttcagcaga ggccaggcca gcccccaaga ctcctaattt atgagatttc taagcgggtc 180

tctggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaaggtaa acaacttcgg 300

acttttggcc aggggaccaa gctggagatc aaa 333

<210> 47
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 47

```
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Thr Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
        35                  40                  45

Pro Arg Leu Leu Ile Tyr Glu Ile Ser Lys Arg Val Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Lys Gln Leu Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

<210> 48
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 48

```
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Thr Ser Ser
            20                  25
```

<210> 49
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 49

```
Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr
1               5                   10
```

<210> 50
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 50

```
Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile
1               5                   10                  15

Tyr
```

<210> 51
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 51

```
Glu Ile Ser
1
```

<210> 52
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 52

```
Lys Arg Val Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly
1               5                   10                  15

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            20                  25                  30

Val Tyr Tyr Cys
        35
```

<210> 53
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 53

Met Gln Gly Lys Gln Leu Arg Thr
1 5

<210> 54
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 54

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 55
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 55

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggctc cgtgagactg 60

tcttgtgcgg cctcaggctt cattcttagc aactttgcca tgagttgggt ccgccaggct 120

ccagggaagg ggctggactg ggtctcaggt aattttggtg gtcgtgaaaa tacatattac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca gttccaagag cacactgtat 240

ctgcaaatga acaatttgag agccgaggac acggccgtat attactgtgc gcgaggcgat 300

taccatggtt cgggggctca ctttgactac tggggccagg gaatactggt caccgtctcc 360

tca 363

<210> 56
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 56

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Val Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Leu Ser Asn Phe
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
        35   40   45

Ser Gly Asn Phe Gly Gly Arg Glu Asn Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Ser Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Asp Tyr His Gly Ser Gly Ala His Phe Asp Tyr Trp Gly
            100   105   110

Gln Gly Ile Leu Val Thr Val Ser Ser
        115   120

<210> 57
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 57

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Val Arg Leu Ser Cys Ala Ala Ser
            20   25

<210> 58
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 58

Gly Phe Ile Leu Ser Asn Phe Ala
1   5

<210> 59
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 59

```
Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val Ser
1               5                   10                  15

Gly
```

<210> 60
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 60

```
Asn Phe Gly Gly Arg Glu Asn Thr
1               5
```

<210> 61
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 61

```
Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser
1               5                   10                  15

Ser Lys Ser Thr Leu Tyr Leu Gln Met Asn Asn Leu Arg Ala Glu Asp
            20                  25                  30

Thr Ala Val Tyr Tyr Cys

                                35
```

<210> 62
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 62

```
Ala Arg Gly Asp Tyr His Gly Ser Gly Ala His Phe Asp Tyr
1               5                   10
```

<210> 63
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 63

```
Trp Gly Gln Gly Ile Leu Val Thr Val Ser Ser
1               5                   10
```

<210> 64
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 64

```
gatattgtga tgacccagag tccactctcc tcacctgtca tccttggaca gccggcctcc      60
atctcctgca ggtctagtca aagcctccta cacagtgatg gaaacaccta cttgagttgg     120
cttcaccaga ggccaggcca gcctcctaga ctcctaattt atcagatttc taaccggttc     180
tctggggtcc cagacagatt cagtggcagt gggacaggga cagatttcac actgaaaatc     240
agcagggtgg aagctgagga tgccgggatt tattactgca tgcaaggtac agaatttcct     300
cggacgttcg gccaagggac caaggtggaa atcaaa                               336
```

<210> 65
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 65

```
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Ile Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
```

20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
35 40 45

Pro Arg Leu Leu Ile Tyr Gln Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Thr Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Ala Gly Ile Tyr Tyr Cys Met Gln Gly
85 90 95

Thr Glu Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 66
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Ile Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
20 25

<210> 67
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 67

Gln Ser Leu Leu His Ser Asp Gly Asn Thr Tyr
1 5 10

<210> 68
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 68

Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile
1   5   10   15

Tyr

<210> 69
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 69

Gln Ile Ser
1

<210> 70
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 70

Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Thr Gly
1   5   10   15

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Ala Gly
            20   25   30

Ile Tyr Tyr Cys
        35

<210> 71
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 71

Met Gln Gly Thr Glu Phe Pro Arg Thr
1   5

<210> 72

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 72

```
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1               5                   10
```

<210> 73
<211> 384
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 73

```
gaggtgcagc tggtggagtc tgggggaggc ttgatacagc ctggggggtc cctgagactc      60
tcctgtgcaa cctctggatt cacctttaga acttcttcca tgagttgggt ccgtcgggct     120
ccagggaagg ggctggaatg ggtctcagct attggtgctg aaagtcatga cacgcactac     180
acagactccg cggagggccg gttcaccatc tccaaagact attcaaagaa cacagtatat     240
ctgcagatga acggcctgag agtcgacgac acggccatat attattgtgc ccatcactat     300
tactatggct cgcggcagaa acccaaagat tggggagatg cttttgatat gtggggccag     360
gggacaatgg tctccgtctc ttca                                            384
```

<210> 74
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 74

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Arg Thr Ser
            20   25   30

Ser Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Gly Ala Glu Ser His Asp Thr His Tyr Thr Asp Ser Ala
    50   55   60

Glu Gly Arg Phe Thr Ile Ser Lys Asp Tyr Ser Lys Asn Thr Val Tyr
65   70   75   80

Leu Gln Met Asn Gly Leu Arg Val Asp Asp Thr Ala Ile Tyr Tyr Cys
                85   90   95

Ala His His Tyr Tyr Tyr Gly Ser Arg Gln Lys Pro Lys Asp Trp Gly
            100   105   110

Asp Ala Phe Asp Met Trp Gly Gln Gly Thr Met Val Ser Val Ser Ser
        115   120   125

<210> 75
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 75

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Thr Ser
            20   25

<210> 76
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76

Gly Phe Thr Phe Arg Thr Ser Ser
1   5

<210> 77
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 77

```
Met Ser Trp Val Arg Arg Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
1               5                   10                  15

Ala
```

<210> 78
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 78

```
Ile Gly Ala Glu Ser His Asp Thr
1               5
```

<210> 79
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 79

```
His Tyr Thr Asp Ser Ala Glu Gly Arg Phe Thr Ile Ser Lys Asp Tyr
1               5                   10                  15

Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Gly Leu Arg Val Asp Asp
            20                  25                  30

Thr Ala Ile Tyr Tyr Cys
        35
```

<210> 80
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 80

Ala His His Tyr Tyr Tyr Gly Ser Arg Gln Lys Pro Lys Asp Trp Gly
1   5   10   15

Asp Ala Phe Asp Met
            20

<210> 81
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 81

Trp Gly Gln Gly Thr Met Val Ser Val Ser Ser
1   5   10

<210> 82
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 82

gacatccaga tgacccagtc tccatcttct gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca ggatattagc acctggttaa cctggtatca gcagagagca 120

gggaaggccc ctaacctcct gatctatggt gcatccactt tggaagatgg ggtcccatcc 180

aggttcagcg gcagtggatc cgggacagat ttcactctca ctatcgacag cctgcagcct 240

gacgattttg caacttacta ttgtcaacag tctcacagtt tcccctacac ttttggccag 300

gggacccagc tggggatctc a 321

<210> 83
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 83

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Thr Trp
            20                  25                  30

Leu Thr Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Phe Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Gln Leu Gly Ile Ser
            100                 105
```

<210> 84
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 84

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
            20                  25
```

<210> 85
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 85

```
Gln Asp Ile Ser Thr Trp
1               5
```

<210> 86
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 86

```
Leu Thr Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Asn Leu Leu Ile
1               5                   10                  15

Tyr
```

<210> 87
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 87

```
Gly Ala Ser
1
```

<210> 88
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 88

```
Thr Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
1               5                   10                  15

Thr Asp Phe Thr Leu Thr Ile Asp Ser Leu Gln Pro Asp Asp Phe Ala
            20                  25                  30

Thr Tyr Tyr Cys
        35
```

<210> 89
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 89

Gln Gln Ser His Ser Phe Pro Tyr Thr
1 5

<210> 90
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 90

Phe Gly Gln Gly Thr Gln Leu Gly Ile Ser
1 5 10

<210> 91
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 91
taatacgact cactataggt tcggggaagt agtccttgac cagg 44

<210> 92
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 92
taatacgact cactataggg atagaagtta ttcagcaggc acac 44

<210> 93
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 93
taatacgact cactataggc gtcaggctca grtagctgct ggccgc 46

<210> 94
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 94
aatacgactc actataggtt cggggaagta gtccttgacc agg 43

<210> 95
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 95
taatacgact cactataggg atagaagtta ttcagcaggc acac 44

<210> 96
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 96
taatacgact cactataggc gtcaggctca grtagctgct ggccgc 46

<210> 97
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 97
tcaccatgga ctgsacctgg a 21

<210> 98
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 98
ccatggacac actttgytcc ac 22

<210> 99
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 99
tcaccatgga gtttgggctg agc 23

<210> 100
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 100
agaacatgaa acayctgtgg ttctt 25

<210> 101
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 101
atggggtcaa ccgccatcct 20

<210> 102
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 102
acaatgtctg tctccttcct cat 23

<210> 103
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 103
gctcagctcc tggggctcct g 21

<210> 104
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 104
ctggggctgc taatgctctg g 21

<210> 105
<211> 21
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 105
ttcctcctgc tactctggct c 21

<210> 106
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 106
cagacccagg tcttcatttc t 21

<210> 107
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 107
cctctcctcc tcaccctcct 20

<210> 108
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 108
ctcctcactc agggcaca 18

<210> 109
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 109
atggcctgga ycsctctcc 19

<210> 110
<211> 19
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 110
gccaggggga agacsgatg 19

<210> 111
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 111
tttcaactgc tcatcagatg gcgg 24

<210> 112
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 112
agctcctcag aggagggygg 20

<210> 113
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 113
caggtscagc tggtrcagtc 20

<210> 114
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 114
cagrtcacct tgaaggagtc 20

<210> 115
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 115

saggtgcagc tggtggagtc 20

<210> 116
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 116
caggtgcagc tgcaggagtc 20

<210> 117
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 117
gargtgcagc tggtgcagtc 20

<210> 118
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 118
caggtacagc tgcagcagtc 20

<210> 119
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 119
cgmcatccrg wtgacccagt 20

<210> 120
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 120
cgatrttgtg atgacycag 19

<210> 121

<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 121
cgaaatwgtg wtgacrcagt ct 22

<210> 122
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 122
cgacatcgtg atgacccagt 20

<210> 123
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 123
ccagtctgtg ctgactcagc 20

<210> 124
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 124
ccagtctgcc ctgactcagc 20

<210> 125
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 125
ctcctatgag ctgacwcagc 20

<210> 126
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 126
gacsgatggg cccttggtgg a 21

<210> 127
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 127
aagatgaaga cagatggtgc 20

<210> 128
<211> 16
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 128
gggaacagag tgaccg 16

<210> 129
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 129
tcactatgga ctggatttgg a 21

<210> 130
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 130
ccatggacay actttgytcc ac 22

<210> 131
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 131
gtaggagaca tgcaaatagg gcc 23

<210> 132
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 132
aacaaagcta tgacatatag atc 23

<210> 133
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 133
atggagttgg ggctgagctg ggtt 24

<210> 134
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 134
agttgttaaa tgtttatcgc aga 23

<210> 135
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 135
aggtaattca tggagaaata gaa 23

<210> 136
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 136
agaacatgaa gcayctgtgg ttctt 25

<210> 137
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 137
atggactgga cctggagcat c 21

<210> 138
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 138
cctctgctga tgaaaaccag ccc 23

<210> 139
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 139
caggtycagc tkgtgcagtc 20

<210> 140
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 140
caratgcagc tggtgcagtc 20

<210> 141
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 141
cagrtcacct tgarggagtc tggt 24

<210> 142
<211> 20
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 142
gargtgcagc tgktggagtc 20

<210> 143
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 143
gaggtacaac tggtggagtc 20

<210> 144
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 144
gaggatcagc tggtggagtc 20

<210> 145
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 145
caggtgcagc tacagcagtg 20

<210> 146
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 146
cagctgcagc tgcaggagtc 20

<210> 147
<211> 20
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 147
caggtgcagc tggtgcaatc 20

<210> 148
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 148

caggtgcagc tgcaggagtc gggcccagga ctggtggagc cttcggggac cctgtccctc 60
acctgcactg tgtctggtgg ctccatcagc aggagtaact ggtggagttg ggtccgccag 120
cccccagggg aggggctgga atggattgga gaaatccatc acattgggag gtccagctac 180
aatccgtccc tcaagagtcg agtcaccatg tctgtagaca agtcccagaa ccagttctcc 240
ctgaggctga cctctgtgac cgccgcggac acggccgtgt attactgtgc gaaaaatggc 300
tactacgcta tggacgtctg gggccaaggg accacggtca ccgtctcctc g 351

<210> 149
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 149

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Glu Pro Ser Gly
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Arg Ser
            20                  25                  30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp
        35                  40                  45

Ile Gly Glu Ile His His Ile Gly Arg Ser Ser Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Met Ser Val Asp Lys Ser Gln Asn Gln Phe Ser
65                  70                  75                  80

Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asn Gly Tyr Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 150
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 150

```
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc    60
ctctcctgca gggccagtca gagtgttagc agcgacttcc tagcctggta ccagcagaaa   120
cctggccagg ctcccaggct cctcatctac gctacatcct tcagggccac tggcatctca   180
gacaggttca gtggcagtgg gtctgggaca gacttctctc tcaccatcaa cagactggaa   240
cctgaagatt ttgcagtgta ttactgtcag cactatcgta gttcacctcc gtggtacact   300
tttgcccagg ggaccaagct ggacatgaga cgtacggtgg ctgcaccatc tgtc         354
```

<210> 151
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 151

```
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 Ser Val Ser Ser Asp
            20                  25                  30

Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Ala Thr Ser Phe Arg Ala Thr Gly Ile Ser Asp Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Asn Arg Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Arg Ser Ser Pro
                85                  90                  95

Pro Trp Tyr Thr Phe Ala Gln Gly Thr Lys Leu Asp Met Arg Arg Thr
            100                 105                 110

Val Ala Ala Pro Ser Val
        115
```

<210> 152
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 152

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Glu Pro Ser Gly
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser
            20                  25
```

<210> 153
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 153

```
Gly Gly Ser Ile Ser Arg Ser Asn Trp
1               5
```

<210> 154
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 154

```
Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp Ile Gly
1               5                   10                  15

Glu
```

<210> 155
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 155

```
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
1               5                   10
```

<210> 156
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 156

```
Ile His His Ile Gly Arg Ser
1               5
```

<210> 157
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 157

Ser Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met Ser Val Asp Lys
1   5   10   15

Ser Gln Asn Gln Phe Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp
            20   25   30

Thr Ala Val Tyr Tyr
        35

<210> 158
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 158

Cys Ala Lys Asn Gly Tyr Tyr Ala Met Asp Val Trp
1   5   10

<210> 159
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 159

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
            20   25

<210> 160
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 160

Gln Ser Val Ser Ser Asp Phe
1   5

<210> 161
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 161

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
1               5                   10                  15

Tyr
```

<210> 162
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 162

```
Ala Thr Ser
1
```

<210> 163
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 163

```
Phe Arg Ala Thr Gly Ile Ser Asp Arg Phe Ser Gly Ser Gly Ser Gly
1               5                   10                  15

Thr Asp Phe Ser Leu Thr Ile Asn Arg Leu Glu Pro Glu Asp Phe Ala
            20                  25                  30

Val Tyr Tyr
        35
```

<210> 164
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 164

Cys Gln His Tyr Arg Ser Ser Pro Pro Trp Tyr Thr Phe
1   5   10

<210> 165
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 165

Ala Gln Gly Thr Lys Leu Asp Met Arg Arg Thr Val Ala Ala Pro Ser
1   5   10   15

Val

<210> 166
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 166

Asn Ser Asn Pro Ser Leu Lys Ser Arg Val Ile Ile Ser Val Asp Lys
1   5   10   15

Ser Lys Asn His Phe Ser Leu Thr Leu Asn Ser Val Thr Ala Ala Asp
            20   25   30

Thr Ala Val Tyr Tyr
        35

<210> 167
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 167

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggggac cctgtccctc 60
acctgcgctg tctctggtgc ctccattacc aatggtgcct ggtggagttg ggtccgccag 120
cccccaggga aggggctgga gtggattgga gaaatctatc ttaatgggaa caccaactcc 180
aacccgtccc tgaagagtcg agtcatcata tcagtggaca agtccaagaa ccacttctcg 240
ctgaccctga actctgtgac cgccgcggac acggccgtgt attactgtgc gaagaacgct 300
gcctacaacc ttgagttctg gggccaggga gccctggtca ccgtctcctc a 351

<210> 168
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 168

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Ala Ser Ile Thr Asn Gly
20 25 30

Ala Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Glu Ile Tyr Leu Asn Gly Asn Thr Asn Ser Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Ile Ile Ser Val Asp Lys Ser Lys Asn His Phe Ser
65 70 75 80

Leu Thr Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asn Ala Ala Tyr Asn Leu Glu Phe Trp Gly Gln Gly Ala Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 169
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 169

```
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc    60
ctctcctgca gggccagtca gactgttagc agcccctacg tagcctggta ccagcagaaa   120
cgtggccagg ctcccaggct cctcatctat ggtgcatcca ccagggccac cggcatccca   180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag   240
cctgaagatt ttgcagtgta ttactgtcag cagtatgata gatcatacta ttacactttt   300
ggccagggga ccaagctgga gatcaaa                                       327
```

<210> 170
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 170

```
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 Thr Val Ser Ser Pro


            20                  25                  30

Tyr Val Ala Trp Tyr Gln Gln Lys Arg Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Thr 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 Tyr Asp Arg Ser Tyr
                85                  90                  95

Tyr Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 171
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 171

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser
            20   25

<210> 172
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 172

Gly Ala Ser Ile Thr Asn Gly Ala Trp
1   5

<210> 173
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 173

Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
1   5   10   15

Glu

<210> 174
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 174

Ile Tyr Leu Asn Gly Asn Thr
1   5

<210> 175
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 175

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
1   5   10

<210> 176
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 176

Cys Ala Lys Asn Ala Ala Tyr Asn Leu Glu Phe Trp
1   5   10

<210> 177
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 177

Gly Gln Gly Ala Leu Val Thr Val Ser Ser
1   5   10

<210> 178
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 178

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
            20   25

<210> 179
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 179

Gln Thr Val Ser Ser Pro Tyr
1 5

<210> 180
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 180

Val Ala Trp Tyr Gln Gln Lys Arg Gly Gln Ala Pro Arg Leu Leu Ile
1 5 10 15

Tyr

<210> 181
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 181

Gly Ala Ser
1

<210> 182
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 182

Thr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
1 5 10 15

Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala
20 25 30

Val Tyr Tyr
35

<210> 183
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 183

```
Cys Gln Gln Tyr Asp Arg Ser Tyr Tyr Tyr Thr Phe
1               5                   10
```

<210> 184
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 184

```
Gly Gln Gly Thr Lys Leu Glu Ile Lys
1               5
```

<210> 185
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 185

```
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagaa cctgtcgctc      60
acctgcactg tctctgatgc ctccatgagt gattatcact ggagctggat ccggcaggcc     120
gccgggaagg gactggagtg gattgggcgt atgtacagca ctgggagtcc ctactacaaa     180
ccctccctca aaggtcgggt caccatgtca atagacacgt ccaagaacca gttctccctg     240
aagctggcct ctgtgaccgc cgcagacacg gccatctatt attgtgcgag cggacaacat     300
attggtggct gggtcccccc tgacttctgg ggccagggaa ccctggtcac cgtctcctca     360
```

<210> 186
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 186

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

Asn Leu Ser Leu Thr Cys Thr Val Ser Asp Ala Ser Met Ser Asp Tyr
            20                  25                  30

His Trp Ser Trp Ile Arg Gln Ala Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Met Tyr Ser Thr Gly Ser Pro Tyr Tyr Lys Pro Ser Leu Lys
    50                  55                  60

Gly Arg Val Thr Met Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ala Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95

Ser Gly Gln His Ile Gly Gly Trp Val Pro Pro Asp Phe Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 187
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 187

```
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc      60
atctcctgca ggtctagtga aggcctcgta tatagtgatg gagacaccta cttgagttgg     120
tttcaccaga ggccaggcca gcctccaaga ctcctgattt ataaaatttc taaccggttc     180
tctggggtcc ccgacagatt cagtggcagt ggggcaggca cagatttcac actgaaaatc     240
agcagggtgg aggctgagga tgtcggggtt tattactgca tgcaagctac acattttccg     300
tggacgttcg gccaggggac caaagtggaa gtcaaacgt                            339
```

<210> 188
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 188

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Glu Gly Leu Val Tyr Ser
20 25 30

Asp Gly Asp Thr Tyr Leu Ser Trp Phe His Gln Arg Pro Gly Gln Pro
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Thr His Phe Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys
100 105 110

Arg

<210> 189
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 189

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Asn Leu Ser Leu Thr Cys Thr Val Ser
20 25

<210> 190
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 190

Asp Ala Ser Met Ser Asp Tyr His
1 5

<210> 191
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 191

```
Trp Ser Trp Ile Arg Gln Ala Ala Gly Lys Gly Leu Glu Trp Ile Gly
1               5                   10                  15

Arg
```

<210> 192
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 192

```
Met Tyr Ser Thr Gly Ser Pro
1               5
```

<210> 193
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 193

```
Tyr Tyr Lys Pro Ser Leu Lys Gly Arg Val Thr Met Ser Ile Asp Thr
1               5                   10                  15

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ala Ser Val Thr Ala Ala Asp
            20                  25                  30

Thr Ala Ile Tyr Tyr
        35
```

<210> 194
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 194

Cys Ala Ser Gly Gln His Ile Gly Gly Trp Val Pro Pro Asp Phe Trp
1   5   10   15

<210> 195
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 195

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1   5   10

<210> 196
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 196

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1   5   10   15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
            20   25

<210> 197
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 197

Glu Gly Leu Val Tyr Ser Asp Gly Asp Thr Tyr
1   5   10

<210> 198
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 198

Leu Ser Trp Phe His Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile
1   5   10   15

Tyr

<210> 199
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 199

Lys Ile Ser
1

<210> 200
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 200

Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly
1   5   10   15

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            20   25   30

Val Tyr Tyr
        35

<210> 201
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 201

Cys Met Gln Ala Thr His Phe Pro Trp Thr Phe
1   5   10

<210> 202
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 202

Gly Gln Gly Thr Lys Val Glu Val Lys Arg
1   5   10

<210> 203
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 203

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagt tcatatggct tgacctggat acgccaggct 120

ccggggaagg gcctggagtg ggtctcaagt atcagtggca gtggcaataa cacatactac 180

gcagactctg tgaagggccg gttcaccatc tccagagaca aagtcaagaa gacactatat 240

ctacaaatgg acagcctgac agtcggagac acggccgtct attactgctt aggagtcggt 300

cagggccacg gaattccggt catcgtctcc tca 333

<210> 204
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 204

```
Glu Val Gln Leu Leu 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

Gly Leu Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Ser Gly Ser Gly Asn Asn Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys Val Lys Lys Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asp Ser Leu Thr Val Gly Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Leu Gly Val Gly Gln Gly His Gly Ile Pro Val Ile Val Ser Ser
            100                 105                 110
```

<210> 205
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 205

```
gatattgtga tgacccagac tccactctcc tcacctgtca cccttggaca gccggcctcc      60
atctcctgca ggtctagtca gagcctcgta caccgtgatg gaaacaccta cttgagttgg     120
tttctgcaga ggccaggcca ggctccaaga ctcctaattt atcggatttc taaccggttc     180
tctggggtcc cagacagatt cagtggcagt ggggcaggga cggatttcac actgaaaatc     240
agcagggtgg aagctgagga tgtcggcgtt tactactgca tgcaagctac acaaatcccc     300
aacacttttg gccaggggac caagctggag atcaag                               336
```

<210> 206
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 206

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Arg
20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Phe Leu Gln Arg Pro Gly Gln Ala
35 40 45

Pro Arg Leu Leu Ile Tyr Arg Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Thr Gln Ile Pro Asn Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 207
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 207

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser
20 25

<210> 208
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 208

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 209
<211> 17
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 209

```
Leu Thr Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
1               5                   10                  15

Ser
```

<210> 210
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 210

```
Ile Ser Gly Ser Gly Asn Asn Thr
1               5
```

<210> 211
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 211

```
Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Lys
1               5                   10                  15

Val Lys Lys Thr Leu Tyr Leu Gln Met Asp Ser Leu Thr Val Gly Asp
            20                  25                  30

Thr Ala Val Tyr Tyr
        35
```

<210> 212
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 212

Cys Leu Gly Val Gly Gln
1 5

<210> 213
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 213

Gly His Gly Ile Pro Val Ile Val Ser Ser
1 5 10

<210> 214
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 214

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
20 25

<210> 215
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 215

Gln Ser Leu Val His Arg Asp Gly Asn Thr Tyr
1 5 10

<210> 216
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 216

```
Leu Ser Trp Phe Leu Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile
1               5                   10                  15

Tyr
```

<210> 217
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 217

```
Arg Ile Ser
1
```

<210> 218
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 218

```
Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly
1               5                   10                  15

Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            20                  25                  30

Val Tyr Tyr
        35
```

<210> 219
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 219

```
Cys Met Gln Ala Thr Gln Ile Pro Asn Thr Phe
1               5                   10
```

<210> 220
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 220

```
Gly Gln Gly Thr Lys Leu Glu Ile Lys
1               5
```

<210> 221
<211> 363
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 221

```
gaggtgcagc tggtggagtc tggaggaggc ttaatccagc cgggggggtc cctaagactc      60
tcctgtgcag cctcgggctt cctcatcagt agttatttca tgagctgggt ccgccaggct     120
ccagggaagg ggccggagtg ggtctcagtt atttatagcg atggtagtac atattacgta     180
gactccgtga agggccgatt caccatctcc acagacaatt ccaagaacac actatatctt     240
cagatgaaca gcctgagagc cgaggacacg gcccgatatt actgtgcgac acggcatttg     300
aattatgacg gtgaccactg gggccaggga accctggtca ccgtctcctc agcctccacc     360
aag                                                                   363
```

<210> 222
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 222

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Leu Ile Ser Ser Tyr
            20                  25                  30

Phe Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45

Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Val Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Thr Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Arg Tyr Tyr Cys Ala
                85                  90                  95

Thr Arg His Leu Asn Tyr Asp Gly Asp His Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120
```

<210> 223
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 223

```
gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc    60
atctcctgca ggtctagtca aagcctcgta cacagtgacg gaaacaccta cttgaattgg   120
tttcaccaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taagcgggac   180
tctggggtcc cagacagatt cagcggcagt gggtcaggta gtgatttcac actgaaaatc   240
agcagggtgg aggctgagga tgttggaatt tattactgca tgcaaggtac acattggccg   300
acgttcggcc aagggaccaa ggtggaaatc aaacgaactg tggctgca                348
```

<210> 224
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 224

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
            20                  25                  30

Asp Gly Asn Thr Tyr Leu Asn Trp Phe His Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Arg Arg Leu Ile Tyr Lys Val Ser Lys Arg Asp Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly
                85                  90                  95

Thr His Trp Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110

Thr Val Ala Ala
        115
```

<210> 225
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 225

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser
            20                  25
```

<210> 226
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 226

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Gly Phe Leu Ile Ser Ser Tyr Phe
1               5
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<210> 227
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 227

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Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val Ser
1               5                   10                  15

Val
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<210> 228
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 228

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Ile Tyr Ser Asp Gly Ser Thr
1               5
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<210> 229
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 229

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Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Thr Asp Asn
1               5                   10                  15

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            20                  25                  30

Thr Ala Arg Tyr Tyr
        35
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<210> 230
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 230

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Cys Ala Thr Arg His Leu Asn Tyr Asp Gly Asp His Trp
1               5                   10
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<210> 231
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 231

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Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser
            20                  25
```

<210> 232
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 232

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Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr
1               5                   10
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<210> 233
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 233

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Leu Asn Trp Phe His Gln Arg Pro Gly Gln Ser Pro Arg Arg Leu Ile
1               5                   10                  15

Tyr
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<210> 234
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 234

Lys Val Ser
1

<210> 235
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 235

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Lys Arg Asp Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
1               5                   10                  15

Ser Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly
            20                  25                  30

Ile Tyr Tyr
        35
```

<210> 236
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 236

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Cys Met Gln Gly Thr His Trp Pro Thr Phe
1               5                   10
```

<210> 237
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 237

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Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
1               5                   10
```

<210> 238
<211> 15

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 238

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Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
1               5                   10                  15
```

Claims

1. A composition comprising an antibody or antibody fragment that immunospecifically binds to MHC class I polypeptide-related sequence A (MICA), wherein the antibody or antibody fragment comprises a heavy chain variable region (V_H) and a light chain variable region (V_L) and,

   (a) complementarity determining region (CDR) 3 set forth in SEQ ID NO:212 of the V_H of antibody ID 9; or
   (b) complementarity determining region (CDR) 3 set forth in SEQ ID NO: 158 of the V_H of antibody ID 6.

2. The composition of claim 1, wherein the antibody or antibody fragment comprises,

   (a) complementarity determining region (CDR) 3 set forth in SEQ ID NO:212 of the V_H of antibody ID 9, and CDR3 set forth in SEQ ID NO:219 of the V_L of antibody ID 9; or
   (b) complementarity determining region (CDR) 3 set forth in SEQ ID NO:158 of the V_H of antibody ID 6, and CDR3 set forth in SEQ ID NO:164 of the V_L of antibody ID 6.

3. The composition of claim 1 or claim 2, wherein the antibody or antibody fragment set forth in (a) further comprises complementarity determining region CDR2 set forth in SEQ ID NO:210 of the V_H of antibody ID 9, and CDR2 set forth in SEQ ID NO:217 of the V_L of antibody ID 9; or wherein the peptide set forth in (b) further comprises complementarity determining region CDR2 set forth in SEQ ID NO: 156 of the V_H of antibody ID 6, and CDR2 set forth in SEQ ID NO: 162 of the V_L of antibody ID 6.

4. The composition any one of claims 1-3, wherein the antibody or antibody fragment set forth in (a) comprises complementarity determining region CDR1 set forth in SEQ ID NO:208 of the V_H of antibody ID 9, and CDR1 set forth in SEQ ID NO:215 of the V_L of antibody ID 9; or wherein the peptide set forth in (b) comprises complementarity determining region CDR1 set forth in SEQ ID NO:153 of the V_H of antibody ID 6, and CDR1 set forth in SEQ ID NO:160 of the V_L of antibody ID 6.

5. The composition of any one of claims 1-4, wherein the antibody or antibody fragment comprises:

   (a) a V_H chain with at least 95%, 96%, 97%, 98 or 99% identity to SEQ ID NO: 204; or
   (b) a V_H chain with at least 95%, 96%, 97%, 98 or 99% identity to SEQ ID NO: 149.

6. The composition of any one of claims 1-5, wherein the antibody or antibody fragment comprises

   (a) a V_L chain with at least 95%, 96%, 97%, 98 or 99% identity to the amino acid sequence set forth in SEQ ID NO: 206, wherein the V_L comprises no more than one amino acid substitution within the CDRs relative to the V_L CDR1 amino acid sequence set forth in SEQ ID NO: 215, the V_L CDR2 amino acid sequence set forth in SEQ ID NO: 217, and the V_L CDR3 amino acid sequence set forth in SEQ ID NO:219; or
   (b) a V_L chain with at least 95%, 96%, 97%, 98 or 99% identity to the amino acid sequence set forth in SEQ ID NO: 151, wherein the V_L comprises no more than one amino acid substitution within the CDRs relative to the V_L CDR1 amino acid sequence set forth in SEQ ID NO: 160, the V_L CDR2 amino acid sequence set forth in SEQ ID NO: 162, and the V_L CDR3 amino acid sequence set forth in SEQ ID NO: 164.

7. The composition of any one of claims 1-6, wherein the antibody or antibody fragment comprises,

(a) a V_H CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 208, a V_H CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 210, a V_H CDR3 comprising the amino acid sequence set forth in SEQ ID NO:212, a V_L CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 215, a V_L CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 217 and a V_L CDR3 comprising the amino acid sequence set forth in SEQ ID NO:219; or
(b) a V_H CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 153, a V_H CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 156, a V_H CDR3 comprising the amino acid sequence set forth in SEQ ID NO:158, a V_L CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 160, a V_L CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 162 and a V_LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:164.

8. The composition of claim 7, wherein the antibody or antibody fragment comprises,

(a) a V_H with at least 95%, 96%, 97%, 98% or 99% identity to the amino acid sequence set forth in SEQ ID NO: 204 and a V_L chain with at least 95%, 96%, 97%, 98% or 99% identity to the amino acid sequence set forth in SEQ ID NO: 206; or V_H chain with at least 95%, 96%, 97%, 98% or 99% identity to the amino acid sequence set forth in SEQ ID NO: 149 and a V_L chain with at least 95%, 96%, 97%, 98% or 99% identity to the amino acid sequence set forth in SEQ ID NO: 151.

9. The composition of claim 8, wherein the antibody or antibody fragment comprises a V_H chain comprising SEQ ID NO: 204 and a V_L chain comprising SEQ ID NO: 206; or a V_H chain comprising SEQ ID NO: 149 and a V_L chain comprising SEQ ID NO: 151.

10. The composition of any one of claims 1-9, further comprising an anti-cancer therapeutic.

11. The composition of any one of claims 1-10, formulated as a pharmaceutical composition.

12. The composition of any one of claims 1-11, further comprising an histone deacetylase inhibitor (HDAC) selected from the group consisting of hydroxamic acid, vorinostat, suberoylanilide hydroxamic acid (SAHA, trichostatin A (TSA), LAQ824, panobinostat (LBH589), belinostat (PXD101), ITF2357 italfarmaco SpA, cyclic tetrapeptide, depsipeptide (romidepsin, FK228), benzamide; entinostat (SNDX-275/MS-275), MGCD0103, short-chain aliphatic acids, valproic acid, phenyl butyrate, AN-9, pivanex, CHR-3996, and CHR-2845.

13. The composition of any one of claims 1-12, further comprising a proteasome inhibitor selected from the group consisting of bortezomib, NPI-0052, carfilzomib (PR-171), CEP 18770, and MLN9708.

14. The composition of any one of claims 1-13, further comprising an antibody selected from the group consisting of an anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-PDL-1 antibody and a combination of one or more thereof.

Patentansprüche

1. Zusammensetzung, umfassend einen Antikörper oder ein Antikörperfragment, der/das an die Polypeptid-bezogene Sequenz A der MHC-Klasse I (MICA) spezifisch bindet, wobei der Antikörper oder das Antikörperfragment eine variable Region einer schweren Kette (V_H) und eine variable Region einer leichten Kette (V_L) und

(a) die in SEQ ID NO: 212 der V_H von Antikörper ID 9 angeführte komplementätsbestimmende Region (CDR) 3; oder
(b) die in SEQ ID NO: 158 der V_H von Antikörper ID 6 angeführte komplementätsbestimmende Region (CDR) 3

umfasst.

2. Zusammensetzung nach Anspruch 1, wobei der Antikörper oder das Antikörperfragment

(a) die in SEQ ID NO: 212 der V_H von Antikörper ID 9 angeführte komplementätsbestimmende Region (CDR) 3 und die in SEQ ID NO: 219 der V_L von Antikörper ID 9 angeführte CDR3; oder
(b) die in SEQ ID NO: 158 der V_H von Antikörper ID 6 angeführte komplementätsbestimmende Region (CDR) 3 und die in SEQ ID NO: 164 der V_L von Antikörper ID 6 angeführte CDR3

umfasst.

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, wobei der/das in (a) angeführte Antikörper oder Antikörperfragment ferner die in SEQ ID NO: 210 der V_H von Antikörper ID 9 angeführte komplementätsbestimmende Region CDR2 und die in SEQ ID NO: 217 der V_L von Antikörper ID 9 angeführte CDR2 umfasst; oder wobei das in (b) angeführte Peptid ferner die in SEQ ID NO: 156 der V_H von Antikörper ID 6 angeführte komplementätsbestimmende Region CDR2 und die in SEQ ID NO: 162 der V_L von Antikörper ID 6 angeführte CDR2 umfasst.

4. Zusammensetzung nach einem der Ansprüche 1-3, wobei der/das in (a) angeführte Antikörper oder Antikörperfragment die in SEQ ID NO: 208 der V_H von Antikörper ID 9 angeführte komplementätsbestimmende Region CDR1 und die in SEQ ID NO: 215 der V_L von Antikörper ID 9 angeführte CDR1 umfasst; oder wobei das in (b) angeführte Peptid die in SEQ ID NO: 153 der V_H von Antikörper ID 6 angeführte komplementätsbestimmende Region CDR1 und die in SEQ ID NO: 160 der V_L von Antikörper ID 6 angeführte CDR1 umfasst.

5. Zusammensetzung nach einem der Ansprüche 1-4, wobei der Antikörper oder das Antikörperfragment umfasst:

(a) eine V_H-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit SEQ ID NO: 204; oder
(b) eine V_H-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit SEQ ID NO: 149.

6. Zusammensetzung nach einem der Ansprüche 1-5, wobei der Antikörper oder das Antikörperfragment umfasst

(a) eine V_L-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 206 angeführten Aminosäuresequenz, wobei die V_L nicht mehr als eine Aminosäure-Substitution in den CDRs relativ zu der in SEQ ID NO: 215 angeführten V_L-CDR1-Aminosäuresequenz, der in SEQ ID NO: 217 angeführten V_L-CDR2-Aminosäuresequenz und der in SEQ ID NO: 219 angeführten V_L-CDR3-Aminosäuresequenz umfasst; oder
(b) eine V_L-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 151 angeführten Aminosäuresequenz, wobei die V_L nicht mehr als eine Aminosäure-Substitution in den CDRs relativ zu der in SEQ ID NO: 160 angeführten V_L-CDRl-Aminosäuresequenz, der in SEQ ID NO: 162 angeführten V_L-CDR2-Aminosäuresequenz und der in SEQ ID NO: 164 angeführten V_L-CDR3-Aminosäuresequenz umfasst.

7. Zusammensetzung nach einem der Ansprüche 1-6, wobei der Antikörper oder das Antikörperfragment umfasst

(a) eine V_H-CDR1, umfassend die in SEQ ID NO: 208 angeführte Aminosäuresequenz, eine V_H-CDR2, umfassend die in SEQ ID NO: 210 angeführte Aminosäuresequenz, eine V_H-CDR3, umfassend die in SEQ ID NO: 212 angeführte Aminosäuresequenz, eine V_L-CDR1, umfassend die in SEQ ID NO: 215 angeführte Aminosäuresequenz, eine V_L-CDR2, umfassend die in SEQ ID NO: 217 angeführte Aminosäuresequenz, und eine V_L-CDR3, umfassend die in SEQ ID NO: 219 angeführte Aminosäuresequenz; oder
(b) eine V_H-CDR1, umfassend die in SEQ ID NO: 153 angeführte Aminosäuresequenz, eine V_H-CDR2, umfassend die in SEQ ID NO: 156 angeführte Aminosäuresequenz, eine V_H-CDR3, umfassend die in SEQ ID NO: 158 angeführte Aminosäuresequenz, eine V_L-CDR1, umfassend die in SEQ ID NO: 160 angeführte Aminosäuresequenz, eine V_L-CDR2, umfassend die in SEQ ID NO: 162 angeführte Aminosäuresequenz, und eine V_L-CDR3, umfassend die in SEQ ID NO: 164 angeführte Aminosäuresequenz.

8. Zusammensetzung nach Anspruch 7, wobei der Antikörper oder das Antikörperfragment umfasst

(a) eine V_H mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 204 angeführten Aminosäuresequenz und eine V_L-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 206 angeführten Aminosäuresequenz; oder eine V_H-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 149 angeführten Aminosäuresequenz und eine V_L-Kette mit mindestens 95 %, 96 %, 97 %, 98 % oder 99 % Identität mit der in SEQ ID NO: 151 angeführten Aminosäuresequenz.

9. Zusammensetzung nach Anspruch 8, wobei der Antikörper oder das Antikörperfragment eine V_H-Kette, umfassend SEQ ID NO: 204, und eine V_L-Kette, umfassend SEQ ID NO: 206; oder eine V_H-Kette, umfassend SEQ ID NO: 149, und eine V_L-Kette, umfassend SEQ ID NO: 151, umfasst.

10. Zusammensetzung nach einem der Ansprüche 1-9, ferner umfassend ein Antikrebs-Therapeutikum.

11. Zusammensetzung nach einem der Ansprüche 1-10, formuliert als eine pharmazeutische Zusammensetzung.

12. Zusammensetzung nach einem der Ansprüche 1-11, ferner umfassend einen Histon-Deacetylase-Hemmer (HDAC), ausgewählt aus der Gruppe, bestehend aus Hydroxamsäure, Vorinostat, Suberoylanilid-hydroxamsäure (SAHA), Trichostatin A (TSA), LAQ824, Panobinostat (LBH589), Belinostat (PXD101), ITF2357 Italfarmaco SpA, cyclischem Tetrapeptid, Depsipeptid (Romidepsin, FK228), Benzamid; Entinostat (SNDX-275/MS-275), MGCD0103, kurzkettigen aliphatischen Säuren, Valproinsäure, Phenylbutyrat, AN-9, Pivanex, CHR-3996 und CHR-2845.

13. Zusammensetzung nach einem der Ansprüche 1-12, ferner umfassend einen Proteasom-Hemmer, ausgewählt aus der Gruppe, bestehend aus Bortezomib, NPI-0052, Carfilzomib (PR-171), CEP 18770 und MLN9708.

14. Zusammensetzung nach einem der Ansprüche 1-13, ferner umfassend einen Antikörper, ausgewählt aus der Gruppe, bestehend aus einem Anti-CTLA-4-Antikörper, einem Anti-PD-1-Antikörper, einem Anti-PDL-1-Antikörper und einer Kombination von einem oder mehreren davon.

Revendications

1. Composition comprenant un anticorps ou fragment d'anticorps qui se lie immunospécifiquement à une séquence A associée à un polypeptide du CMH de classe I (MICA), dans laquelle l'anticorps ou fragment d'anticorps comprend une région variable de chaîne lourde (V_H) et une région variable de chaîne légère (V_L) et,

    (a) une région déterminante complémentaire (CDR) 3 présentée dans la SEQ ID NO: 212 de la V_H de l'anticorps ID 9; ou bien
    (b) une région déterminante complémentaire (CDR) 3 présentée dans la SEQ ID NO: 158 de la V_H de l'anticorps ID 6.

2. Composition selon la revendication 1, dans laquelle l'anticorps ou fragment d'anticorps comprend,

    (a) une région déterminante complémentaire (CDR) 3 présentée dans la SEQ ID NO: 212 de la V_H de l'anticorps ID 9, et CDR3 présentée dans la SEQ ID NO: 219 de la V_L de l'anticorps ID 9; ou bien
    (b) une région déterminante complémentaire (CDR) 3 présentée dans la SEQ ID NO: 158 de la V_H de l'anticorps ID 6, et CDR3 présentée dans la SEQ ID NO: 164 de la V_L de l'anticorps ID 6.

3. Composition selon la revendication 1 ou la revendication 2, dans laquelle l'anticorps ou fragment d'anticorps présenté sous (a) comprend en outre une région déterminante complémentaire CDR2 présentée dans la SEQ ID NO: 210 de la V_H de l'anticorps ID 9, et CDR2 présentée dans la SEQ ID NO: 217 de la V_L de l'anticorps ID 9; ou bien dans laquelle le peptide présenté sous (b) comprend en outre une région déterminante complémentaire CDR2 présentée dans la SEQ ID NO: 156 de la V_H de l'anticorps ID 6, et CDR2 présentée dans la SEQ ID NO: 162 de la V_L de l'anticorps ID 6.

4. Composition selon l'une quelconque des revendications 1-3, dans laquelle l'anticorps ou fragment d'anticorps présenté sous (a) comprend une région déterminante complémentaire CDR1 présentée dans la SEQ ID NO: 208 de la V_H de l'anticorps ID 9, et CDR1 présentée dans la SEQ ID NO: 215 de la V_L de l'anticorps ID 9; ou bien dans laquelle le peptide présenté sous (b) comprend une région déterminante complémentaire CDR1 présentée dans la SEQ ID NO: 153 de la V_H de l'anticorps ID 6, et CDR1 présentée dans la SEQ ID NO: 160 de la V_L de l'anticorps ID 6.

5. Composition selon l'une quelconque des revendications 1-4, dans laquelle l'anticorps ou le fragment d'anticorps comprend:

    (a) une chaîne V_H ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la SEQ ID NO: 204; ou bien
    (b) une chaîne V_H ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la SEQ ID NO: 149.

6. Composition selon l'une quelconque des revendications 1-5, dans laquelle l'anticorps ou fragment d'anticorps comprend:

    (a) une chaîne V_L ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 206, où la V_L ne comprend pas plus d'une substitution d'acides aminés dans

les CDR par rapport à la séquence d'acides aminés de la CDR1 de V_L présentée dans la SEQ ID NO: 215, à la séquence d'acides aminés de la CDR2 de V_L présentée dans la SEQ ID NO: 217, et à la séquence d'acides aminés de la CDR3 de V_L présentée dans la SEQ ID NO: 219; ou bien
(b) une chaîne V_L ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 151, où la V_L ne comprend pas plus d'une substitution d'acides aminés dans les CDR par rapport à la séquence d'acides aminés de la CDR1 de V_L présentée dans la SEQ ID NO: 160, à la séquence d'acides aminés de la CDR2 de V_L présentée dans la SEQ ID NO: 162, et à la séquence d'acides aminés de la CDR3 de V_L présentée dans la SEQ ID NO: 164.

7. Composition selon l'une quelconque des revendications 1-6, dans laquelle l'anticorps ou le fragment d'anticorps comprend:

(a) une CDR1 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 208, une CDR2 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 210, une CDR3 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 212, une CDR1 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 215, une CDR2 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 217 et une CDR3 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 219; ou bien
(b) une CDR1 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 153, une CDR2 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 156, une CDR3 de V_H comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 158, une CDR1 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 160, une CDR2 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 162 et une CDR3 de V_L comprenant la séquence d'acides aminés présentée dans la SEQ ID NO: 164.

8. Composition selon la revendication 7, dans laquelle l'anticorps ou fragment d'anticorps comprend:

(a) une V_H ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 204 et une chaîne V_L ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 206; ou bien une chaîne V_H ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 149 et une chaîne V_L ayant au moins 95 %, 96 %, 97 %, 98 % ou 99 % d'identité avec la séquence d'acides aminés présentée dans la SEQ ID NO: 151.

9. Composition selon la revendication 8, dans laquelle l'anticorps ou fragment d'anticorps comprend une chaîne V_H comprenant la SEQ ID NO: 204 et une chaîne V_L comprenant la SEQ ID NO; 206; ou bien une chaîne V_H comprenant la SEQ ID NO: 149 et une chaîne V_L comprenant la SEQ ID NO: 151.

10. Composition selon l'une quelconque des revendications 1-9, comprenant en outre une substance thérapeutique anticancéreuse.

11. Composition selon l'une quelconque des revendications 1-10, formulée comme une composition pharmaceutique.

12. Composition selon l'une quelconque des revendications 1-11, comprenant en outre un inhibiteur d'histone désacétylase (HDAC) sélectionné parmi le groupe consistant en acide hydroxamique, vorinostat, acide subéroylanalide hydroxamide (SAHA, trichostatine A (TSA), LAQ824, panobinostat (LBH589), bélinostat (PXD101), ITF2357 Italfarmaco SpA, tétrapeptide cyclique, depsipeptide (romidepsine, FK228), benzamide; entinostat (SNDX-275/MS-275), MGDC0103, acides aliphatiques à chaîne courte, acide valproïque, butyrate de phényle, AN-9, pivanex, CHR-3996, et CHR-2845.

13. Composition selon l'une quelconque des revendications 1-12, comprenant en outre un inhibiteur du protéasome sélectionné parmi le groupe consistant en bortézomib, NPI-0052, carfilzomib (PR-171), CEP 18770, et MLN9708.

14. Composition selon l'une quelconque des revendications 1-13, comprenant en outre un anticorps sélectionné parmi le groupe consistant en un anticorps anti-CTLA-4, un anticorps anti-PD-1, un anticorps anti-PDL-1 et une combinaison d'un ou de plusieurs de ceux-ci.

CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGGCCCTCACCTGCGCTGTCTCT
GGTGGGTCCTTCACTGATCATTACTGGAGTTGGATCCGTCAGGCCCCAGGGAAGGGGCTGGAGTGGATTGGAGAA
ATCAATCATAGTGGAGTCACCAACTACAACCCGTCCCTCAAGAGTCGACTCACCATATCAGTAGACACGTCCAAG
AGCCAGTTCTCCCTGAGGCTGACCTCTGTGACCGCCGCGGACACGGCTCTGTACTACTGTGCGAAAACTGGCCTG
TATTATGATGACGTTTGGGGGACTTTTCGTCCACGGGGCGGGTTCGACTCCTGGGGCCAGGGAACCCTGGTCACC
GTCTCCTCA (SEQ ID NO: 1)

FIG. 1

Q V Q L Q Q W G A G L L K P S E T L A L T C A V S
G G S F T D H Y W S W I R Q A P G K G L E W I G E
I N H S G V T N Y N P S L K S R L T I S V D T S K
S Q F S L R L T S V T A A D T A L Y Y C A K T G L
Y Y D D V W G T F R P R G G F D S W G Q G T L V T
V S S (SEQ ID NO: 2)

FIG. 2

GACATCGTGATGACCCAGTCTCCGGACTCCCTGGCTGTGTCTCTGGGCGAGAGGGCCACCATCAACTGCAAGTCC
AGCCAGAGTATTTTATATAGCTCCGACAATAAGAATTACTTAGCTTGGTACCAGCACAAGCCAGGACAGCCTCCT
AAGCTCCTCTTTTACTGGGCATCTATCCGGGAATCCGGGGTCCCTGACCGATTCAGTGGCGGCGGGTCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTCCT
CCTTGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCCAA (SEQ ID NO: 10)

FIG. 3

D I V M T Q S P D S L A V S L G E R A T I N C K S
S Q S I L Y S S D N K N Y L A W Y Q H K P G Q P P
K L L F Y W A S I R E S G V P D R F S G G G S G T
D F T L T I S S L Q A E D V A V Y Y C Q Q Y Y S P
P C S F G Q G T K L E I Q (SEQ ID NO: 11)

FIG. 4

```
1     GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGAGACTC
61    TCCTGTGCAG CCTCTGGATT CACCTTTAGT AGTTATGCCA TGAGCTGGGT CCGCCAGGCT
121   CCAGGGAAGG GGCTGGAGTG GGTCTCAGGT ATTTATTGGA GTGGTGGTAG CACATACTAC
181   GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCAGAGACA TATCCAAGAA CACGCTGTAT
241   CTGCAAATGA ACAGTCTGAG AGCCGACGAC ACGGCCGTGT ATTACTGTGC GAGAGGCGAT
301   TACTATGGTT CGGGGGCTCA CTTTGACTAC TGGGGCCAGG GAACCCTGGT CACCGTCTCC
361   TCA   (SEQ ID NO: 19)
```

FIG. 5

1	EVQLVESGGG	LVQPGGSLRL	
21	SCAAS**GFTFS**	**SYA**MSWVRQA	**CDR1**
41	PGKGLEWVSG	**IYWSGGST**YY	**CDR2**
61	ADSVKGRFTI	SRDISKNTLY	
81	LQMNSLRADD	TAVYYC**ARGD**	**CDR3**
101	**YYGSGAHFDY**	WGQGTLVTVS	
121	S	(SEQ ID NO: 20)	

FIG. 6

```
1     GATATTGTGA TGACCCAGAC TCCACTCTCC TCACCTGTCA CCCTTGGACA GCCGGCCTCC
61    ATCTCCTGCA GGTCTAGCCA AAGCCTCGTA CACAGTGATG GAAACACCTA CTTGAGTTGG
121   CTTCAGCAGA GGCCAGGCCA GCCTCCAAGA CTCCTAATTT ATCAGATTTC TAACCGGTTC
181   TCTGGGGTCC CAGACAGATT CAGTGGCAGT GGGGCAGGGA CAGATTTCAC ACTGAAAATC
241   AGCAGGGTGG AAGCTGAGGA TGTCGGGGTT TACTACTGCA TGCAAGGTAC ACAATTTCCT
301   CGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAA
```

(SEQ ID NO: 28)

FIG. 7

1 DIVMTQTPLS SPVTLGQPAS
21 ISCRSS**QSLV HSDGNTY**LSW **CDR1**
41 LQQRPGQPPR LLIY**QIS**NRF **CDR2**
61 SGVPDRFSGS GAGTDFTLKI
81 SRVEAEDVGV YYC**MQGTQFP CDR3**
101 **RT**FGQGTKVE IK

(SEQ ID NO: 29)

FIG. 8

```
1     GAGGTGCAGC TGGTGGAGTC CGGGGGAGGC TTAGTTCAGC CTGGGGGATC CCTGAGACTC
61    TCCTGTGCAG CCTCAGGGTT CACCTTTAGT AATAACTGGA TGCACTGGGT CCGCCAGGCT
121   CCAGGGAAGG GGCTGGAGTG GATCTCAGAG ATTAGAAGTG ATGGGAATTT CACAAGGTAC
181   GCGGACTCCA TGAAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAG CACACTGTAT
241   TTGCAAATGA ACAGTCTGAG AGTCGAGGAC ACGGGTCTGT ATTACTGTGC AAGAGACTAC
301   CCCTATAGCA TTGACTACTG GGGCCAGGGA ACCCTGGTCA CCGTCTCCTC A (SEQ ID NO: 37)
```

FIG. 9

1 EVQLVESGGG LVQPGGSLRL

21 SCAAS**GFTFS NNW**MHWVRQA **CDR1**

41 PGKGLEWISE **IRSDGNFT**RY **CDR2**

61 ADSMKGRFTI SRDNAKSTLY

81 LQMNSLRVED TGLYYC**ARDY** **CDR3**

101 **PYSIDY**WGQG TLVTVSS (SEQ ID NO: 38)

FIG. 10

```
1     GATATTGTGA TGACCCAGAC TCCACTCTCC TCACCTGTCA CCCTTGGACA GCCGGCCTCC
61    ATCTCCTGCA CATCTAGTCA AAGCCTCGTA CACAGTAATG GAAACACCTA CTTGAGTTGG
121   CTTCAGCAGA GGCCAGGCCA GCCCCCAAGA CTCCTAATTT ATGAGATTTC TAAGCGGGTC
181   TCTGGGGTCC CAGACAGATT CAGTGGCAGT GGGGCAGGGA CAGATTTCAC ACTGAAAATC
241   AGCAGGGTGG AAGCTGAGGA TGTCGGGGTT TATTACTGCA TGCAAGGTAA ACAACTTCGG
301   ACTTTTGGCC AGGGGACCAA GCTGGAGATC AAA
```

(SEQ ID NO: 46)

FIG. 11

1 DIVMTQTPLS SPVTLGQPAS

21 ISCTSS**QSLV HSNGNTY**LSW **CDR1**

41 LQQRPGQPPR LLIY**EIS**KRV **CDR2**

61 SGVPDRFSGS GAGTDFTLKI

81 SRVEAEDVGV YYC**MQGKQLR CDR3**

101 **T**FGQGTKLEI K

(SEQ ID NO: 47)

FIG. 12

```
1      GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGCTC CGTGAGACTG
61     TCTTGTGCGG CCTCAGGCTT CATTCTTAGC AACTTTGCCA TGAGTTGGGT CCGCCAGGCT
121    CCAGGGAAGG GGCTGGACTG GGTCTCAGGT AATTTTGGTG GTCGTGAAAA TACATATTAC
181    GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCAGAGACA GTTCCAAGAG CACACTGTAT
241    CTGCAAATGA ACAATTTGAG AGCCGAGGAC ACGGCCGTAT ATTACTGTGC GCGAGGCGAT
301    TACCATGGTT CGGGGGCTCA CTTTGACTAC TGGGGCCAGG GAATACTGGT CACCGTCTCC
361    TCA   (SEQ ID NO: 55)
```

FIG. 13

1	EVQLVESGGG	LVQPGGSVRL	
21	SCAAS**GFILS**	**NFA**MSWVRQA	**CDR1**
41	PGKGLDWVSG	**NFGGRENT**YY	**CDR2**
61	ADSVKGRFTI	SRDSSKSTLY	
81	LQMNNLRAED	TAVYYC**ARGD**	**CDR3**
101	**YHGSGAHFDY**	WGQGILVTVS	
121	S		

(SEQ ID NO: 56)

FIG. 14

```
1     GATATTGTGA TGACCCAGAG TCCACTCTCC TCACCTGTCA TCCTTGGACA GCCGGCCTCC
61    ATCTCCTGCA GGTCTAGTCA AAGCCTCCTA CACAGTGATG GAAACACCTA CTTGAGTTGG
121   CTTCACCAGA GGCCAGGCCA GCCTCCTAGA CTCCTAATTT ATCAGATTTC TAACCGGTTC
181   TCTGGGGTCC CAGACAGATT CAGTGGCAGT GGGACAGGGA CAGATTTCAC ACTGAAAATC
241   AGCAGGGTGG AAGCTGAGGA TGCCGGGATT TATTACTGCA TGCAAGGTAC AGAATTTCCT
301   CGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAA
```

(SEQ ID NO: 64)

FIG. 15

1 DIVMTQSPLS SPVILGQPAS

21 ISCRSS**QSLL HSDGNTY**LSW **CDR1**

41 LHQRPGQPPR LLIY**QIS**NRF **CDR2**

61 SGVPDRFSGS GTGTDFTLKI

81 SRVEAEDAGI YYC**MQGTEFP CDR3**

101 **RT**FGQGTKVE IK

(SEQ ID NO: 65)

FIG. 16

1	GAGGTGCAGC	TGGTGGAGTC	TGGGGGAGGC	TTGATACAGC	CTGGGGGGTC	CCTGAGACTC
61	TCCTGTGCAA	CCTCTGGATT	CACCTTTAGA	ACTTCTTCCA	TGAGTTGGGT	CCGTCGGGCT
121	CCAGGGAAGG	GGCTGGAATG	GGTCTCAGCT	ATTGGTGCTG	AAAGTCATGA	CACGCACTAC
181	ACAGACTCCG	CGGAGGGCCG	GTTCACCATC	TCCAAAGACT	ATTCAAAGAA	CACAGTATAT
241	CTGCAGATGA	ACGGCCTGAG	AGTCGACGAC	ACGGCCATAT	ATTATTGTGC	CCATCACTAT
301	TACTATGGCT	CGCGGCAGAA	ACCCAAAGAT	TGGGGAGATG	CTTTTGATAT	GTGGGGCCAG
361	GGGACAATGG	TCTCCGTCTC	TTCA	(SEQ ID NO: 73)		

FIG. 17

1	EVQLVESGGG	LIQPGGSLRL	
21	SCATS**GFTFR**	**TSS**MSWVRRA	**CDR1**
41	PGKGLEWVSA	**IGAESHDT**HY	**CDR2**
61	TDSAEGRFTI	SKDYSKNTVY	
81	LQMNGLRVDD	TAIYYC**AHHY**	**CDR3**
101	**YYGSRQKPKD**	**WGDAFDM**WGQ	
121	GTMVSVSS	(SEQ ID NO: 74)	

FIG. 18

```
1     GACATCCAGA TGACCCAGTC TCCATCTTCT GTGTCTGCAT CTGTAGGAGA CAGAGTCACC
61    ATCACTTGTC GGGCGAGTCA GGATATTAGC ACCTGGTTAA CCTGGTATCA GCAGAGAGCA
121   GGGAAGGCCC CTAACCTCCT GATCTATGGT GCATCCACTT TGGAAGATGG GGTCCCATCC
181   AGGTTCAGCG GCAGTGGATC CGGGACAGAT TTCACTCTCA CTATCGACAG CCTGCAGCCT
241   GACGATTTTG CAACTTACTA TTGTCAACAG TCTCACAGTT TCCCCTACAC TTTTGGCCAG
301   GGGACCCAGC TGGGGATCTC A
```

(SEQ ID NO: 82)

FIG. 19

1 DIQMTQSPSS VSASVGDRVT

21 ITCRAS**QDIS TW**LTWYQQRA **CDR1**

41 GKAPNLLIY**G AS**TLEDGVPS **CDR2**

61 RFSGSGSGTD FTLTIDSLQP

81 DDFATYYC**QQ SHSFPYT**FGQ **CDR3**

101 GTQLGIS

(SEQ ID NO: 83)

FIG. 20

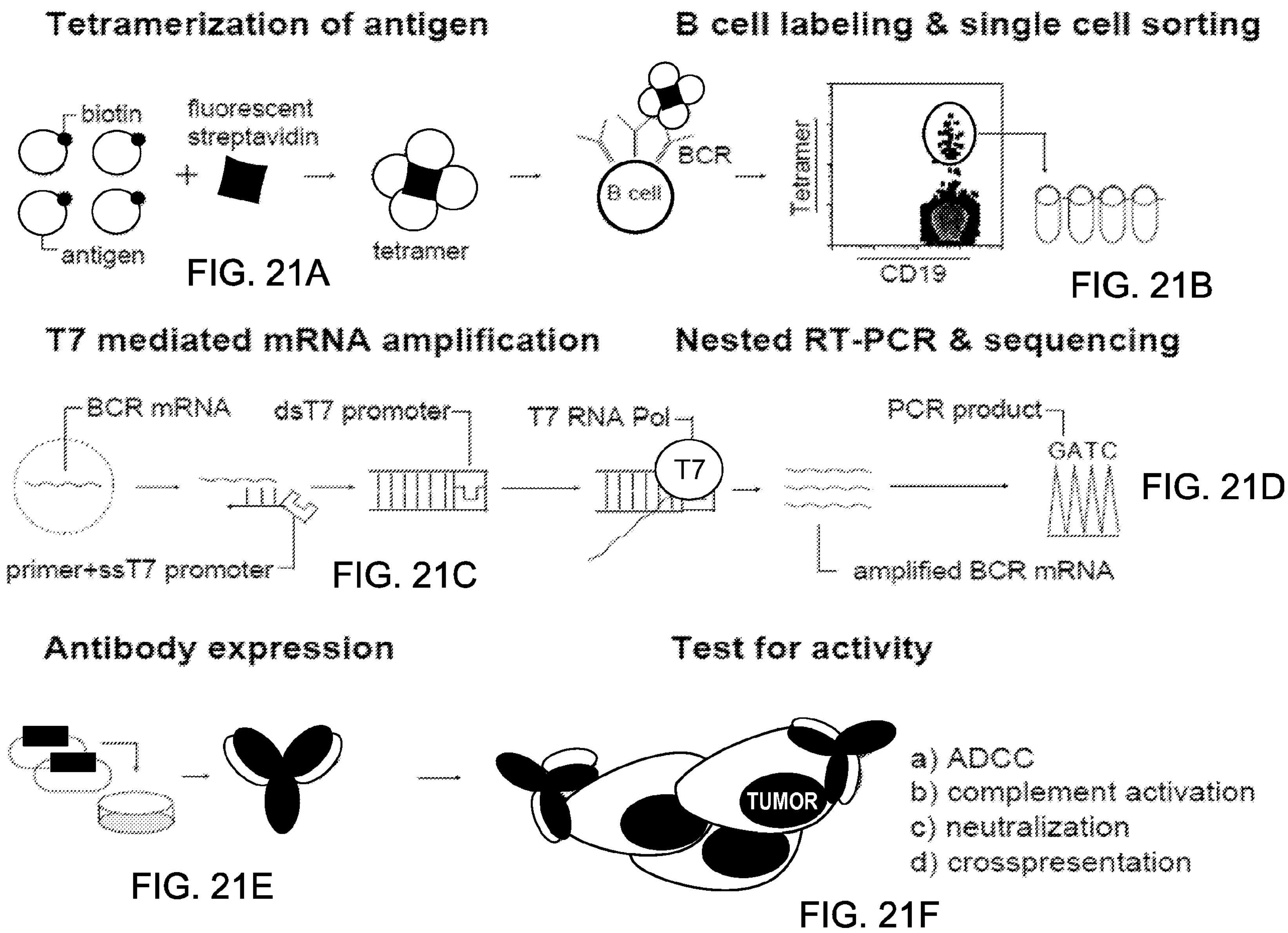


FIG. 21A FIG. 21B FIG. 21C FIG. 21D FIG. 21E FIG. 21F

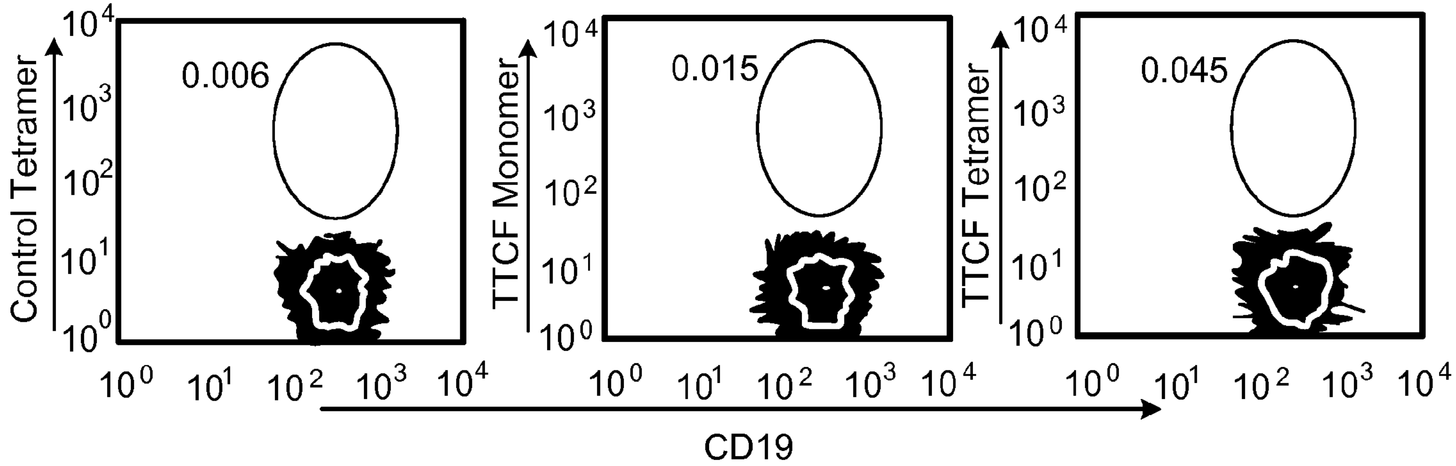


FIG. 22A

	Control Tet/ 10^5 B cells	TTCF Moncmen/ 10^4 B cells	TTCF Tet/# 10^4 B cells	#Tet/#Mono Foldchange
Donor 1	3.98	2.53	18.41	7.3
Donor 2	15.03	38.64	117.18	3.1
Donor 3	4.14	48.92	77.55	1.6

FIG. 22B

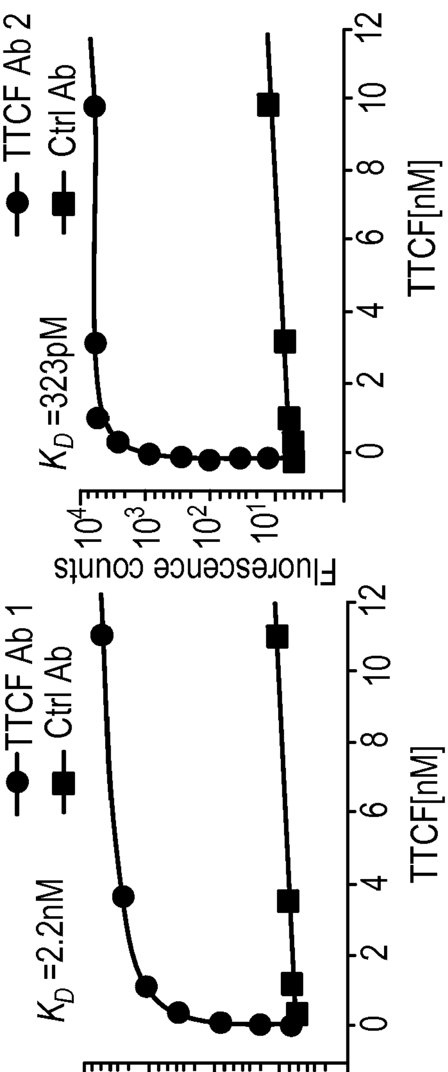


FIG. 23A

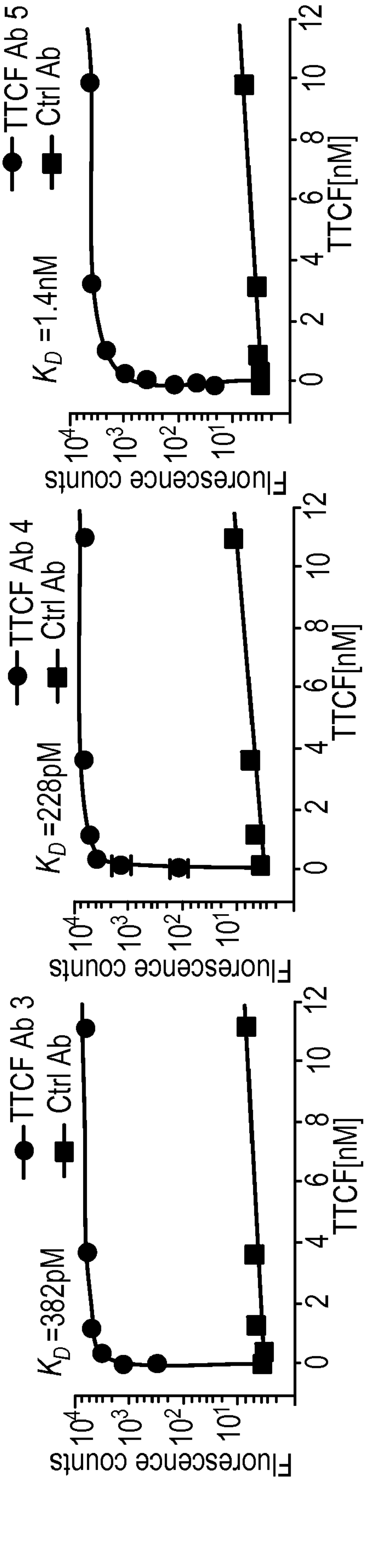


FIG. 23B

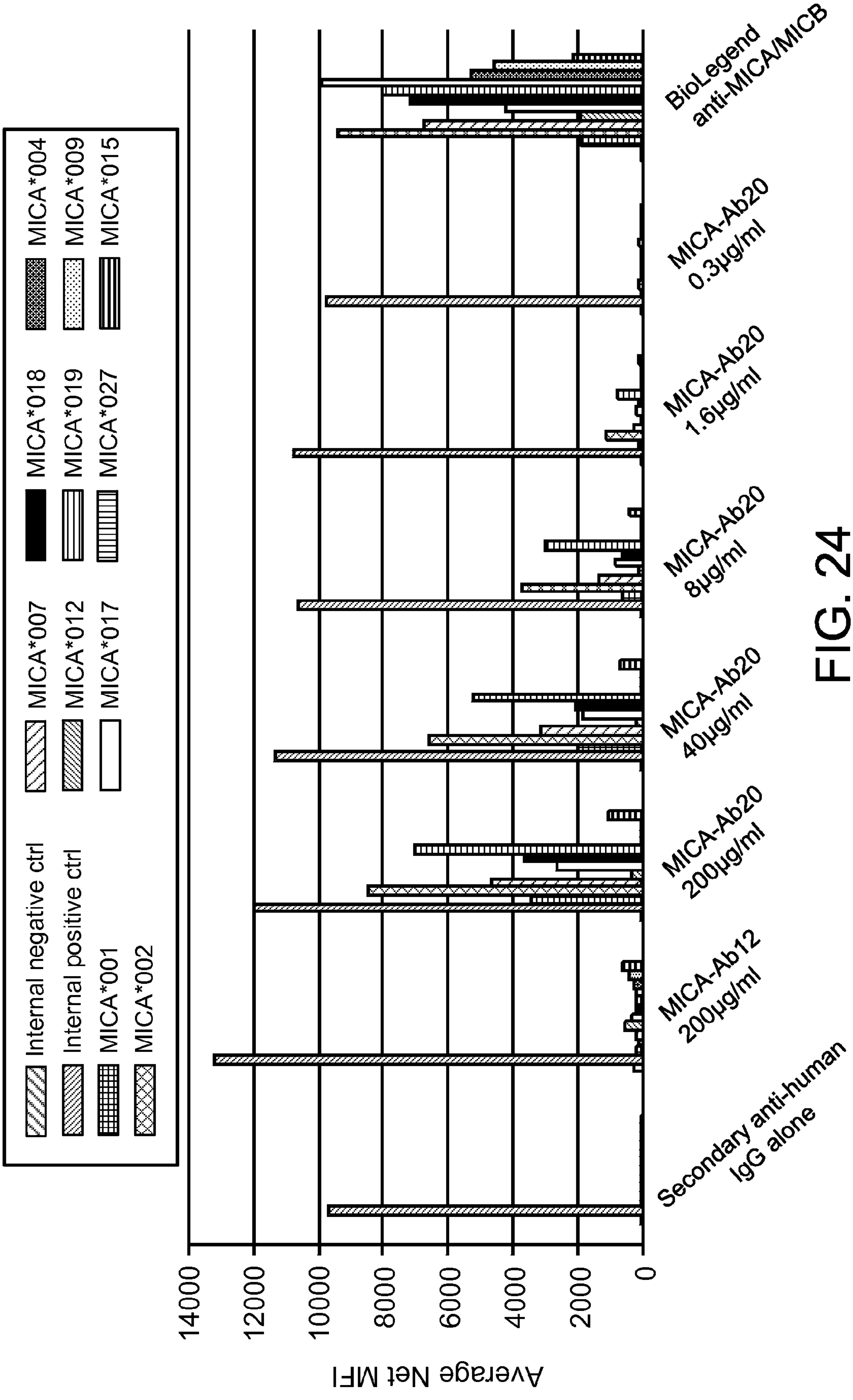

Internal negative ctrl
Internal positive ctrl
MICA*001
MICA*002
MICA*007
MICA*012
MICA*017
MICA*018
MICA*019
MICA*027
MICA*004
MICA*009
MICA*015
Average Net MFI
0
2000
4000
6000
8000
10000
12000
14000
Secondary anti-human IgG alone
MICA-Ab12 200µg/ml
MICA-Ab20 200µg/ml
MICA-Ab20 40µg/ml
MICA-Ab20 8µg/ml
MICA-Ab20 1.6µg/ml
MICA-Ab20 0.3µg/ml
BioLegend anti-MICA/MICB

FIG. 24

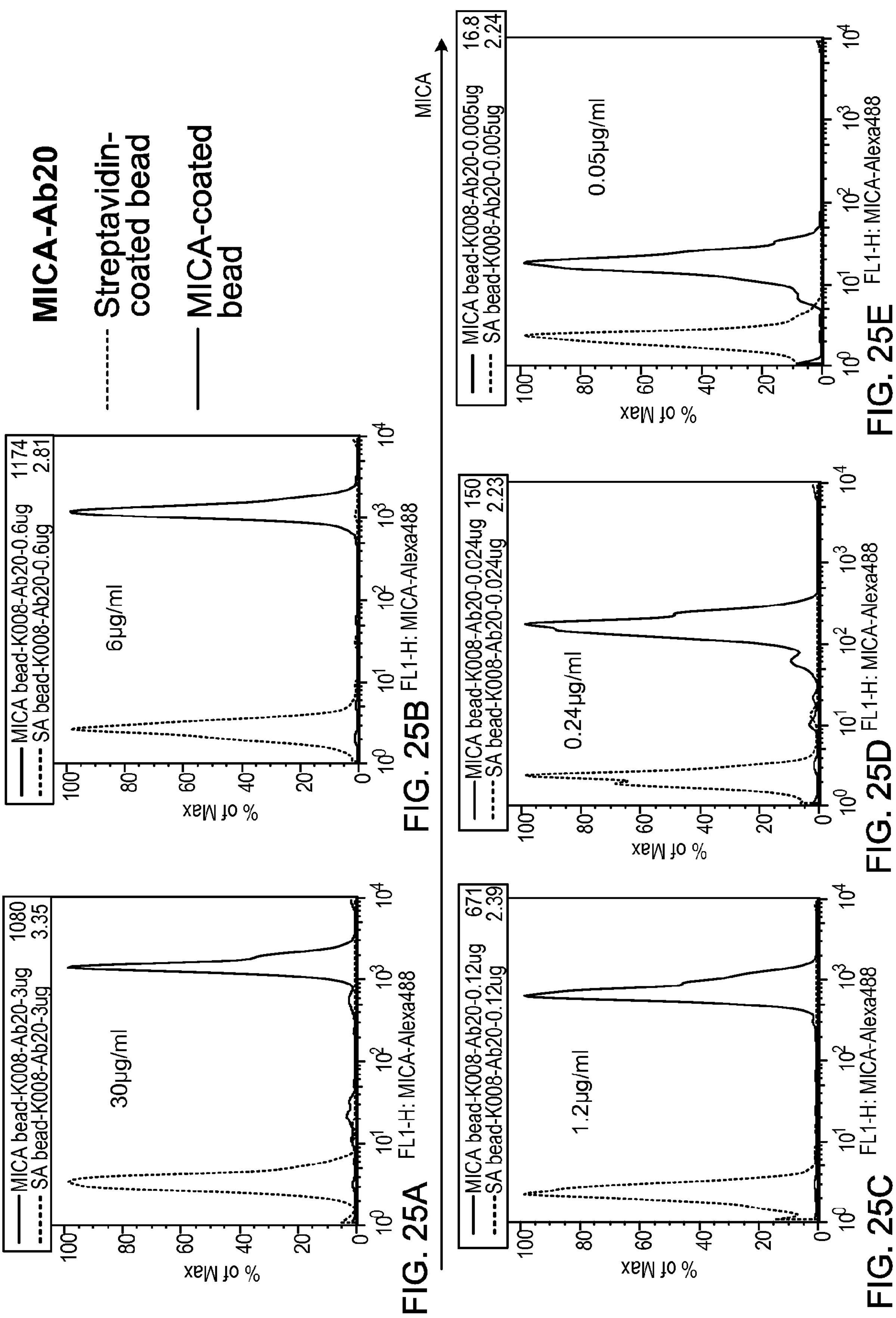


FIG. 25A

FIG. 25B

FIG. 25C

FIG. 25D

FIG. 25E

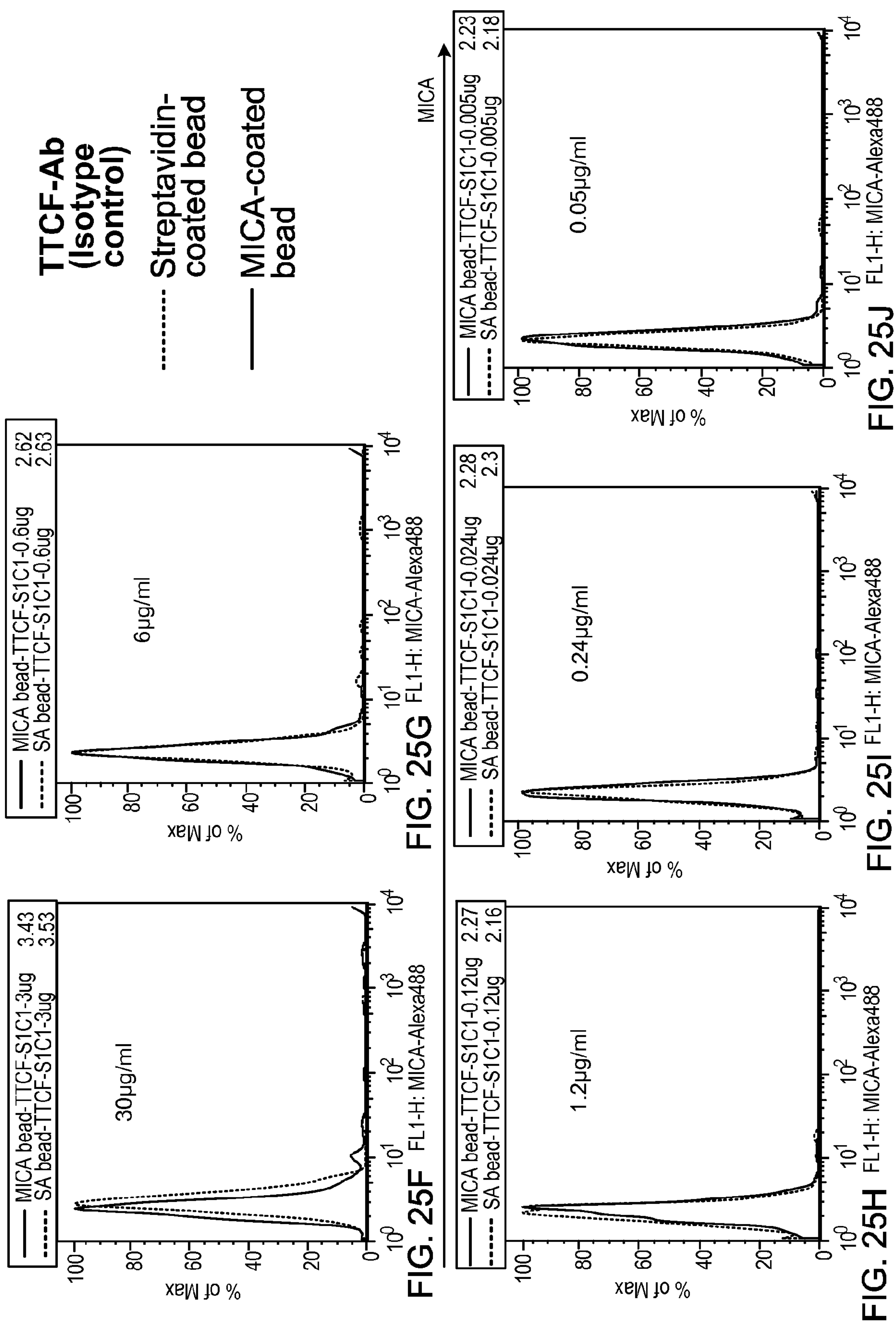


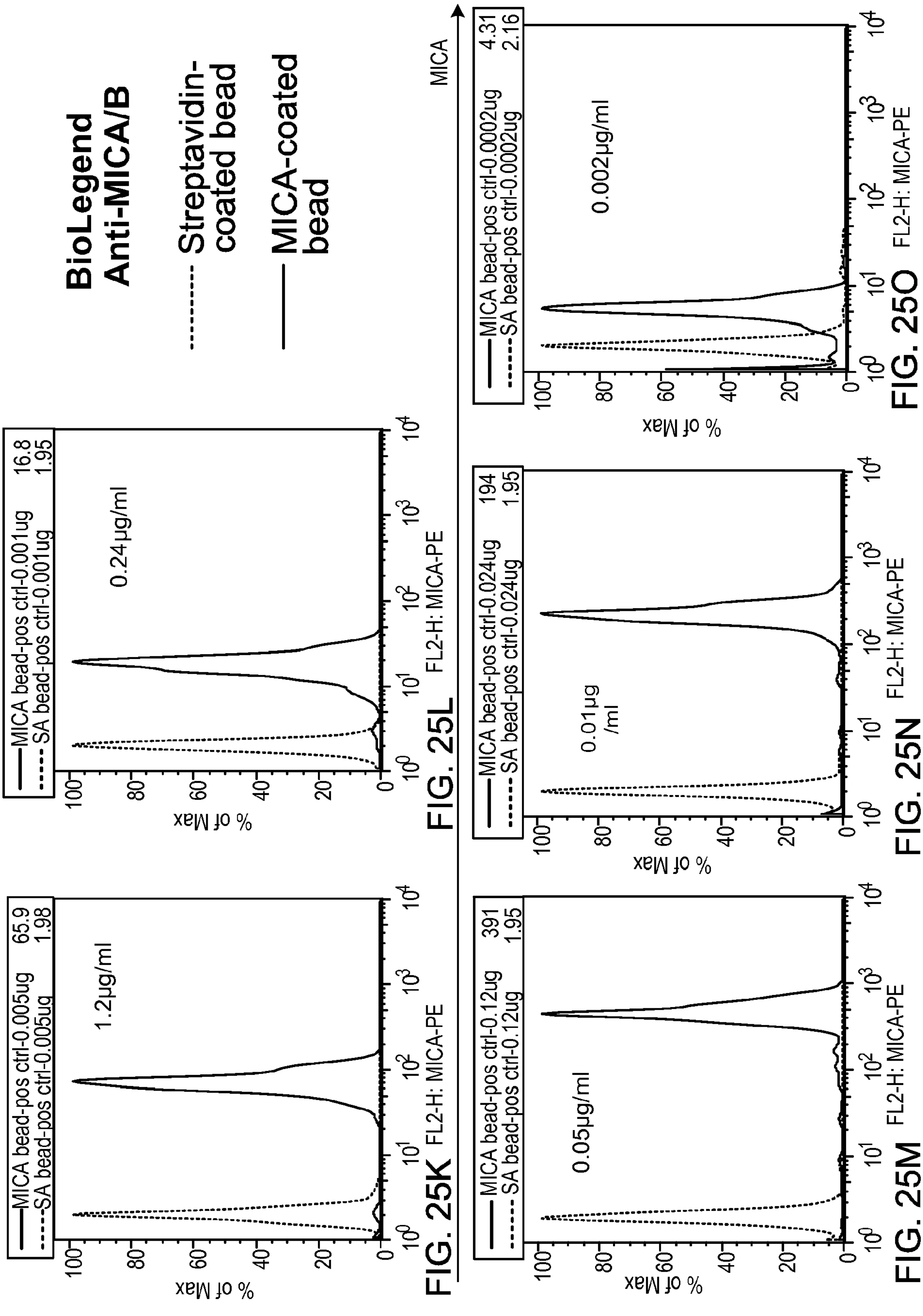
FIG. 25F

FIG. 25G

FIG. 25H

FIG. 25I

FIG. 25J



BioLegend
Anti-MICA/B
Streptavidin-coated bead
MICA-coated bead
MICA
MICA bead-pos ctrl-0.005ug 65.9
SA bead-pos ctrl-0.005ug 1.98
1.2µg/ml
FIG. 25K
MICA bead-pos ctrl-0.001ug 16.8
SA bead-pos ctrl-0.001ug 1.95
0.24µg/ml
FIG. 25L
MICA bead-pos ctrl-0.12ug 391
SA bead-pos ctrl-0.12ug 1.95
0.05µg/ml
FIG. 25M
MICA bead-pos ctrl-0.024ug 194
SA bead-pos ctrl-0.024ug 1.95
0.01µg /ml
FIG. 25N
MICA bead-pos ctrl-0.0002ug 4.31
SA bead-pos ctrl-0.0002ug 2.16
0.002µg/ml
FIG. 25O
% of Max
FL2-H: MICA-PE

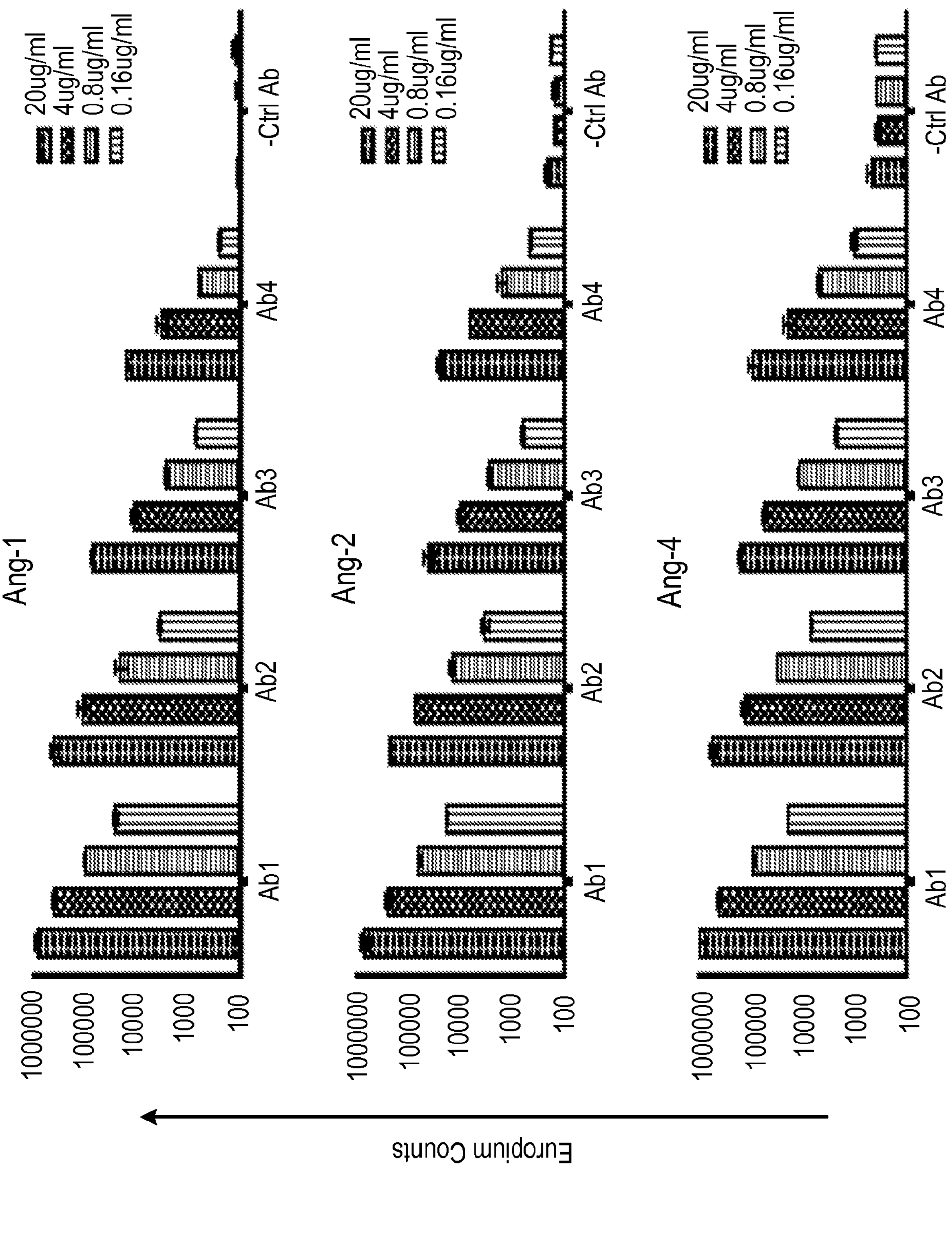


FIG. 26A

FIG. 26B

FIG. 26C


Ang-like-3
20ug/ml
4ug/ml
0.8ug/ml
0.16ug/ml
1000000
100000
10000
1000
100
Ab1
Ab2
Ab3
Ab4
-Ctrl Ab

FIG. 26D

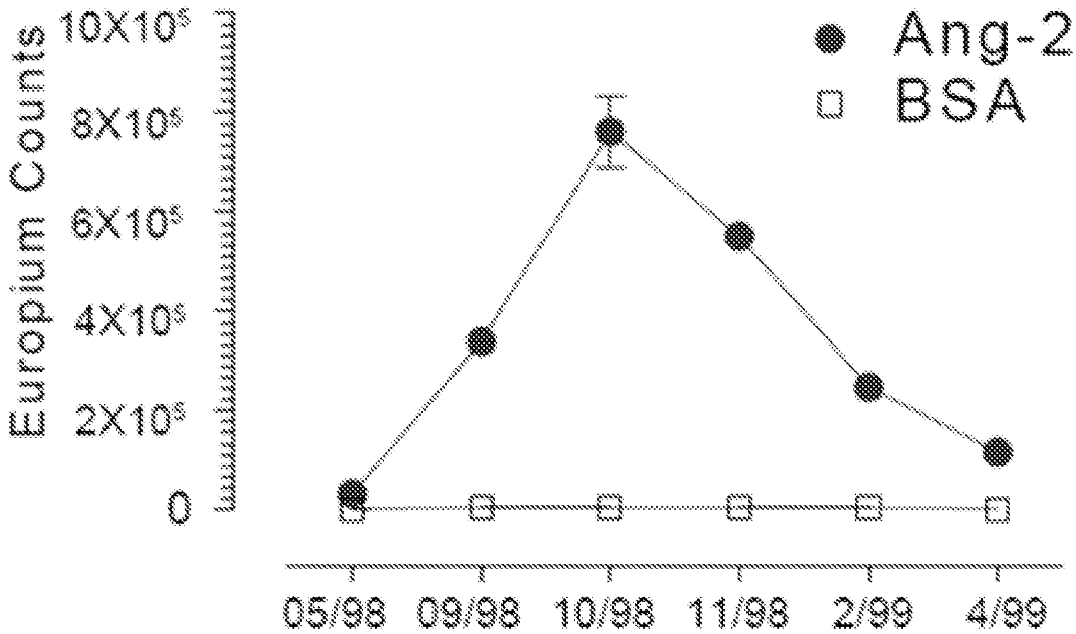


FIG. 27A

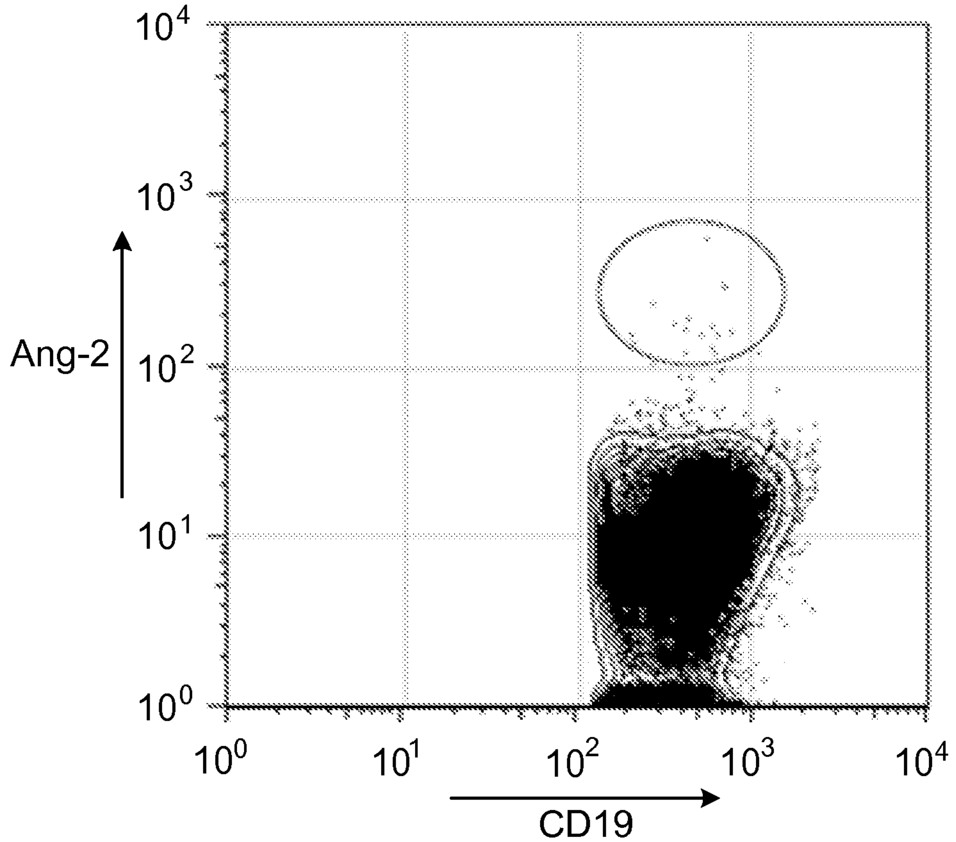


FIG. 27B

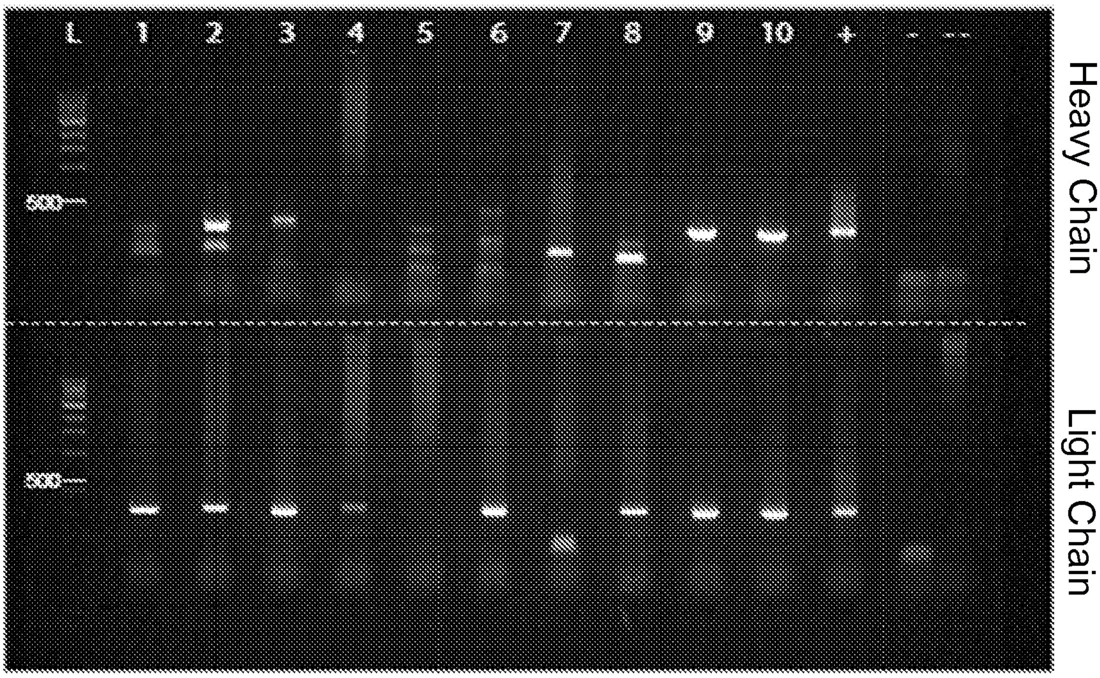


FIG. 27C

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGGAGCCTTCGGGGACCCTGTCCCT
CACCTGCACTGTGTCTGGTGGCTCCATCAGCAGGAGTAACTGGTGGAGTTGGGTCCGCC
AGCCCCCAGGGGAGGGGCTGGAATGGATTGGAGAAATCCATCACATTGGGAGGTCCAGC
TACAATCCGTCCCTCAAGAGTCGAGTCACCATGTCTGTAGACAAGTCCCAGAACCAGTT
CTCCCTGAGGCTGACCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAAAA
ATGGCTACTACGCTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCG
(SEQ ID NO. 148)

FIG. 28

QVQLQESGPGLVEPSGTLSLTCTVSGGSISRSNWWSWVRQPPGEGLEWIGEIHHIGRSS
YNPSLKSRVTMSVDKSQNQFSLRLTSVTAADTAVYYCAKNGYYAMDVWGQGTTVTVSS
(SEQ ID NO. 149)

FIG. 29

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCAC
CCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCGACTTCCTAGCCTGGTACCAGCAGA
AACCTGGCCAGGCTCCCAGGCTCCTCATCTACGCTACATCCTTCAGGGCCACTGGCATC
TCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCTCTCTCACCATCAACAGACT
GGAACCTGAAGATTTTGCAGTGTATTACTGTCAGCACTATCGTAGTTCACCTCCGTGGT
ACACTTTTGCCCAGGGGACCAAGCTGGACATGAGACGTACGGTGGCTGCACCATCTGTC
(SEQ ID NO. 150)

FIG. 30

EIVLTQSPGTLSLSPGERATLSCRASQSVSSDFLAWYQQKPGQAPRLLIYATSFRATGI
SDRFSGSGSGTDFSLTINRLEPEDFAVYYCQHYRSSPPWYTFAQGTKLDMRRTVAAPSV
(SEQ ID NO. 151)

FIG. 31

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGGACCCTGTCCCTC
ACCTGCGCTGTCTCTGGTGCCTCCATTACCAATGGTGCCTGGTGGAGTTGGGTCCGCCAG
CCCCCAGGGAAGGGGCTGGAGTGGATTGGAGAAATCTATCTTAATGGGAACACCAACTCC
AACCCGTCCCTGAAGAGTCGAGTCATCATATCAGTGGACAAGTCCAAGAACCACTTCTCG
CTGACCCTGAACTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCGAAGAACGCT
GCCTACAACCTTGAGTTCTGGGGCCAGGGAGCCCTGGTCACCGTCTCCTCA (SEQ ID NO: 167)

FIG. 32

QVQLQESGPGLVKPSGTLSLTCAVSGASITNGAWWSWVRQPPGKGLEWIGEIYLNGNTNS
NPSLKSRVIISVDKSKNHFSLTLNSVTAADTAVYYCAKNAAYNLEFWGQGALVTVSS (SEQ ID NO: 168)

FIG. 33

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACC
CTCTCCTGCAGGGCCAGTCAGACTGTTAGCAGCCCCTACGTAGCCTGGTACCAGCAGAAA
CGTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCACCAGGGCCACCGGCATCCCAG
ACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTGGAGC
CTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGATAGATCATACTATTACACTTTT
GGCCAGGGGACCAAGCTGGAGATCAAA (SEQ ID NO: 169)

FIG. 34

EIVLTQSPGTLSLSPGERATLSCRASQTVSSPYVAWYQQKRGQAPRLLIYGASTRATGIPDR
FSGSGSGTDFTLTISRLEPEDFAVYYCQQYDRSYYYTFGQGTKLEIK (SEQ ID NO: 170)

FIG. 35

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGAACCTGTCGCTC
ACCTGCACTGTCTCTGATGCCTCCATGAGTGATTATCACTGGAGCTGGATCCGGCAGGCC
GCCGGGAAGGGACTGGAGTGGATTGGGCGTATGTACAGCACTGGGAGTCCCTACTACAA
ACCCTCCCTCAAAGGTCGGGTCACCATGTCAATAGACACGTCCAAGAACCAGTTCTCCCT
GAAGCTGGCCTCTGTGACCGCCGCAGACACGGCCATCTATTATTGTGCGAGCGGACAACA
TATTGGTGGCTGGGTCCCCCCTGACTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTC
A (SEQ ID NO: 185)

FIG. 36

QVQLQESGPGLVKPSENLSLTCTVSDASMSDYHWSWIRQAAGKGLEWIGRMYSTGSPYY
KPSLKGRVTMSIDTSKNQFSLKLASVTAADTAIYYCASGQHIGGWVPPDFWGQGTLVTVS
S (SEQ ID NO: 186)

FIG. 37

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCA
TCTCCTGCAGGTCTAGTGAAGGCCTCGTATATAGTGATGGAGACACCTACTTGAGTTGGT
TTCACCAGAGGCCAGGCCAGCCTCCAAGACTCCTGATTTATAAAATTTCTAACCGGTTCT
CTGGGGTCCCCGACAGATTCAGTGGCAGTGGGGCAGGCACAGATTTCACACTGAAAATCA
GCAGGGTGGAGGCTGAGGATGTCGGGGTTTATTACTGCATGCAAGCTACACATTTTCCGT
GGACGTTCGGCCAGGGGACCAAAGTGGAAGTCAAACGT (SEQ ID NO: 187)

FIG. 38

DIVMTQTPLSSPVTLGQPASISCRSSEGLVYSDGDTYLSWFHQRPGQPPRLLIYKISNRFSG
VPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATHFPWTFGQGTKVEVKR (SEQ ID NO: 188)

FIG. 39

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACCTTTAGTTCATATGGCTTGACCTGGATACGCCAGGCT
CCGGGGAAGGGCCTGGAGTGGGTCTCAAGTATCAGTGGCAGTGGCAATAACACATACTA
CGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCAGAGACAAAGTCAAGAAGACACTATA
TCTACAAATGGACAGCCTGACAGTCGGAGACACGGCCGTCTATTACTGCTTAGGAGTCGG
TCAGGGCCACGGAATTCCGGTCATCGTCTCCTCA (SEQ ID NO. 203)

FIG. 40

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGLTWIRQAPGKGLEWVSSISGSGNNTYYA
DSVKGRFTISRDKVKKTLYLQMDSLTVGDTAVYYCLGVGQGHGIPVIVSS (SEQ ID NO. 204)

FIG. 41

GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCCTTGGACAGCCGGCCTCCA
TCTCCTGCAGGTCTAGTCAGAGCCTCGTACACCGTGATGGAAACACCTACTTGAGTTGGT
TTCTGCAGAGGCCAGGCCAGGCTCCAAGACTCCTAATTTATCGGATTTCTAACCGGTTCT
CTGGGGTCCCAGACAGATTCAGTGGCAGTGGGGCAGGGACGGATTTCACACTGAAAATC
AGCAGGGTGGAAGCTGAGGATGTCGGCGTTTACTACTGCATGCAAGCTACACAAATCCCC
AACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAG (SEQ ID NO. 205)

FIG. 42

DIVMTQTPLSSPVTLGQPASISCRSSQSLVHRDGNTYLSWFLQRPGQAPRLLIYRISNRFSG
VPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQIPNTFGQGTKLEIK (SEQ ID NO. 206)

FIG. 43

GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTAATCCAGCCGGGGGGGTCCCTAAGACT
CTCCTGTGCAGCCTCGGGCTTCCTCATCAGTAGTTATTTCATGAGCTGGGTCCGCCAGG
CTCCAGGGAAGGGGCCGGAGTGGGTCTCAGTTATTTATAGCGATGGTAGTACATATTAC
GTAGACTCCGTGAAGGGCCGATTCACCATCTCCACAGACAATTCCAAGAACACACTATA
TCTTCAGATGAACAGCCTGAGAGCCGAGGACACGGCCCGATATTACTGTGCGACACGGC
ATTTGAATTATGACGGTGACCACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCC
TCCACCAAG (SEQ ID NO: 221)

FIG. 44

EVQLVESGGGLIQPGGSLRLSCAASGFLISSYFMSWVRQAPGKGPEWVSVIYSDGSTYY
VDSVKGRFTISTDNSKNTLYLQMNSLRAEDTARYYCATRHLNYDGDHWGQGTLVTVSSA
STK (SEQ ID NO: 222)

FIG. 45

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCTTGGACAGCCGGCCTC
CATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACAGTGACGGAAACACCTACTTGAATT
GGTTTCACCAGAGGCCAGGCCAATCTCCAAGGCGCCTAATTTATAAGGTTTCTAAGCGG
GACTCTGGGGTCCCAGACAGATTCAGCGGCAGTGGGTCAGGTAGTGATTTCACACTGAA
AATCAGCAGGGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATGCAAGGTACACATT
GGCCGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAACTGTGGCTGCA (SEQ
ID NO: 223)

FIG. 46

DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSDGNTYLNWFHQRPGQSPRRLIYKVSKR
DSGVPDRFSGSGSGSDFTLKISRVEAEDVGIYYCMQGTHWPTFGQGTKVEIKRTVAA
(SEQ ID NO: 224)

FIG. 47

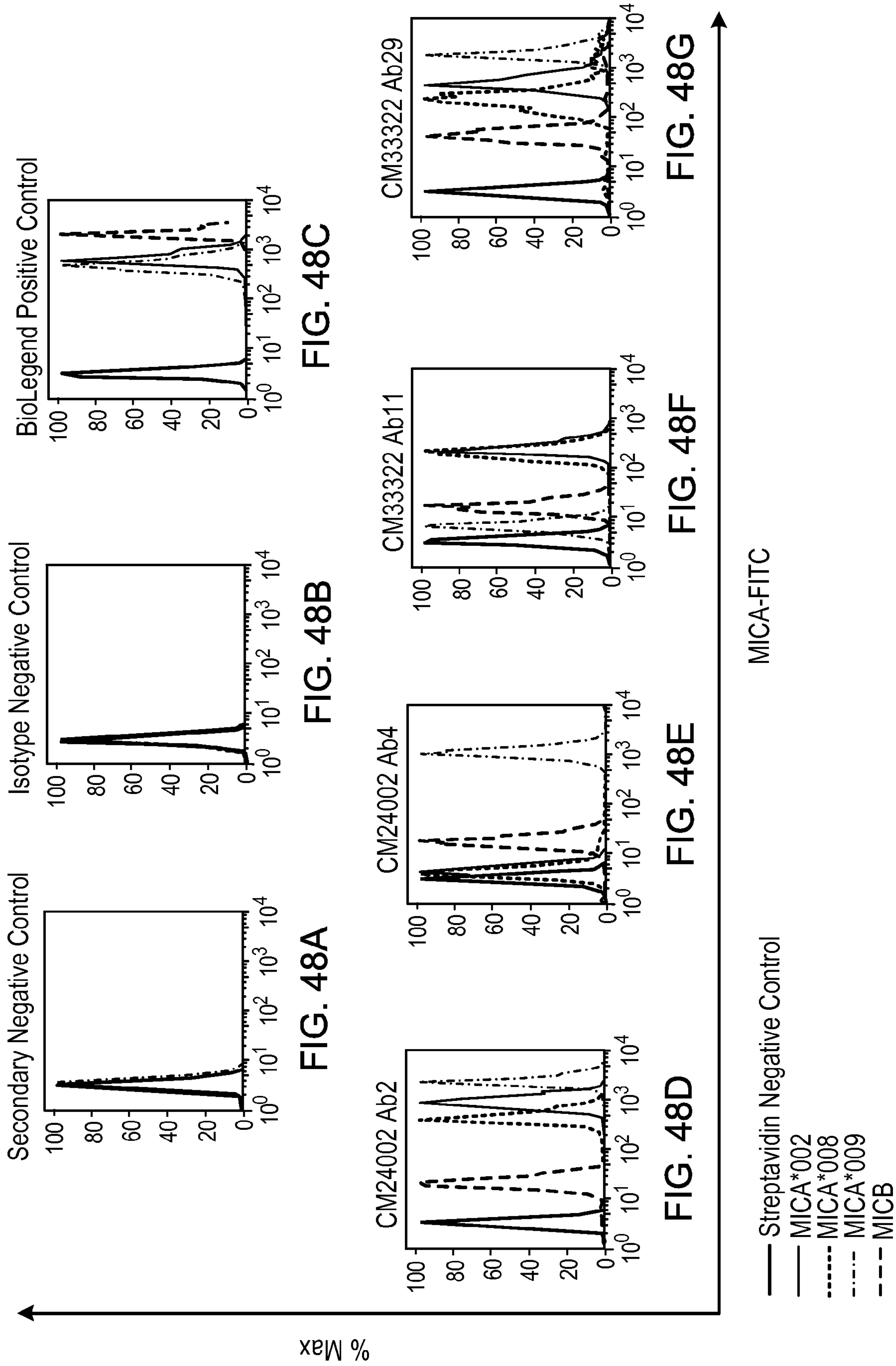


FIG. 48A FIG. 48B FIG. 48C FIG. 48D FIG. 48E FIG. 48F FIG. 48G

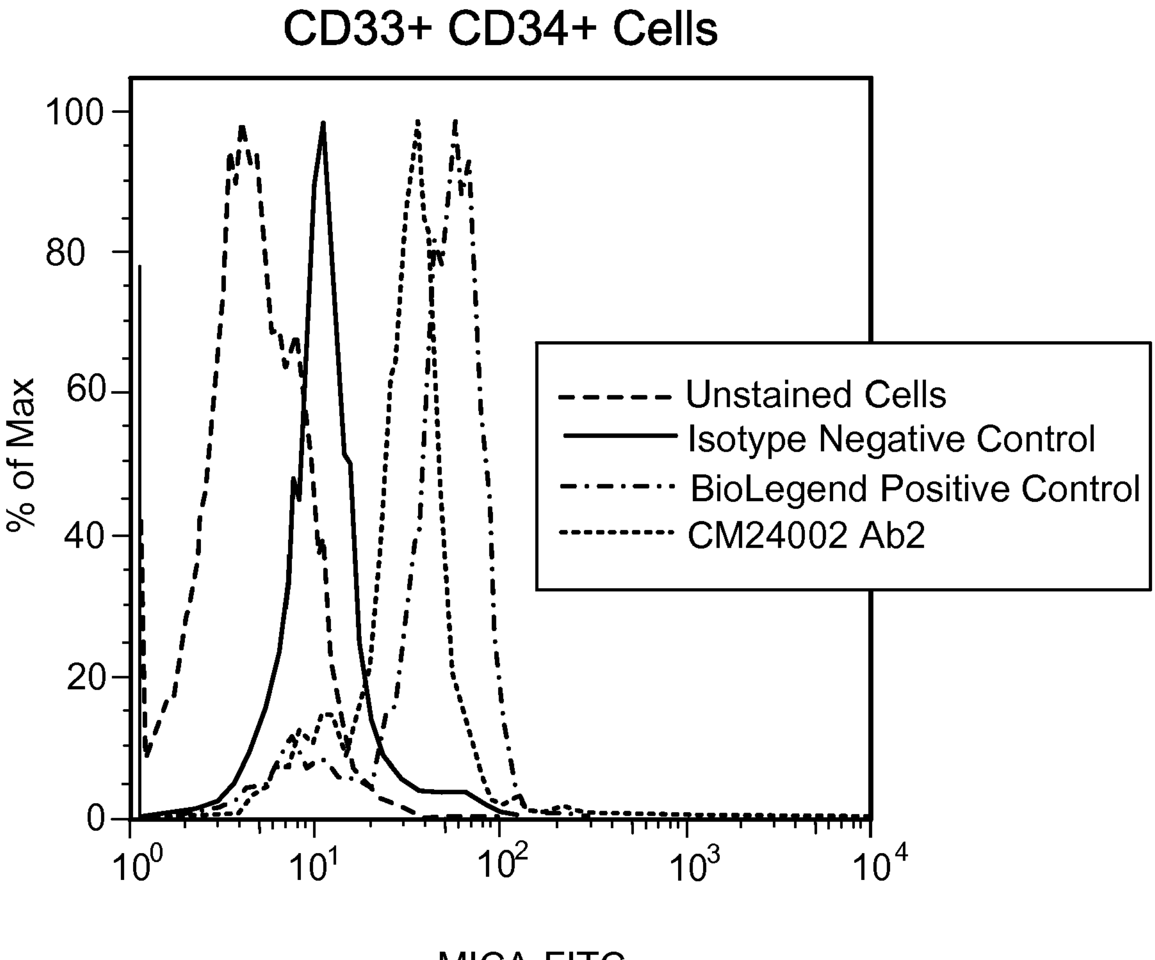

CD33+ CD34+ Cells
100
80
60
40
20
0
% of Max
10^0
10^1
10^2
10^3
10^4
MICA-FITC
Unstained Cells
Isotype Negative Control
BioLegend Positive Control
CM24002 Ab2

FIG. 49

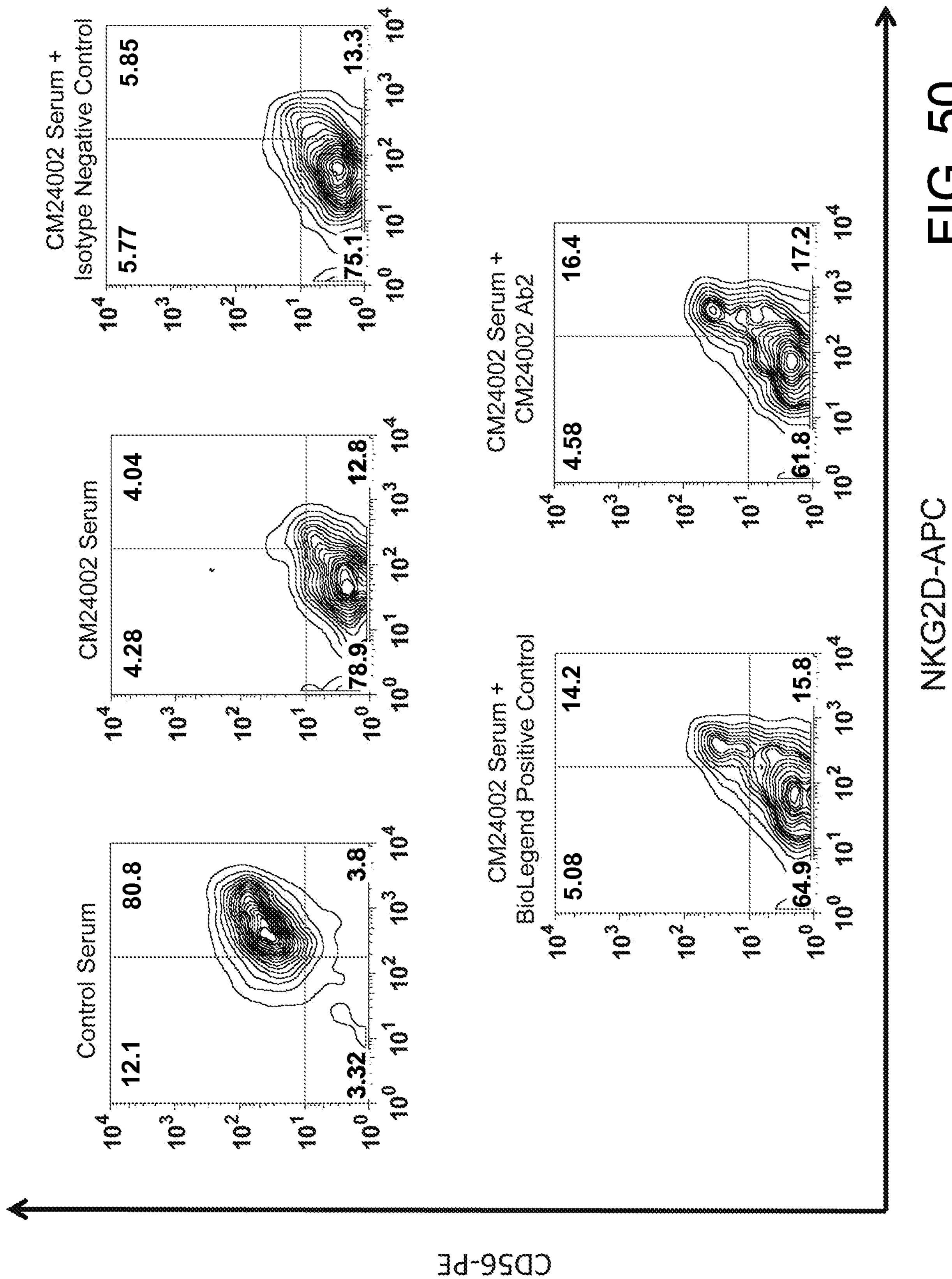

Control Serum
12.1
80.8
3.32
3.8
CM24002 Serum
4.28
4.04
78.9
12.8
CM24002 Serum +
Isotype Negative Control
5.77
5.85
75.1
13.3
CM24002 Serum +
BioLegend Positive Control
5.08
14.2
64.9
15.8
CM24002 Serum +
CM24002 Ab2
4.58
16.4
61.8
17.2
10^0 10^1 10^2 10^3 10^4
NKG2D-APC
CD56-PE

FIG. 50

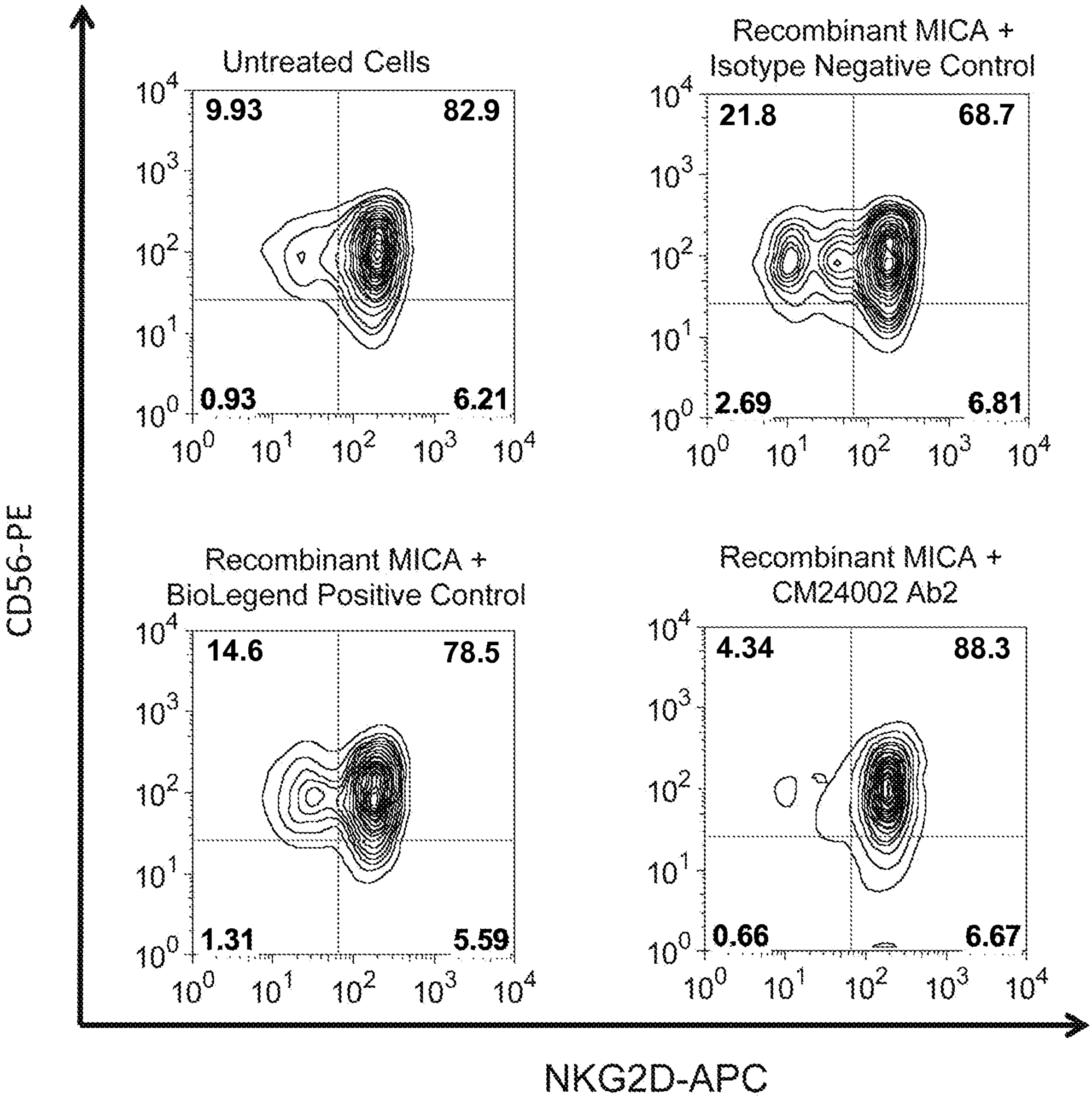

Untreated Cells
9.93
82.9
0.93
6.21
Recombinant MICA +
Isotype Negative Control
21.8
68.7
2.69
6.81
Recombinant MICA +
BioLegend Positive Control
14.6
78.5
1.31
5.59
Recombinant MICA +
CM24002 Ab2
4.34
88.3
0.66
6.67
10^0 10^1 10^2 10^3 10^4
CD56-PE
NKG2D-APC

FIG. 51

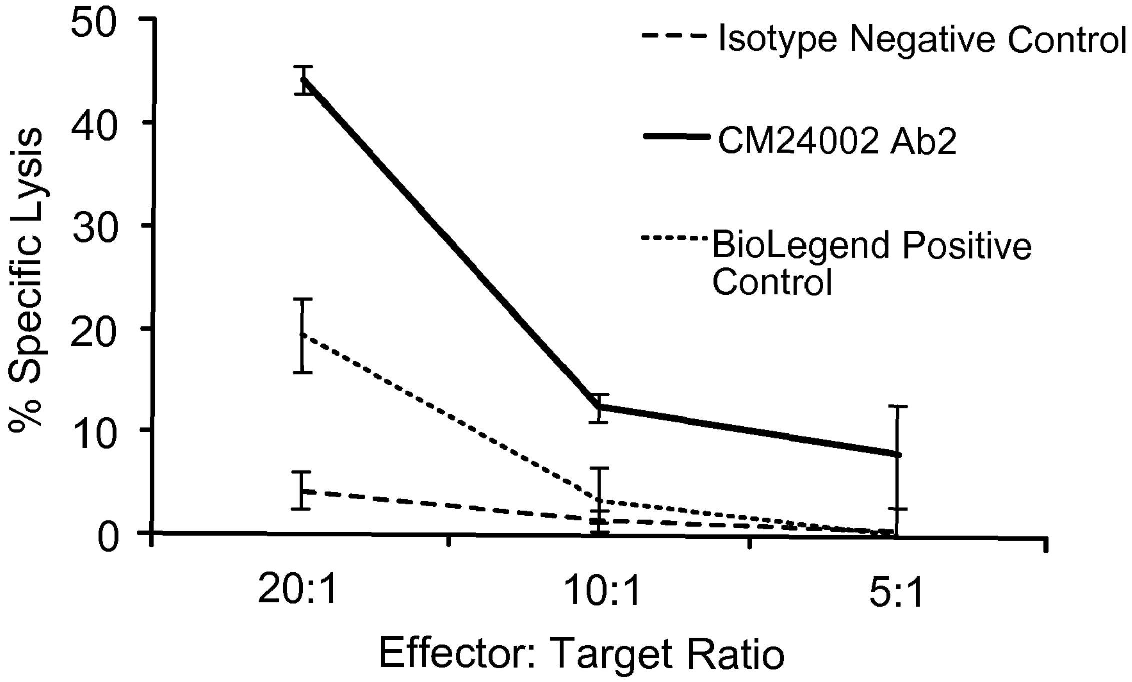

50
40
30
20
10
0
% Specific Lysis
Isotype Negative Control
CM24002 Ab2
BioLegend Positive Control
20:1
10:1
5:1
Effector: Target Ratio

FIG. 52

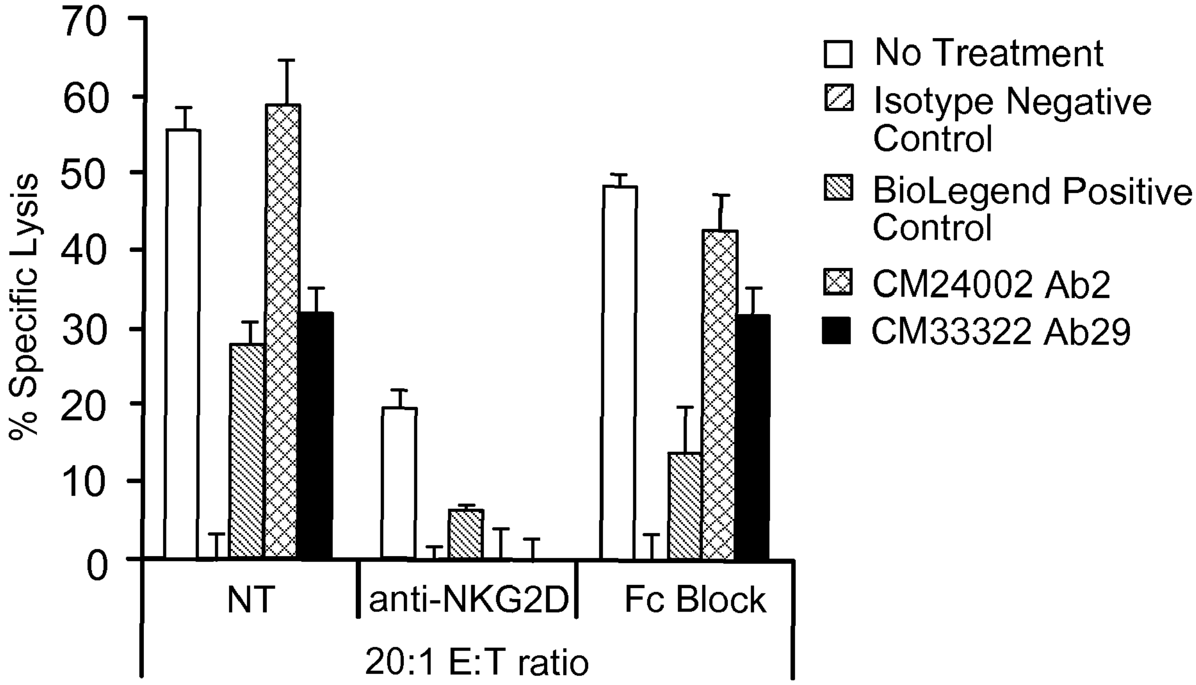

70
60
50
40
30
20
10
0
% Specific Lysis
No Treatment
Isotype Negative Control
BioLegend Positive Control
CM24002 Ab2
CM33322 Ab29
NT
anti-NKG2D
Fc Block
20:1 E:T ratio

FIG. 53

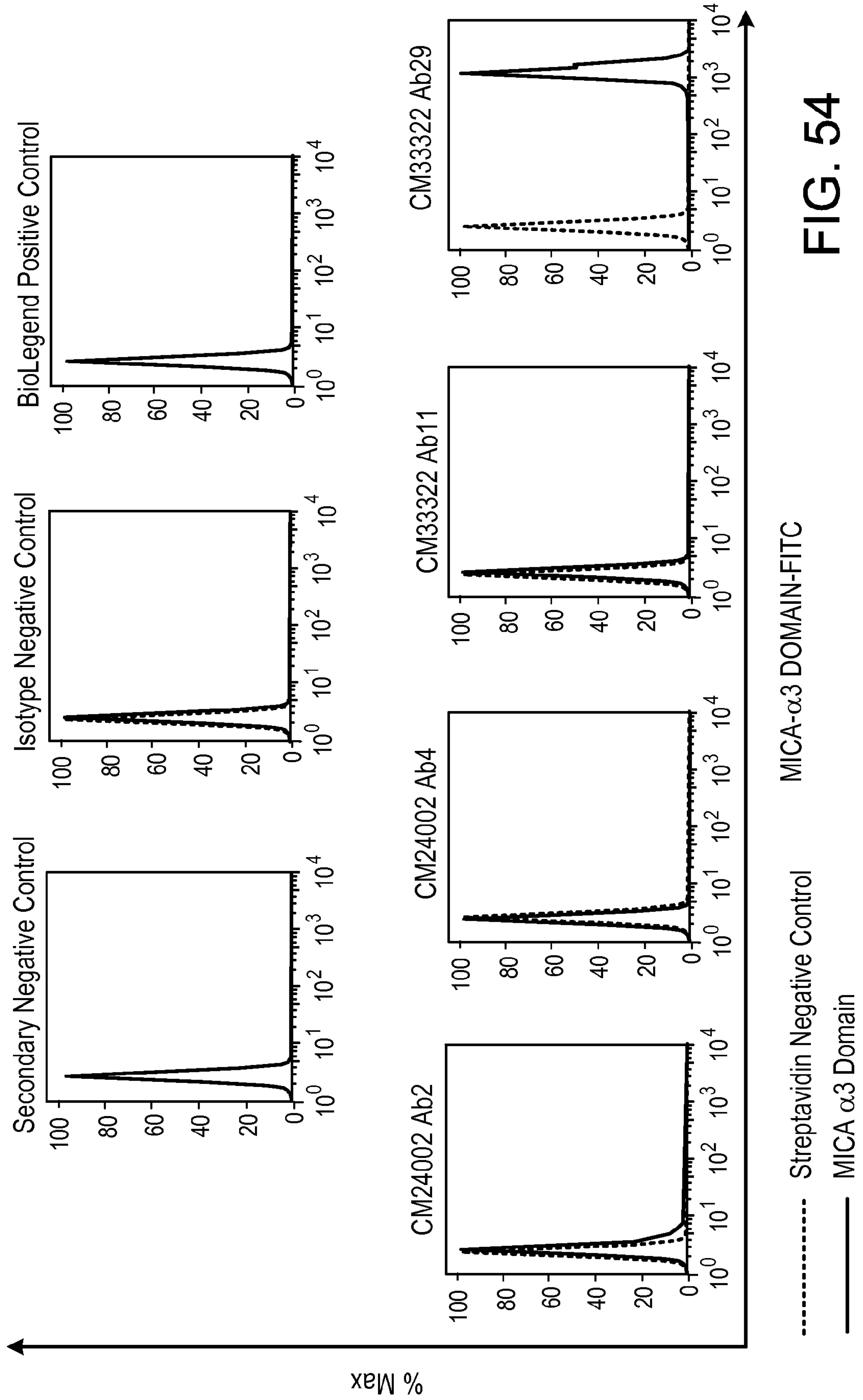

Secondary Negative Control
Isotype Negative Control
BioLegend Positive Control
CM24002 Ab2
CM24002 Ab4
CM33322 Ab11
CM33322 Ab29
100
80
60
40
20
0
10^0
10^1
10^2
10^3
10^4
% Max
MICA-α3 DOMAIN-FITC
Streptavidin Negative Control
MICA α3 Domain

FIG. 54

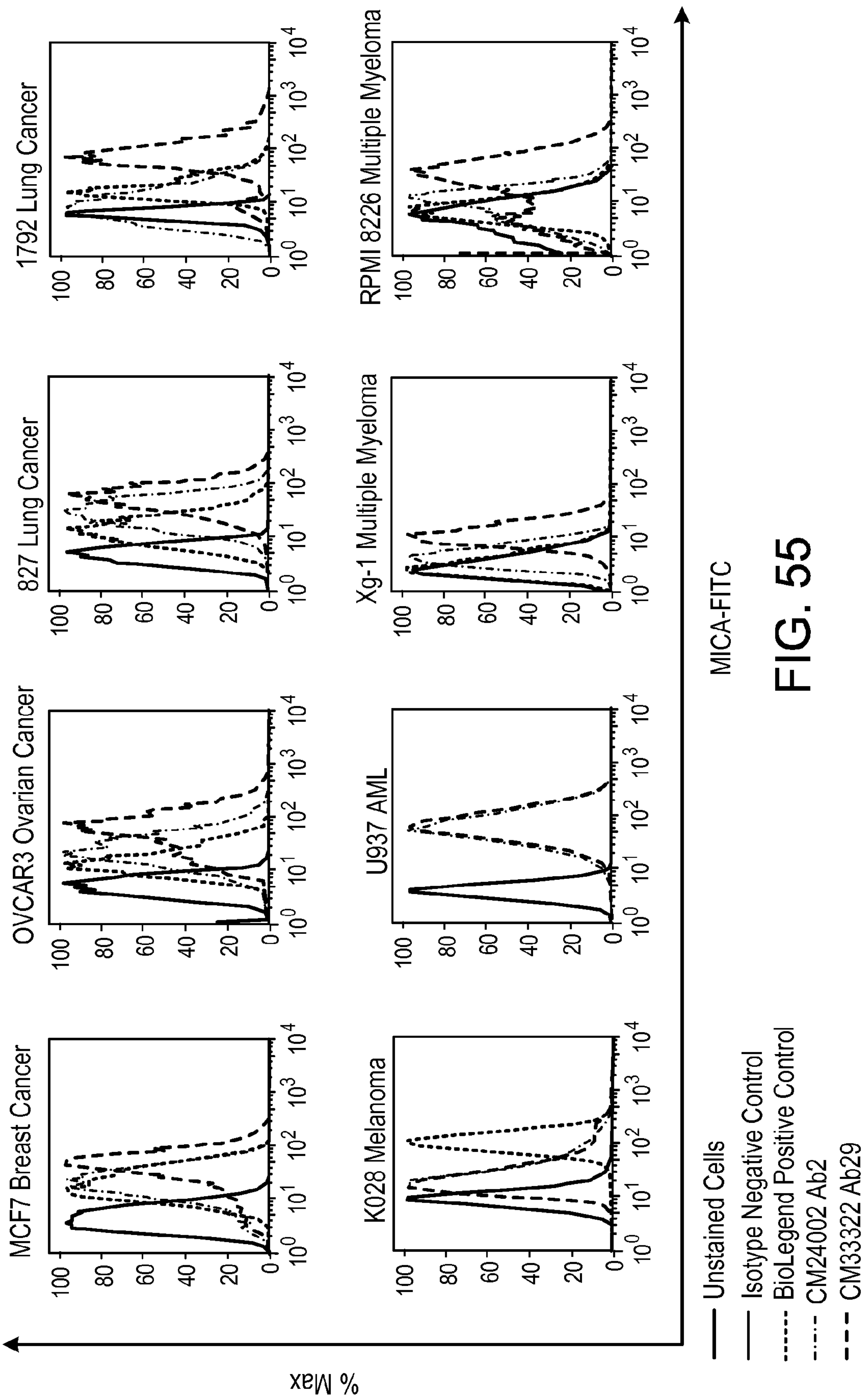

MCF7 Breast Cancer
OVCAR3 Ovarian Cancer
827 Lung Cancer
1792 Lung Cancer
K028 Melanoma
U937 AML
Xg-1 Multiple Myeloma
RPMI 8226 Multiple Myeloma
% Max
MICA-FITC
0
20
40
60
80
100
10^0
10^1
10^2
10^3
10^4
Unstained Cells
Isotype Negative Control
BioLegend Positive Control
CM24002 Ab2
CM33322 Ab29

FIG. 55

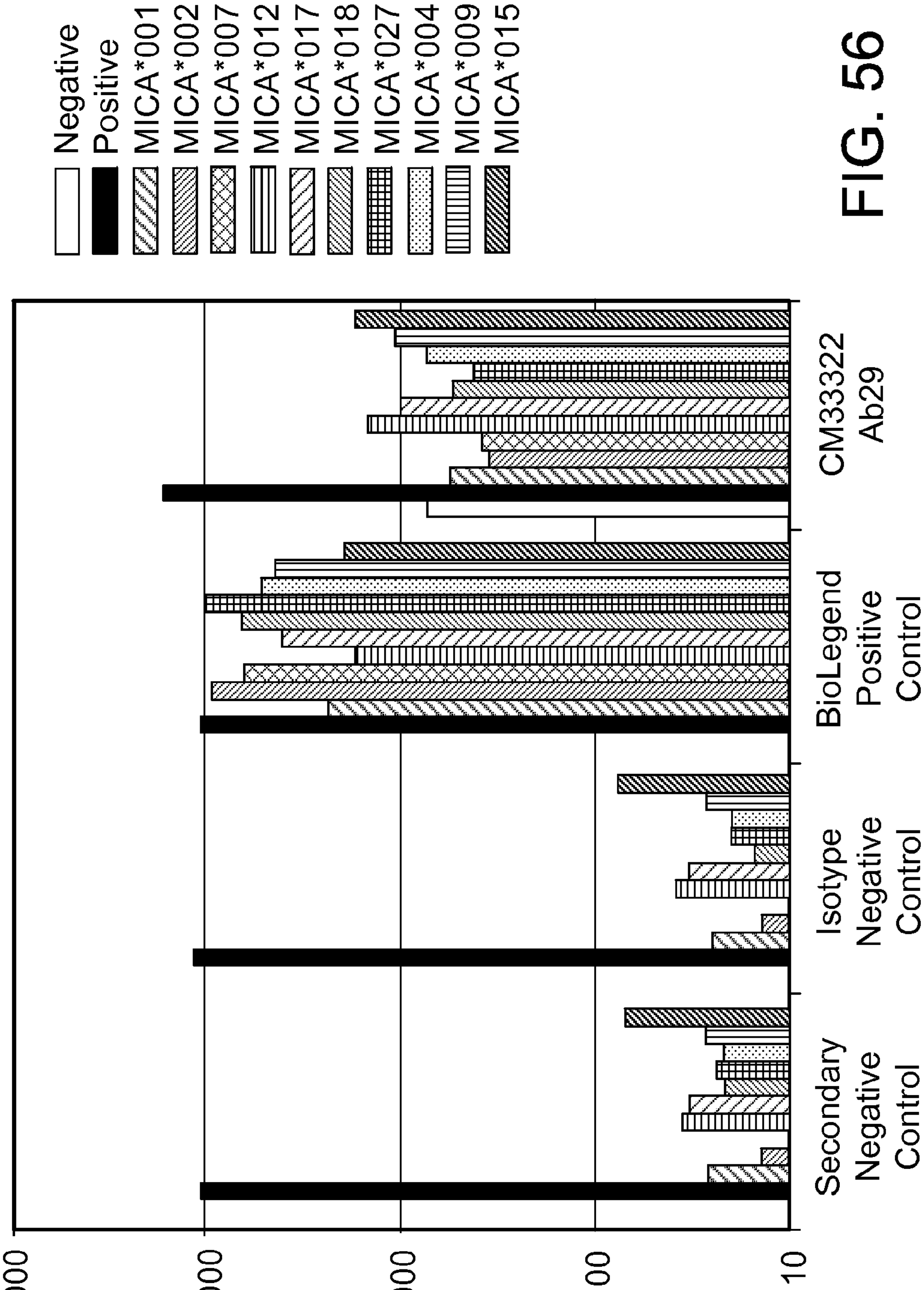
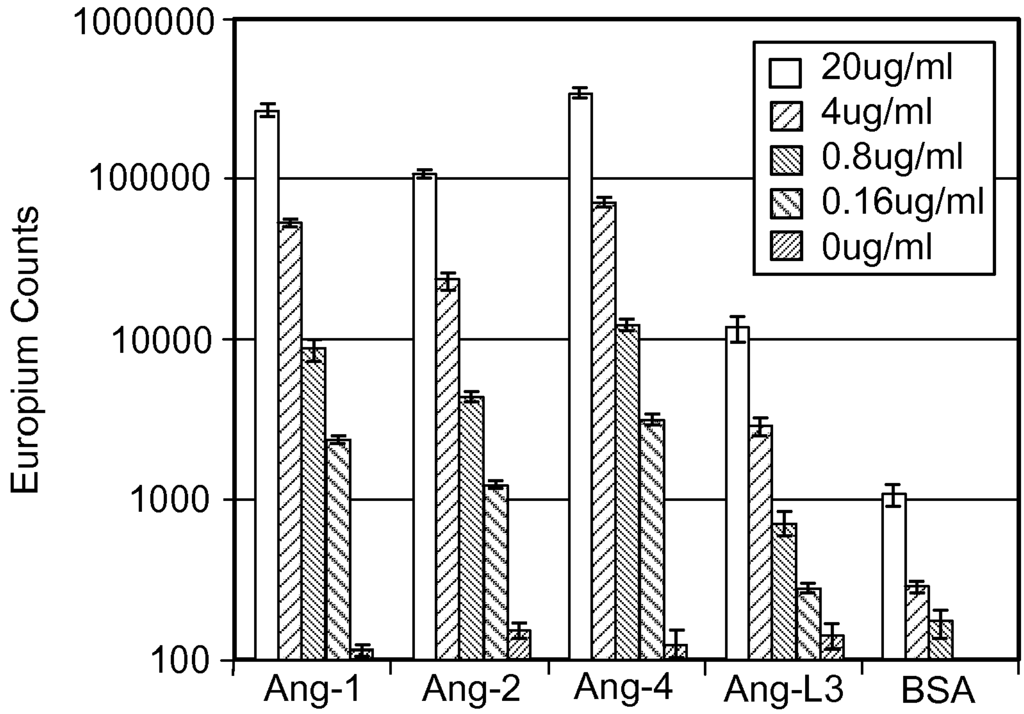

100000
10000
1000
100
10
Secondary Negative Control
Isotype Negative Control
BioLegend Positive Control
CM33322 Ab29
Negative
Positive
MICA*001
MICA*002
MICA*007
MICA*012
MICA*017
MICA*018
MICA*027
MICA*004
MICA*009
MICA*015

FIG. 56



1000000
100000
10000
1000
100
Europium Counts
20ug/ml
4ug/ml
0.8ug/ml
0.16ug/ml
0ug/ml
Ang-1
Ang-2
Ang-4
Ang-L3
BSA

FIG. 57

REFERENCES CITED IN THE DESCRIPTION

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