

KIR3DL3 IS AN INHIBITORY RECEPTOR OF THE IMMUNE SYSTEM AND USES THEREOF

STATEMENT OF GOVERNMENT SUPPORT

[0001] The present invention was made with government support under Grant Nos. R01CA175498 and R01DK100525 awarded by the National Institutes of Health. The Government has certain rights in the invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of U.S. Provisional Patent Application No. 62/911,169 filed on October 4, 2019, the content of which is incorporated by reference in its entirety.

SEQUENCE LISTING

[0003] This application contains a Sequence Listing, which was submitted in ASCII format via USPTO EFS-Web, and is hereby incorporated by reference in its entirety. The ASCII copy, created on October 1, 2020, is named SequenceListing.txt and is 140 kilobytes in size.

BACKGROUND

[0004] Killer-cell immunoglobulin-like receptor (KIR) proteins include either two (KIR2D) or three (KIR3D) immunoglobulin-like extracellular domains (Beziat 2017). KIR3DL3 is a member of the KIR family, but its functions were previously unknown (Beziat 2017). The present disclosure provides results demonstrating that KIR3DL3 is an inhibitory receptor of the immune system. The present disclosure further provides antibodies and immunogenic fragments thereof against KIR3DL3, or one or more epitopes thereof, and compositions and methods for using the same. According to certain embodiments provided herein, blocking KIR3DL3 function by antibodies or immunogenic fragments thereof, ligand fusion polypeptides, or small molecules can be used to treat cancers and infection, whereas stimulating KIR3DL3 function by antibodies or immunogenic fragments thereof, ligand fusion polypeptide, or small molecules can be used to treat autoimmune diseases and transplant.

[0005] Drugs that function to suppress immune response can be used to effectively treat patients having autoimmune diseases or to help prevent transplant rejection. For example, among currently available treatments for rheumatoid arthritis and kidney transplant are Abatacept (Orencia®) and Betacept (Nulojix®), modified antibody fusion polypeptides comprising the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the Fc region of IgG1. Conversely, drugs that activate immune responses may be used to effectively treat diseases or disorders including cancers or infectious diseases. For example, ipilimumab (Yervoy®) is a monoclonal antibody that activates immune responses by targeting CTLA-4 and can be used to treat melanoma. Pembrolizumab (Keytruda®) is a humanized antibody against human programmed death receptor-1 (PD-1) and is prescribed as an anti-PD-1 immunotherapy against certain cancers. Nivolumab (Opdivo®) is another anti-PD-1 antibody used as an immunotherapy to treat certain cancers.

SUMMARY

[0006] In one aspect, the disclosure relates to an antibody or an immunogenic fragment thereof that specifically binds to KIR3DL3 protein (SEQ ID NO: 335). In certain embodiments, the disclosure relates to an antibody or an immunogenic fragment thereof that specifically binds to KIR3DL3 protein, wherein the antibody or the immunogenic fragment thereof specifically binds to a KIR3DL3 epitope comprising the whole extracellular domain or a portion thereof. In some embodiments, the antibody or the immunogenic fragment thereof binds to the KIR3DL3 D0 domain (SEQ ID NO: 337), the KIR3DL3 D1 domain (SEQ ID NO: 338), or KIR3DL3 D2 domain (SEQ ID NO: 339).

[0007] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VH region comprising CDR1, CDR2, and CDR3, having an amino acid sequence of SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0008] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VH region comprising at least one CDR that is 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0009] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VH region comprising at least two CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0010] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VH region comprising at least three CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0011] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VL region comprising CDR1, CDR2, and CDR3, having an amino acid sequence of SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0012] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VL region comprising at least one CDR that is 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0013] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VL region comprising at least two CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0014] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise a VL region comprising at least three CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0015] In certain aspects, antibodies or immunogenic fragments thereof provided herein comprise a monoclonal antibody.

[0016] In certain aspects, antibodies or immunogenic fragments thereof provided herein comprise a chimeric antibody, a human antibody, or a humanized antibody.

[0017] In one aspect, antibodies or immunogenic fragments thereof provided herein comprise an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 19, 21, 23, 31, 33, 35, 43, 45, 47, 54, 56, 64, 66, 68, 76, 78, 80, 88, 90, 92, 100, 102, 104, 112, 114, 116, 124, 126, 128, 136, 138, 140, 148, 150, 152, 160, 162, 164, 172, 174, 176, 184, 186, 188, 196, 198, 200, 208, 210, 212, 220, 222, 224, 232, 234, 236, 244, 246, 248, 256, 258, 260, 268, 270, 272, 280, 282, 284, 292, 294, 296, 304, 306, 308, 316, 318, 320, 328, 330, or 332.

[0018] In one aspect, antibodies or immunogenic fragments thereof are provided herein, wherein the antibody is monoclonal 8G7, monoclonal 26E10, monoclonal 26E2, monoclonal 31C4, monoclonal 34B10, monoclonal 37A3, monoclonal 12A10, monoclonal 3B7, monoclonal 11G8, monoclonal 14F8, monoclonal 15D2, monoclonal 29H7, monoclonal 30D10, or monoclonal 51C3.

[0019] In one aspect, antibodies or immunogenic fragments thereof are provided herein, wherein the antibody is humanized 8G7, humanized 26E10, humanized 26E2, humanized 31C4, humanized 34B10, humanized 37A3, humanized 12A10, humanized 3B7, humanized 11G8, humanized 14F8, humanized 15D2, humanized 29H7, humanized 30D10, or humanized 51C3.

[0020] In another aspect, fusion polypeptides comprising an antibody or an immunogenic fragment thereof according to the present disclosure are provided.

[0021] In certain aspects, compositions comprising an antibody or an immunogenic fragment thereof or fusion proteins according the present disclosure are provided.

[0022] In another aspect, compositions provided herein further comprise a pharmaceutically acceptable carrier.

[0023] In another aspect, compositions provided herein further comprise a pharmaceutically acceptable excipient.

[0024] In certain aspects, antibodies or immunogenic fragments thereof, fusion polypeptides, or compositions according to the present disclosure may be or comprise a component of a chimeric antigen receptor or an antibody-drug conjugate (e.g., an antibody or immunogenic fragment thereof attached to a cytotoxic agent or molecule).

[0025] In certain aspects, antibodies or immunogenic fragments thereof, fusion polypeptides, or compositions according to the present disclosure for use in a therapy are provided.

[0026] In certain aspects, antibodies or immunogenic fragments thereof, fusion polypeptides, or compositions according to the present disclosure for use in the production of a medicament are provided.

[0027] In another aspect, nucleic acids comprising a nucleic acid encoding an antibody or an immunogenic fragment thereof according to the present disclosure are provided.

[0028] In another aspect, nucleic acids comprising a nucleic acid encoding a fusion polypeptide according to the present disclosure are provided.

[0029] In certain aspects, methods of treating a subject having a condition, comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure are provided.

[0030] In some aspects, methods of treating a subject having a condition comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure are provided, wherein the subject has a condition and wherein the condition is cancer. In some embodiments, the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell lymphoma, B-cell lymphoma, T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B-cell prolymphocytic leukemia, T-cell lymphoma, Hodgkin's Disease, B-cell non-Hodgkin's lymphoma, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell follicular lymphoma, large cell follicular lymphoma, malignant

lymphoproliferative conditions, mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, or preleukemia. In other embodiments, the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, lung cancer, kidney cancer, gastric cancer, gallbladder cancer, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, environmentally induced cancers, combinations of the cancers, and metastatic lesions of the cancers. In other embodiments, the cancer is a human hematologic malignancy. In certain embodiments, the human hematologic malignancy is selected from myeloid neoplasm, acute myeloid leukemia (AML), AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, acute leukemias of ambiguous lineage, myeloproliferative neoplasm, essential thrombocythemia, polycythemia vera, myelofibrosis (MF), primary myelofibrosis, systemic mastocytosis, myelodysplastic syndromes (MDS), myeloproliferative/myelodysplastic syndromes, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, myelodysplastic syndromes (MDS), refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (type 1), refractory anemia with excess blasts (type 2), MDS with isolated del (5q), unclassifiable MDS, myeloproliferative/myelodysplastic syndromes, chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, unclassifiable

myeloproliferative/myelodysplastic syndromes, lymphoid neoplasms, precursor lymphoid neoplasms, B lymphoblastic leukemia, B lymphoblastic lymphoma, T lymphoblastic leukemia, T lymphoblastic lymphoma, mature B-cell neoplasms, diffuse large B-cell lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, Burkitt's lymphoma/leukemia, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, marginal zone lymphomas, post-transplant lymphoproliferative disorders, HIV-associated lymphomas, primary effusion lymphoma, intravascular large B-cell lymphoma, primary cutaneous B-cell lymphoma, hairy cell leukemia, multiple myeloma, monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma, or solitary plasmacytomas (solitary bone and extramedullary).

[0031] In some embodiments, the cancer is a metastatic cancer.

[0032] In some embodiments, methods of treating a subject having cancer comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure further comprise subjecting the subject to one or more additional cancer therapies selected from chemotherapy, radiation therapy, immunotherapy, surgery and a combination thereof.

[0033] In some aspects, methods of treating a subject having a condition comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure are provided, wherein the subject has a condition and wherein the condition is an infection. In certain embodiments, the infection is caused by a pathogen. In certain embodiments, the pathogen is a virus. In some embodiments, the virus is selected from the group consisting of human immunodeficiency viruses, influenza viruses, papillomaviruses, coronaviruses, hepatitis viruses, or herpesviruses. In other embodiments, the pathogen is a bacterium. In some embodiments, the bacterium is mycobacterium tuberculosis. In other embodiments, the pathogen is a prion. In other embodiments, the pathogen is a fungus. In certain embodiments, the fungus is *Pneumocystis jirovecii* (PJP). In other embodiments, the pathogen is a parasite.

[0034] In some aspects, methods of treating a subject having a condition comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure are provided, wherein the subject has a condition and wherein the condition is an autoimmune disease or disorder. In some embodiments, the autoimmune disease or disorder is selected from the group consisting of acute disseminated encephalomyelitis (ADEM), alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lipoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticarial, autoimmune uveitis, Behçet's disease, celiac disease, Chagas disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's syndrome, Guillain-Barré syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis. In certain embodiments, the autoimmune disease or disorder is adult rheumatoid arthritis.

[0035] In some aspects, methods of treating a subject having a condition comprising administering to the subject a therapeutically effective amount of an antibody or an immunogenic fragment thereof, a fusion polypeptide, or a composition according to the present disclosure are provided, wherein the subject has a condition and wherein the condition is a transplant. In some embodiments, the transplant is selected from a stem cell transplant or a bone marrow transplant. In some embodiments, the transplant is selected from the group consisting of a kidney transplant, a lung transplant, a heart transplant, a pancreas transplant, a cornea transplant, or a liver transplant.

[0036] In certain aspects, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided.

[0037] In some aspects, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided, wherein the condition is cancer. In some embodiments, the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell lymphoma, B-cell lymphoma, T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B-cell prolymphocytic leukemia, T-cell lymphoma, Hodgkin's Disease, B-cell non-Hodgkin's lymphoma, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell follicular lymphoma, large cell follicular lymphoma, malignant lymphoproliferative conditions, mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, or preleukemia. In other embodiments, the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, lung cancer, kidney cancer, gastric cancer, gallbladder cancer, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, environmentally induced cancers, combinations of the cancers, and metastatic

lesions of the cancers. In other embodiments, the cancer is a human hematologic malignancy. In certain embodiments, the human hematologic malignancy is selected from myeloid neoplasm, acute myeloid leukemia (AML), AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, acute leukemias of ambiguous lineage, myeloproliferative neoplasm, essential thrombocythemia, polycythemia vera, myelofibrosis (MF), primary myelofibrosis, systemic mastocytosis, myelodysplastic syndromes (MDS), myeloproliferative/myelodysplastic syndromes, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, myelodysplastic syndromes (MDS), refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (type 1), refractory anemia with excess blasts (type 2), MDS with isolated del (5q), unclassifiable MDS, myeloproliferative/myelodysplastic syndromes, chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, unclassifiable myeloproliferative/myelodysplastic syndromes, lymphoid neoplasms, precursor lymphoid neoplasms, B lymphoblastic leukemia, B lymphoblastic lymphoma, T lymphoblastic leukemia, T lymphoblastic lymphoma, mature B-cell neoplasms, diffuse large B-cell lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, Burkitt's lymphoma/leukemia, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, marginal zone lymphomas, post-transplant lymphoproliferative disorders, HIV-associated lymphomas, primary effusion lymphoma, intravascular large B-cell lymphoma, primary cutaneous B-cell lymphoma, hairy cell leukemia, multiple myeloma, monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma, or solitary plasmacytomas (solitary bone and extramedullary).

[0038] In some embodiments, the cancer is a metastatic cancer.

[0039] In some embodiments, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided, wherein the compositions are co-administered to the subject with one or more additional cancer therapies selected from chemotherapy, radiation therapy, immunotherapy, surgery, or a combination thereof.

[0040] In some aspects, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided, wherein the condition is an infection. In certain embodiments, the infection is caused by a pathogen. In certain embodiments, the pathogen is a virus. In some embodiments, the virus is selected from the group consisting of human immunodeficiency viruses, influenza viruses, papillomaviruses, coronaviruses, hepatitis viruses, or herpesviruses. In other embodiments, the pathogen is a bacterium. In some embodiments, the bacterium is mycobacterium tuberculosis. In other embodiments, the pathogen is a prion. In other embodiments, the pathogen is a fungus. In certain embodiments, the fungus is *Pneumocystis jirovecii* (PJP). In other embodiments, the pathogen is a parasite.

[0041] In some aspects, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided, wherein the condition is an autoimmune disease or disorder. In some embodiments, the autoimmune disease or disorder is selected from the group consisting of acute disseminated encephalomyelitis (ADEM), alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lipoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticarial, autoimmune uveitis, Behçet's disease, celiac disease, Chagas disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's syndrome, Guillain-Barré syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis. In certain embodiments, the autoimmune disease or disorder is adult rheumatoid arthritis.

[0042] In some aspects, compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof according to the present technology for use in treating a subject having a condition are provided, wherein the condition is a transplant. In some embodiments, the transplant is selected from a stem cell transplant or a bone marrow transplant. In some embodiments, the transplant is selected from the group consisting of a kidney transplant, a lung transplant, a heart transplant, a pancreas transplant, a cornea transplant, and liver transplant.

[0043] This listing is intended to be exemplary and illustrative rather than comprehensive and limiting. Additional aspects and embodiments may be set out in, or apparent from, the remainder of this technology and the claims.

DESCRIPTION OF THE DRAWINGS

[0044] Figures (FIGS.) 1A–1B show that KIR3DL3 protein is expressed on the cell surface of human adaptive immune cells and innate immune cells. FIG. 1A depicts a series of plots showing Fluorescence-Activated Cell Sorting (FACS) analysis of peripheral blood mononuclear cells (PBMCs). FACS analysis showed that KIR3DL3 protein was detected on the cells surface of human innate immune cells, including natural killer (NK) cells, natural killer T (NKT) cells and $\gamma\delta$ T cells, and adaptive immune cells, including CD8⁺ T cells and CD4⁺ T cells. FIG. 1B is a chart depicting the percentage of KIR3DL3 positive cells in different populations of immune cells in PBMCs from six different donors.

[0045] FIGS. 2A–2C show that HHLA2 binds KIR3DL3, but not its closest homologues KIR3DL1 and KIR3DL2, and that the D0 domain and the whole extracellular portion of KIR3DL3 bind HHLA2. FIG. 2A depicts histograms of 3T3 cell lines expressing KIR3DL1, KIR3DL2, or KIR3DL3 stained with HHLA2-Ig fusion polypeptide (open histograms) or control Ig (shaded histograms). FIG. 2B depicts a plot showing results of an intercellular conjugate assay that indicate 3T3 cell line expressing HHLA2 bound to 3T3 cell line expressing KIR3DL3, but not the control 3T3 cell line. FIG. 2C depicts histograms of a 3T3 cell line expressing HHLA2 bound by the D0 domain (red) and the whole extracellular portion (red) of KIR3DL3.

[0046] FIGS. 3A–3B show results indicating that TMIGD2 and KIR3DL3 bind non-overlapping sites on HHLA2. FIG. 3A is a chart depicting mean fluorescent intensity

(MFI) of 3T3 cells expressing HHLA2 that were incubated with TMIGD2-mIg fusion polypeptide or control mIgG at the indicated concentrations prior to staining with 10 µg/ml KIR3DL3-hlg followed by Allophycocyanin (APC)-conjugated anti-human IgG Fc. FIG. 3B is a chart depicting MFI of 3T3 cells expressing HHLA2 that were incubated with KIR3DL3-hlg fusion polypeptide or control hlgG at the indicated concentrations prior to staining with 10 µg/ml TMIGD2-mIg followed by APC anti-mouse IgG Fc.

[0047] FIGS. 4A–4B show results indicating that KIR3DL3 inhibits functions of immune cells. FIG. 4A depicts plots of FACS analysis and charts quantifying specific lysis. KIR3DL3⁺ or KIR3DL3⁻ NK92 cells were sorted and KIR3DL3 expression was examined by FACS. Cytotoxicity assays were performed by incubating NK92 cells with target control K562 or HHLA2 expressing K562 (HHLA2/K562) at the indicated ratios of effector and target cells (E:T=1, 2, 5, 10). FIG. 4B is a chart depicting specific lysis percentages following a cytotoxicity assay in KIR3DL3⁺ CD8⁺ T cells (terminally differentiated effector cells) from PBMCs were sorted out by FACS and expanded with anti-CD3/CD28, IL-2, and feeder cells *in vitro*. Cytotoxicity assays were performed by incubating KIR3DL3⁺ CD8⁺ T cells with target control K562 or HHLA2/K562 at the indicated ratios of effector and target cells. **P* < 0.05; ***P* < 0.01.

[0048] FIGS. 5A–5B show that anti-KIR3DL3 blocking monoclonal antibodies (mAbs) neutralize KIR3DL3-induced immune suppression. FIG. 5A depicts a series of histograms of KIR3DL3⁺ NK92 cells pre-incubated with anti-KIR3DL3 mAbs (Clone 26E10, 34B10, 30D10, 8G7) for 45 min at room temperature (RT). FIG. 5B depicts a chart quantifying specific lysis percentages in the indicated cells following a cytotoxicity assay. Cytotoxicity assays were performed with target control K562 or HHLA2/K562 at an E:T ratio of 5:1. **P* < 0.05; ***P* < 0.01.

[0049] FIGS. 6A–6B show that monoclonal antibodies against the IgV1 domain of HHLA2 can block the binding of HHLA2 to KIR3DL3 and neutralize KIR3DL3-induced immune suppression. FIG. 6A is a chart depicting the mean fluorescence intensity (MFI) of HHLA2 expressing 3T3 cells that were pre-incubated with anti-HHLA2 mAbs or control mouse IgG and then stained with KIR3DL3-Ig protein at different concentrations. The binding of KIR3DL3-Ig protein to HHLA2 was examined by FACS. FIG. 6B is a chart depicting specific lysis percentages following a toxicity assay in HHLA2/K562 target cells that were pre-incubated with anti-HHLA2 mAbs (Clone B5B5,

A3H11, 566.1) or isotype mIgG1. Cytotoxicity assays were performed by incubating KIR3DL3⁺ NK92 cells with control K562 or HHLA2/K562 at an E:T ratio of 5:1 at 37°C for 4 hours. **P* < 0.05; ***P* < 0.01.

[0050] FIG. 7 depicts a series of FACS plots showing the expression patterns of two receptors KIR3DL3 and TMIGD2 on human NK cells, CD8⁺ T cells and CD4⁺ T cells.

[0051] FIG. 8 depicts two charts depicting histograms of 3T3 cell lines expressing TMIGD2 that were stained with HHLA2 EC-Ig-Fc fusion polypeptide (left, red histograms), HHLA2-IgV1-hIgG fusion polypeptide (right, red histograms) or control Ig (black histograms).

[0052] FIG. 9 KIR3DL3 depicts a table including corresponding color-coded percent of expression potential of KIRDL3 mRNA levels in 1425 human tumor lines. KIR3DL3 mRNA was expressed in many tumor lines of human hematologic malignancies. The top 40 lines expressing the highest levels of KIR3DL3 mRNA are depicted in FIG. 9.

[0053] FIGS. 10A–10D show that the ITIM motif of KIR3DL3 mediates NK-cell suppression through recruiting SHP1/2. FIG. 10A depicts wildtype (WT) KIR3DL3 and ITIM mutant (Y381F) of KIR3DL3 with tyrosine (Y) to phenylalanine (F) mutation at the ITIM sequences (YAQL), and their expression by flow cytometry. FIG. 10B depicts tyrosine phosphorylation of KIR3DL3 WT and Y381F mutant upon pervanadate treatment. FIG. 10C shows cytotoxicity assays performed by incubating KIR3DL3 WT or Y381F NK92 cells with K562 (top, control K562 or HHLA2/K562) or Raji (bottom, control Raji or HHLA2/Raji) at the indicated E:T ratios. One representative of 3 independent experiments is shown. **P* < 0.05, ***P* < 0.01; NS, not significant. FIG. 10D depicts co-immunoprecipitation demonstrating that KIR3DL3 interacted with both SHP-1 and SHP-2.

[0054] FIG. 11 shows that KIR3DL3 is expressed on tumor-infiltrating immune cells in various human cancers, including kidney, gastric, lung, gallbladder and pancreatic cancer. Representative images of indicated human cancer with co-expression of KIR3DL3 and CD45 (DAPI: blue, CD45: red, KIR3DL3: green). Left: overlay of all markers; Middle: CD45 and DAPI; Right: KIR3DL3 and DAPI. Scale bars, 50 μm.

[0055] FIGS. 12A–12F show that KIR3DL3 blockade promotes anti-tumor immunity. FIGS. 12A–12B show intraperitoneal tumor mouse models treated by primary NK cells and anti-KIR3DL3 mAb. FIG. 12A depicts an outline of the experiment procedure. FIG. 12B depicts bioluminescence measurement of tumor growth in the 26E10 (blue line) and mIgG1 (black line) group. Data are mean $\pm$ SEM of the total flux from ventral imaging for each mouse. FIGS. 12C–12D show lung metastasis tumor mouse models treated by primary NK cells and anti-KIR3DL3 mAb. FIG. 12C depicts an outline of the experiment procedure. FIG. 12D depicts bioluminescence measurement of tumor growth in the 26E10 (blue) and mIgG1 (black) group. Data are mean $\pm$ SEM of the average of total flux from dorsal and ventral imaging for each mouse. P values two-way ANOVA. FIGS. 12E–12F show subcutaneous tumor mouse models treated with primary NK cells and anti-KIR3DL3 mAb. FIG. 12E depicts an outline of the experiment procedure. FIG. 12 F depicts assessment of the tumor growth. Mean tumor volumes $\pm$ SEM are shown. i.p., intraperitoneally. i.v., intravenously. s.c., subcutaneously.

DETAILED DESCRIPTION

[0056] Killer-cell immunoglobulin-like receptor (KIR) proteins include either two (KIR2D) or three (KIR3D) immunoglobulin-like extracellular domains (Beziat 2017). KIR3DL3 is a member of the KIR family, but its functions are yet unknown (Beziat 2017). KIR3DL3 protein is expressed on the surface of human adaptive immune cells and innate immune cells. According to results provided herein, KIR3DL3 inhibits functions of human immune cells. Consequently, blocking KIR3DL3 function by antibodies, ligand fusion polypeptides, or small molecules can be used to treat cancers or infections, whereas stimulating KIR3DL3 function by antibodies, ligand fusion polypeptides, or small molecules can be used to treat an autoimmune disease or transplant. KIR3DL3 is expressed in various human hematologic malignancies, therefore using antibodies and other molecules to kill KIR3DL3-positive tumor cells can be used to treat human hematologic malignancies. The present technology provides antibodies against KIR3DL3, or one or more epitopes thereof, and compositions and methods for using the same.

[0057] The present technology provides results demonstrating that KIR3DL3 inhibits immune cell function. Further, by administering anti-KIR3DL3 blocking mAbs,

such as those provided herein, KIR3DL3-induced immune suppression is neutralized. As such, isolated antibodies against KIR3DL3, including monoclonal antibodies, antibodies against KIR3DL3 can act to block KIR3DL3 function, thereby enhancing immune cell function. Moreover, additional results provided herein demonstrate that HHLA2 binds KIR3DL3, but not its closet homologues KIR3DL1 and KIR3DL2. Thus, antibodies against the IgV1 domain of HHLA2 can block the binding of HHLA2 to KIR3DL3, thereby neutralizing KIR3DL3-induced immune suppression.

Definitions and abbreviations

[0058] Unless otherwise specified, each of the following terms has the meaning set forth in this section.

[0059] The indefinite articles "a" and "an" denote at least one of the associated noun and are used interchangeably with the terms "at least one" and "one or more." For example, the phrase "a module" means at least one module, or one or more modules.

[0060] The conjunctions "or" and "and/or" are used interchangeably.

[0061] The term "antibody" as used herein is used to denote, in addition to natural antibodies, genetically engineered or otherwise modified forms of immunoglobulins, including chimeric antibodies, human antibodies, humanized antibodies, or synthetic antibodies. The antibodies disclosed herein may be monoclonal or polyclonal antibodies. In those embodiments wherein an antibody is an immunogenically active portion of an immunoglobulin molecule, the antibody may include, but are not limited to, a single chain Fv antibody (scFv), disulfide-linked Fv, single domain antibody (dAb), Fab, Fab', Fab fragment, F(ab')₂, or diabody. The antibodies disclosed herein, including those that comprise an immunogenically active portion of an immunoglobulin molecule, retain the ability to bind a specific antigen, for example, KIR3DL3, or one or more epitopes thereof.

[0062] "Domain" is used to describe a segment of a protein or nucleic acid. Unless otherwise indicated, a domain is not required to have any specific functional property.

[0063] "Subject" means a human, mouse, or non-human primate. A human subject can be any age (e.g., an infant, child, young adult, or adult), and may suffer from a disease, such as a cancer. In some embodiments, a subject is suffering from a

relevant disease, disorder or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms or characteristics of a disease, disorder or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0064] "Treat," "treating," and "treatment" as used herein mean the treatment of a disease in a subject (*e.g.*, a human subject), including one or more of inhibiting the disease, *i.e.*, arresting or preventing its development or progression; relieving the disease, *i.e.*, causing regression of the disease state; relieving one or more symptoms of the disease; and curing the disease.

[0065] "Prevent," "preventing," and "prevention" as used herein means the prevention of a disease in a subject, *e.g.*, in a human, including (a) avoiding or precluding the disease; (b) affecting the predisposition toward the disease; (c) preventing or delaying the onset of and/or reduction in frequency and/or severity of at least one symptom of the disease.

[0066] The terms "polynucleotide," "nucleotide sequence," "nucleic acid," "nucleic acid molecule," "nucleic acid sequence," and "oligonucleotide" refer to a series of nucleotide bases (also called "nucleotides") in DNA and RNA and mean any chain of two or more nucleotides. The polynucleotides can be chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, its hybridization parameters, etc. A nucleotide sequence typically carries genetic information, including the information used by cellular machinery to make proteins and enzymes. These terms include double- or single-stranded genomic DNA, RNA, any synthetic and genetically manipulated polynucleotide, and both sense and antisense polynucleotides. This also includes nucleic acids containing modified bases.

[0067] Conventional IUPAC notation is used in nucleotide sequences presented herein, as shown in **Table 1**, below (see also Cornish-Bowden 1985, incorporated by

reference herein). It should be noted, however, that "T" denotes "Thymine or Uracil" insofar as a given sequence (such as a gRNA sequence) may be encoded by either DNA or RNA.

Table 1: IUPAC nucleic acid notation

Character	Base
A	Adenine
T	Thymine
G	Guanine
C	Cytosine
U	Uracil
K	G or T/U
M	A or C
R	A or G
Y	C or T/U
S	C or G
W	A or T/U
B	C, G, or T/U
V	A, C, or G
H	A, C, or T/U
D	A, G, or T/U
N	A, C, G, or T/U

[0068] The terms "protein," "peptide" and "polypeptide" are used interchangeably to refer to a sequential chain of amino acids linked together via peptide bonds. The terms include individual proteins, groups or complexes of proteins that associate together, as well as fragments, variants, derivatives and analogs of such proteins. Peptide sequences are presented using conventional notation, beginning with the amino or N-terminus on the left, and proceeding to the carboxyl or C-terminus on the right. Standard one-letter or three-letter abbreviations may be used.

Generation and sequences of mAbs against human KIR3DL3

[0069] KIR3DL3 is a member of the KIR family, but its functions were previously unknown (Beziat 2017). The extracellular portion of KIR3DL3 is composed of three domains (D0, D1, and D2). According to embodiments provided herein, the following fusion polypeptides were generated: 1) KIR3DL3 D0-Ig fusion polypeptide by fusing the KIR3DL3 D0 coding region (Q26-A128) to a human IgG1 Fc tag; and 2) KIR3DL3 D0D1D2-Ig fusion polypeptide by fusing the KIR3DL3 D0D1D2 coding region (Q26-L325) to a human IgG1 Fc tag using previously reported methods (Zhao 2013). In some embodiments, the fusion polypeptides were expressed in a S2 system and then purified.

Mice were immunized with KIR3DL3 D0(Q26-A128)-Ig fusion polypeptide or KIR3DL3 D0(Q26-A128)-Ig fusion polypeptide and hybridomas were generated by standard techniques from splenocytes fused to NS0 myeloma cells. Human KIR3DL3 sequences are as shown below in **Table 2**.

Table 2: Human KIR3DL3 sequences

Sequence	SEQ ID NO.
Open Reading Frame: atgtcgctcatggtcgtcagcatggcgtgtgtgggttcttctgctggaggggcccctggccacatg tgggtggcaggacaagccctcctctgctgctggccggcactgtgtgtctgaaggacaacat gtgactctcagtgctcgtctgtgtggttaataaattcagtcgtccaaagaagacgggatgc ctgtccctgagctctacaacagaatattccggaacagctttctcatgggcccctgtgacccagca catgcagggaacctacagatgttgcagttcacacccacactccccactgggtggtcggcacc agcaaccctgtgtgatcatggtcacaggagtccacagaaaacctccctcctgcccaccca ggccctgtgtgaaatcaggagagacgggtcatcctgcaatgttggtcagatgtcaggttgagcg ctcctctgcacagagaggggatcactgaggacccttgcgcctcgttgacagctccacgat gcggttcccaggtaactattccatgggtccatgacacctgccctgcagggaacctacagat gcttggttctgtcactcactaccctatgagttgctggctcccagtgaccctctggacatcgtggtc gtaggtctatatgggaaaccttctctcagcccagccgggccccacggttcaggcaggagag aatgtgacctgtctgcagctcccggagctgtttgacatttaccatctatccaggaggcgag gccggtgaacttaggtcactgcagtgctgagggcaatggaacattccaggccaactccctct gggcccctgtgaccacggagggaactacagatgtctcggctcttccgtgccctgccccatgct ggtcagacccgagtgaccactgcccgttctgtcacaggttaactccagaaacctgcacgttct gattgggacctcagtggtcatcatccccttctctcctcctcttctccttcatcgctggtgtgcca acaaaaagaatgctgttgtaatggaccaagagcctgcagggaacagaacagtgaacagg aggactctgatgaacaagaccctcaggaggtgacatagcacagttgaatcactgcgtttcac acagagaaaaatcactcgcccttctcagaggccaagacacccccaacagataccagcgtg taa	SEQ ID NO: 334
Protein: MSLMVVSMAVGVFFLLEGPWPHVGGQDKPFLSAWPGTVVSEGQH VTLQCRSRLGFNEFSLSKEDGMPVPELYNRIFRNSFLMGPVTPAHA GTYRCCSSHPHSPTGWSAPSNPVVIMVTGVHRKPSLLAHPGPLVK SGETVILQCWSDVRFERFLLHREGITEDPLRLVGLHDAGSQVNYS MGPMTPALAGTYRCFSGVTHLPYELSDPLDIVVGLYGKPSLS AQPGPTVQAGENVTLSCSSRSLFDIYHLSREAEAGELRLTAVLRVN GTFQANFPLGPVTHGGNYRCFGSFRALPHAWSDPDPLPVSVTGN SRNLHVLIGTSVVIIPFAILLFLLHRWCANKKNAVVMQEPAGNRTV NREDSDEQDPQEVTYAQLNHCVFTRKIRPSQRPKTPPTDTSV	SEQ ID NO: 335
Signal Peptide: MSLMVVSMAVGVFFLLEGPWPHVGG	SEQ ID NO: 336
D0 domain: WPGTVVSEGQHVTLQCRSRLGFNEFSLSKEDGMPVPELYNRIFRN SFLMGPVTPAHAGTYRCCSSHPHSPTGWSAPSNPVVIMVT	SEQ ID NO: 337

D1 domain: HPGPLVKSGETVILQCWSDVRFERFLLHREGITEDPLRLVGQLHDA GSQVNYSMGPMTPALAGTYRCFGSVTHLPYELSAPSDPLDIVV	SEQ ID NO: 338
D2 domain: QPGPTVQAGENVTLSCSSRSLFDIYHLSREAEAGELRLTAVLRVNG TFQANFPLGPVTHGGNYRCFGSFRALPHAWSDPDPLPVSVTGNS RNLHVL	SEQ ID NO: 339
Transmembrane region: NLHVLIGTSVVIIPFAILLFFLL	SEQ ID NO: 340
Cytoplasmic tail: HRWCANKKNAVVMQEPAGNRTVNREDSDEQDPQEVTYAQLNH CVFTQRKITRPSQRPKT	SEQ ID NO: 341
Immunoreceptor tyrosine-based inhibition motif (ITIM): VTYAQL	SEQ ID NO: 342

[0070] In some embodiments, mAbs to KIR3DL3 protein were obtained from the hybridomas discussed above, and the binding affinity of each mAb was determined as shown below in **Table 3**.

Table 3: mAb binding affinities

Clone	KD (nM)
8G7	0.11
26E10	0.17
26E2	0.26
31C4	0.72
34B10	1.51
37A3	8.50
12A10	0.69
3B7	0.51
11G8	0.29
14F8	0.69
15D2	0.56
29H7	1.13
30D10	0.16
51C3	0.19

[0071] In some embodiments, after assessing binding affinity, the hybridomas were sequenced. Sequencing revealed that each of the 14 mAbs generated had unique VH and VL sequences. Each VH or VL has three CDRs (CDR1, CDR2, and CDR3). These sequences are provided in SEQ ID NOs: 1–333 and annotated below in **Table 4**.

Table 4: mAb sequences

Clone	Sequence	SEQ ID NO.
8G7	8G7 heavy chain VH: DNA sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u>	SEQ ID NO: 1
	atgaacttgggtgagattgatttctcctgtcctgttttaaaagggtgtccagtgtagagtgatgctggtaggtctggtgggaggttagtga agcctggagggtccctgaactctcctgtgcagcctctggttccagttacatttccagttaccctatgctcctggttgcgccagactccgga gaagaggctggagtggtgcgaaccattcttagtgggtgtaattacaccctactatccagacagtgtagaagggcggttaccat ctccagagacaatgccaaagaaacacccctgaacctgcaaatgagcagctgaggctgagggacacggccatgtattactgtgtaattcc cctatggtagtagtgcctttgactatggtgggccaaggcaccactctcacagtctctca	
	8G7 heavy chain VH DNA sequence: CDR1 ggattcacttcagttaccctatgccatgtct	SEQ ID NO: 2
	8G7 heavy chain VH DNA sequence: CDR2 attcttagtggtgtaattacacctactatccagacagtgtagaagggg	SEQ ID NO: 3
	8G7 heavy chain VH DNA sequence: CDR3: gtaatccctatggtagtagtcccttttgactat	SEQ ID NO: 4
	8G7 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u>	SEQ ID NO: 5
	MNFGRLRLFLVLVLKGVQCEVMLVESGGGLVKPGGSLKLSCAASGFTFSTYAMSWVRQTPEK <u>RLEWVA</u> <u>TILSGGNYTYPPDSVKGRFTISRDN</u> <u>AKNTLNLQMSSLR</u> <u>SEDTAMYYC</u> <u>VI</u> <u>PGSSPFD</u> <u>YWGGTTLTVS</u>	
	8G7 heavy chain VH: Amino acid sequence: FR1 EVMLVESGGGLVKPGGSLKLSCAAS	SEQ ID NO: 6
	8G7 heavy chain VH: Amino acid sequence: CDR1 GFTFSTYAMS	SEQ ID NO: 7
	8G7 heavy chain VH: Amino acids sequence: FR2 WVRQTPEKRLWVA	SEQ ID NO: 8
	8G7 heavy chain VH: Amino acid sequence: CDR2 TILSGGNYTYPPDSVKG	SEQ ID NO: 9

Clone	Sequence	SEQ ID NO.
	8G7 heavy chain VH: Amino acid sequence: FR3 RTISRDNAKNTLNQMSSLRSEDAMYYC	SEQ ID NO: 10
	8G7 heavy chain VH: Amino acid sequence: CDR3 VIPYGSSPFDY	SEQ ID NO: 11
	8G7 heavy chain VH: Amino acid sequence: FR4 WGQGTTLLTVS	SEQ ID NO: 12
	8G7 light chain VL: DNA sequence: <u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> ttattactagtcgacacgggcatcaaatgaagtcacagaccaggctctgctgattctactgctgtgtgtgctgctcatggaggtatt gtgataccagactcccaaatctgtgtatcagcaggagacagggttaccataacctgc aaggccagtcagagtgtgagtaa tgat gtagctgtgtaccacagaaagccaggcagctctcctaaactgcgtatatact tatgcatc-caatcgcctacac tggagtcctgat cgcttcactggcagtggtatgtggacggatttcacttcaccatcagcacgtgtagggctgaagacctggcagttattctt gtcagcag gattatagctctccgtggac gttcgtggaggcaccacagctggaatacaacgggctgctgctgca	SEQ ID NO: 14
	8G7 light chain VL: DNA sequence: CDR1 aaggccagtcagagtgtgagtaatatgat	SEQ ID NO: 15
	8G7 light chain VL: DNA sequence: CDR2 tatgcatccaatcgcctacact	SEQ ID NO: 16
	8G7 light chain VL: DNA sequence: CDR3 cagcaggattatagctctccgtggacg	SEQ ID NO: 17
	8G7 light chain VL: Amino acid sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> MKSQTQVFVFLLLCVSGAHGSIVMTQTTPKFLLLVSAGDRVTTTICKASQSVSNDVAWYQQKPGQ <u>SPKLLIY YASNRYTGVPDRFTGSGYGTDFITFTISTVQAEDLAVYFCQQDYSSPWTFGGGKLE</u> IK	SEQ ID NO: 18
	8G7 light chain VL: Amino acid sequence: FR1 SIVMTQTTPKFLLLVSAGDRVTTIC	SEQ ID NO: 19
	8G7 light chain VL: Amino acid sequence: CDR1 KASQSVSND	SEQ ID NO: 19

Clone	Sequence	SEQ ID NO.
26E10	8G7 light chain VL: Amino acid sequence: FR2 VAWYQQKPGQSPKLLIY	SEQ ID NO: 20
	8G7 light chain VL: Amino acid sequence: CDR2 YASNRYT	SEQ ID NO: 21
	8G7 light chain VL: Amino acid sequence: FR3 GVPDRFTGSGYGTDFTFITSTVQAEDLAVYFC	SEQ ID NO: 22
	8G7 light chain VL: Amino acid sequence: CDR3 QQDYSSPWT	SEQ ID NO: 23
	8G7 light chain VL: Amino acid sequence: FR4 FGGGTKLEIK	SEQ ID NO: 24
	26E10 heavy chain VH: DNA sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tggggaattcatggaatgagctgggtttttctctcctctgtcaataatactacagggtgtccacctccaggcttatctacagcagtcgtggg ctgagctggtaggtctggggccctcagtagatgtcctgcaaggctctt ggctacacattaccagttacaaatatcacac atggtggtataa gcagacacctggacagggccctggaatggattgga tatatattatctc tgagatggtgttactaac tacaa tcagaa gttcaagggc aaggccacattgactgcagacacatcctccagcacagccctacatgcagatcagcagcctgacatctgaagactctgcggtctattct gtgcaagatc gggcaactatgtgtaactacgaagggtttgtctact tgggggccaagggaactctgtgctactgtctctgcta	SEQ ID NO: 25
	26E10 heavy chain VH: DNA sequence: CDR1 ggctacacattaccagttacaatatatac	SEQ ID NO: 26
	26E10 heavy chain VH: DNA sequence: CDR2 tatatttctctggagctggtgttactaatacacaatcagaagttcaagggc	SEQ ID NO: 27
	26E10 heavy chain VH: DNA sequence: CDR3 atcggcaactatgtaactacgaagggttgccttac	SEQ ID NO: 28
	26E10 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MEWSWVFLFLLSITTVGVHSGAYLQQSGAELVRSGLVSGASVKMSCKASGYTFTSYNIHMMVKQTPG QGLEWIGYIYPGDGVNTNYNQKFKGKATLTADTSSSTAYMQISLTSED ~~SAV~~ FCARSGNYGN YEGFAWVGQGTI VTVSA	SEQ ID NO: 29

Clone	Sequence	SEQ ID NO.
	26E10 heavy chain VH: Amino acid sequence: FR1 QAYLQQSGAELVRSGASVKMSCKAS	SEQ ID NO: 30
	26E10 heavy chain VH: Amino acid sequence: CDR1 GYTFTSYNIH	SEQ ID NO: 31
	26E10 heavy chain VH: Amino acid sequence: FR2 WVKQTPGGLEWIG	SEQ ID NO: 32
	26E10 heavy chain VH: Amino acid sequence: CDR2 YIYPGDGVTNYNQKFKG	SEQ ID NO: 33
	26E10 heavy chain VH: Amino acid sequence: FR3 KATLTADTSSSTAYMQISLTSSEDSAVYFCAR	SEQ ID NO: 34
	26E10 heavy chain VH: Amino acid sequence: CDR3 SGNYGNIEGFAY	SEQ ID NO: 35
	26E10 heavy chain VH: Amino acid sequence: FR4 WGQGTLLVTVSA	SEQ ID NO: 36
	26E10 light chain VL: DNA sequence: <u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> ttccatgtatgcatctctagagagagagtcactatcactctgcaagggcagtcaggacacactaataagcattttaagcctggtccagca gaaaccagggaatctcctaagaccctgattctatctgcaaacagattggtagatgggtcccatcaaggttcagtgagtgat ctggccaagattattctctcaccatcagcagcctggagatgaagataatggaattattattgctctacagatgtagagtttccgtaca cgttcggaggggggaccacagcctggaaataaac	
	26E10 light chain VL: DNA sequence: CDR1 aaggcgagtcaggacactaataagctatttaagc	SEQ ID NO: 38
	26E10 light chain VL: DNA sequence: CDR2 cgtgcaaacacagattgtagat	SEQ ID NO: 39
	26E10 light chain VL: DNA sequence: CDR3 ctacagtagatgagttccgtacacg	SEQ ID NO: 40
	26E10 light chain VL: Amino acid sequence: <u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> SMYASLGERVTITCKASQDTSYLSWFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGGQDY SLTISSLEYEDMGIYYCLQYDEFPYTFGGGTLKLEIK	SEQ ID NO: 41

Clone	Sequence	SEQ ID NO.
	26E10 light chain VL: Amino acid sequence: FR1 SMYASLGERVTITC	SEQ ID NO: 42
	26E10 light chain VL: Amino acid sequence: CDR1 KASQDTNSYLS	SEQ ID NO: 43
	26E10 light chain VL: Amino acid sequence: FR2 WFQKPGKSPKTLIY	SEQ ID NO: 44
	26E10 light chain VL: Amino acid sequence: CDR2 RANRLVD	SEQ ID NO: 45
	26E10 light chain VL: Amino acid sequence: FR3 GVPSRFSGSGQDYSLTISSEYEDMGIYYC	SEQ ID NO: 46
	26E10 light chain VL: Amino acid sequence: CDR3 LQYDEFPYT	SEQ ID NO: 47
	26E10 light chain VL: Amino acid sequence: FR4 FGGGTKLEIK	SEQ ID NO: 48
	26E2 heavy chain VH: DNA sequence: <u>FR2-CDR2-FR3-CDR3-FR4</u>	SEQ ID NO: 49
	gcgcctgggtaagcagacacccctggacagggccctgggaatggattggatataattatctcctggagatgggtggtactaactgcaatcag aagtccaggc aaggccacattgacitgcagacacatcctccagcacagcctacatgcagatcagcagccitgacatcgaagact ctgcggtctattctgtgcaagat tcggcaactatgtaactacgaagggtttgc ttcttggggccaagggaactctggtcactgtctct gcagc	
	26E2 heavy chain VH: DNA sequence: CDR2 tatattatcctggagatgggtggtactaactgcaatcagaagtccagggc	SEQ ID NO: 50
	26E2 heavy chain VH: DNA sequence: CDR3 tcgggcaactatggtactacgaagggtttgctttc	SEQ ID NO: 51
	26E2 heavy chain VH: Amino acid sequence: FR2-CDR2-FR3-CDR3-FR4	SEQ ID NO: 52
	<u>RWVKQTPGQGLEWIGYYPGDDGNTCNQKFKGKATLTADTSSSTAYMQISLTSED</u>SAVYFC <u>ARSGNYGNYEGFAFWGGTLVT</u>SA	
	26E2 heavy chain VH: Amino acids sequence: FR2 RWVKQTPGQGLEWIG	SEQ ID NO: 53

Clone	Sequence	SEQ ID NO.
	26E2 heavy chain VH: Amino acid sequence: CDR2 YIYPGDGGTNCNQKFQG	SEQ ID NO: 54
	26E2 heavy chain VH: Amino acid sequence: FR3 KATLTADTSSSTAYMQISLTSEDSAVYFCAR	SEQ ID NO: 55
	26E2 heavy chain VH: Amino acid sequence: CDR3 SGNYGNIEGFAF	SEQ ID NO: 56
	26E2 heavy chain VH: Amino acid sequence: FR4 WGQGLTVTSA	SEQ ID NO: 57
	26E2 light chain VL: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> atgagggccctcagtttttggatctgtgctctggtttccagggtatcaaatgacatcaagatgacccagttccatctccatgt atgcatctctagagagagagagtcactatcacttgcaagggcagagtcaggacacactaataagctatttaagctggtccagcagaaaaacc agggaaatctctaaagaccctgatctatctgcaaacagatggtagatgggtcccatcaaggttcagtggtcagtggtggtggtgga agattattctcaccatcagcgcctggagatgaagatgggaattattatgtctacagataatgagtttccgtacacggttcgga ggggggaccacagcggaaataaaacgggctgtagctg	SEQ ID NO: 58
	26E2 light chain VL: DNA sequence: CDR1 aaggcgagtcaggacactaataagctatttaagc	SEQ ID NO: 59
	26E2 light chain VL: DNA sequence: CDR2 cgtgcaaacacagattgtagat	SEQ ID NO: 60
	26E2 light chain VL: DNA sequence: CDR3 ctacagtataatgagtttccgtacacg	SEQ ID NO: 61
	26E2 light chain VL: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MRAPAQFFFGILLWFPGIKCDIKMTQSPSSMYASLGERVTITCKASQDTNSYLSWFFQQKPGKS <u>PKTLIYRANRLVDGVPSRFRFSGSGGQDYSLTISRLEYEDMGIYYCLQYNEFPYTFGGGKLEIK</u> <u>RADA</u>	SEQ ID NO: 62
	26E2 light chain VL: Amino acid sequence: FR1 DIKMTQSPSSMYASLGERVTITC	SEQ ID NO: 63

Clone	Sequence	SEQ ID NO.
	26E2 light chain VL: Amino acid sequence: CDR1 KASQDTNSYLS	SEQ ID NO: 64
	26E2 light chain VL: Amino acid sequence: FR2 WFQKPGKSPKTLIY	SEQ ID NO: 65
	26E2 light chain VL: Amino acid sequence: CDR2 RANRLVD	SEQ ID NO: 66
	Light chain VL: Amino acid sequence: FR3 GVPSRFSGSGGDYSLTISRLEYEDMGIIYC	SEQ ID NO: 67
	26E2 light chain VL: Amino acid sequence: CDR3 LQYNEFPYT	SEQ ID NO: 68
	26E2 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADA	SEQ ID NO: 69
31C4	31C4 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 70
	tgtagggaaattccatggaaatggagctgggttttctctctctgtcaataactacagggtgtccactccaggcttatctatcacgagctctgg ggctgagctgtaggtctggggcctcagtagaatgtctctgcaaggcttctggtctacacatttacagttacacattgacactgggta aagcagacacctggacagggcctggaaatggattggaatatattttcttgagagatgggtggtactaactacaatcagaaggttcaagg gcaaggccacatgtagctgcagacacatctctccagcacagcctacatgcagatcagcagcctgacatctgaagacitctgcggtctattt ctgtgcaagatcgggcacactatggttaactacgaaggggtttgtctactgtgggccaagggaactctgtgtcactgtctctgtctag	
	31C4 heavy chain VH: DNA sequence: CDR1 ggctacacatttaccagttacaatatgcac	SEQ ID NO: 71
	31C4 heavy chain VH: DNA sequence: CDR2 tatatttttctctggagatgggtgtactaactacaatcagaagttcaagggc	SEQ ID NO: 72
	31C4 heavy chain VH: DNA sequence: CDR3 gcaagatcgggcaactatggttaactacgaaggggtttgtctac	SEQ ID NO: 73

Clone	Sequence	SEQ ID NO.
	31C4 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MEWSWFLFLSITTVHSGAYLQQSGAELVRSGASVKMSCKASGYTFTSYNMHWVKQTPG <u>QGLEWIGYIFPGDGGTNYNQKFKGKATLTADTSSSTAYMQISLTSEDSAVYFCARSGNYGN</u> <u>YEGFAYWGQGLTVSA</u>	SEQ ID NO: 74
	31C4 heavy chain VH: Amino acid sequence: FR1 QAYLQQSGAELVRSGASVKMSCKAS	SEQ ID NO: 75
	31C4 heavy chain VH: Amino acid sequence: CDR1 GYTFTSYNMH	SEQ ID NO: 76
	31C4 heavy chain VH: Amino acid sequence: FR2 WVKQTPGQGLEWIG	SEQ ID NO: 77
	31C4 heavy chain VH: Amino acid sequence: CDR2 YIFPGDGGTNYNQKFKG	SEQ ID NO: 78
	31C4 heavy chain VH: Amino acid sequence: FR3 KATLTADTSSSTAYMQISLTSEDSAVYFC	SEQ ID NO: 79
	31C4 heavy chain VH: Amino acid sequence: CDR3 ARSGNYGNYEGFAY	SEQ ID NO: 80
	31C4 heavy chain VH: Amino acid sequence: FR4 WGQGLTVSA	SEQ ID NO: 81
	31C4 light chain VL: DNA sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tactagtgcacatgaggcccccctgctcagtttttgggatctgttgcctgttccagggtatcaaatgtgacatcaagatgacccagtcctcc atcttcacatgatctctctagagagagagtcactatcacttcacacttcacacttcacacttcacacttcacacttcacacttcacacttcacag cagaaaccagggaatctcctaagaccctgatctatc ctgtgcaaacacagattggtagatgggggtcccatcaaggttcagtggtgagtggtg atctgggcaagattatctctaccatcagcagcctggagatgaagatggtggaattattattgt ctacagatgatgaattccgtac acgttcggagggggaccaagctggaaataaaacgggctgatgctgca	
	31C4 light chain VL: DNA sequence: CDR1 aaggcgagtcaggacattaatagctatttaagc	SEQ ID NO: 83

Clone	Sequence	SEQ ID NO.
	31C4 light chain VL: DNA sequence: CDR2 cgtgcaaacagattgtagatg	SEQ ID NO: 84
	31C4 light chain VL: DNA sequence: CDR3 ctacagtatgatgaatttcgtacacg	SEQ ID NO: 85
	31C4 light chain VL: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> LVDMRPPAQFFGILLWFPGIKCDIKMTQSPSSMYASLGERVTITCKASQDINSYLSWFFQQKPG <u>KSPKTLIYRANRLVDGVPSRFRSGSGQDYSLTSSLEYEDMGIYYCLQYDEFPYTFGGGTKL</u> <u>EIKRADAA</u>	SEQ ID NO: 86
	31C4 light chain VL: Amino acid sequence: FR1 DIKMTQSPSSMYASLGERVTITC	SEQ ID NO: 87
	31C4 light chain VL: Amino acid sequence: CDR1 KASQDINSYLS	SEQ ID NO: 88
	31C4 light chain VL: Amino acid sequence: FR2 WFQQKPGKSPKTLIY	SEQ ID NO: 89
	31C4 light chain VL: Amino acid sequence: CDR2 RANRLVD	SEQ ID NO: 90
	31C4 light chain VL: Amino acid sequence: FR3 GVPSRFRSGSGQDYSLTSSLEYEDMGIYYC	SEQ ID NO: 91
	31C4 light chain VL: Amino acid sequence: CDR3 LQYDEFPYT	SEQ ID NO: 92
	31C4 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADAA	SEQ ID NO: 93

Clone	Sequence	SEQ ID NO.
34B10	34B10 heavy chain VH: DNA sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tgggaattcaatggaggtgggttcagctgatttctcttggaacacttttaaatgtatccagtgtaggtgaagctggtgagctctggag gagctcttggtacagcctgggggttctctgagactctctctgcaactctt gattcaccttactattactacatggtggtccgccc agctccaggaaaggcgtgagtggtggt ttttattagaaacaagcctaattgtgtacacaacagagtcacagtcacatctgtgaa gggtc gggttcaccatctccagagataattcccaagcatctcttatcttcaaatgaacacccctgagagctgaggacagtgccacttatt actgtcaaga gattactactccggtagtagcctgactactcggggccaaggcaccactctcacagtcctctca	SEQ ID NO: 94
	34B10 heavy chain VH: DNA sequence: CDR1 ggattcaccttcactgattactacatggc	SEQ ID NO: 95
	34B10 heavy chain VH: DNA sequence: CDR2 tttattagaaacaagctaattgtttacacacagagagtcagtcacatctgtgaagggt	SEQ ID NO: 96
	34B10 heavy chain VH: DNA sequence: CDR3 gattactactcggtagtagcctgactac	SEQ ID NO: 97
	34B10 heavy chain VH: Amino acids sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MELGFSWIFLGTLNIGIQCEVKLVESGGVLVQPGGSLRLSCATSGFTFTDYIMGWVRQPPGK ALEWLG FIRNKANGYTTESASVKGRFTISRDN SQSILYLQMNTLRAEDSATYYCARDYYSGS SLDYWGQGTTLTVSS	SEQ ID NO: 98
	34B10 heavy chain VH: Amino acids sequence: FR1 EVKLVESGGVLVQPGGSLRLSCATS	SEQ ID NO: 99
	34B10 heavy chain VH: Amino acid sequence: CDR1 GFTFTDYIMG	SEQ ID NO: 100
	34B10 heavy chain VH: Amino acid sequence: FR2 WVRQPPGKALEWLG	SEQ ID NO: 101
	34B10 heavy chain VH: Amino acid sequence: CDR2 FIRNKANGYTTESASVKG	SEQ ID NO: 102
	34B10 heavy chain VH: Amino acid sequence: FR3 RFTISRDN	SEQ ID NO: 103

Clone	Sequence	SEQ ID NO.
	34B10 heavy chain VH: Amino acid sequence: CDR3 DYSGSSLDY	SEQ ID NO: 104
	34B10 heavy chain VH: Amino acid sequence: FR4 WQGTTLVSS	SEQ ID NO: 105
	34B10 light chain VL: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tctatactagtcacagaggagcccggtcagattgtgtctcctgtgtctctttttcaaggtaccagatgtatataccagatgacaca gactacatcctcctgtctgtcctctctgtggagacagagtcaccatcagttgc agggaagtcaggacattagcaattattaaat gg tatcagcagaaaccagatggaactgttaaacctcctgatatct tacacatacagattacac tcaggagagtcgccatcaaggtcagtgcc agtggctctggaacagagattatctctcctcattagcaaccctggagcaagaagatattgccacttacttttgc caacaggggttatacgctt ccgtacacg ttcggagggggaccaaagctgaaataaaacgggctgatg	SEQ ID NO: 107
	34B10 light chain VL: DNA sequence: CDR1 agggaagtcaggacattagcaattattaaat	SEQ ID NO: 108
	34B10 light chain VL: DNA sequence: CDR2 tacacatcaagattacacitca	SEQ ID NO: 109
	34B10 light chain VL: DNA sequence: CDR3 caacagggttatagcgttcggtacacg	SEQ ID NO: 110
	34B10 light chain VL: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> SILVDRRTPAQICGLLLFFQGTTRCDIQMTQTTSLSASLGDRVTISCRASQDISNYLWYQQK PDGTVKLLIYYTSRLHSGVPSRFSGSGSGTDYSLISINLEQEDIA TYFCQQGYTLPLYTFGGG GTK LEIKRAD	
	34B10 light chain VL: Amino acid sequence: FR1 DIQMTQTTSLSASLGDRVTISC	SEQ ID NO: 111
	34B10 light chain VL: Amino acid sequence: CDR1 RASQDISNYLN	SEQ ID NO: 112
	34B10 light chain VL: Amino acid sequence: FR2 WYQQKPDGTVKLLIY	SEQ ID NO: 113

Clone	Sequence	SEQ ID NO.
	34B10 light chain VL: Amino acid sequence: CDR2 YTSRLHS	SEQ ID NO: 114
	34B10 light chain VL: Amino acid sequence: FR3 GVPSRFGSGSGTDYSLISNLEQEDVATYFC	SEQ ID NO: 115
	34B10 light chain VL: Amino acid sequence: CDR3 QQGYTLPT	SEQ ID NO: 116
	34B10 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRAD	SEQ ID NO: 117
	37A3 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>FR4</u>	SEQ ID NO: 118
37A3	atgtactgggactgagctgtgtattctgtggccttttgatggtccagtgctcaggtgcagctgttagagaccg9gggaggtgtg aggcctggaaattctctgaaactctcctgtgttacctcg ggattcacttcagtaactaccggaatgcac tggtctgcagcagctccagg gaagaggctggagtgattgci gtaattacagtc aaatc gataatattggaagcaaat ttgcagagtc gtgaaaggc agattc actatttcaagagatgattcaaaaagcagtgctctacctgcagatgaacagattaaagaggaagacacigccacttattt tagtag aggtagtggccagggttgccttacttggggccaagggacitcgtgctactctct	
	37A3 heavy chain VH: DNA sequence: CDR1 ggattcacttcagtaactaccggaatgcac	SEQ ID NO: 119
	37A3 heavy chain VH: DNA sequence: CDR2 gtaattacagtcataatctgataattatggagcaaatgttcagagctctgtgaaaggc	SEQ ID NO: 120
	37A3 heavy chain VH: DNA sequence: CDR3 agtagagtagtgccaggggttgcctac	SEQ ID NO: 121
	37A3 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 122
	MYLGLSCVFLVALLNGVQQ QVQLVETGGGLVRPGNSLKLSCVTS GFTFSNYRMHWLRQPPG KRLEWIAVITVKSDNYGANFAESVKGRFTISRDDSKSSVYLQMNRLREEDTATYYCSRSGSP GFAYWGGTLTVTS	
	37A3 heavy chain VH: Amino acids sequence: FR1 QVQLVETGGGLVRPGNSLKLSCVTS	SEQ ID NO: 123

Clone	Sequence	SEQ ID NO.
	37A3 heavy chain VH: Amino acid sequence: CDR1 GFTFSNYRMH	SEQ ID NO: 124
	37A3 heavy chain VH: Amino acid sequence: FR2 WLRQPPGKRLEWIA	SEQ ID NO: 125
	37A3 heavy chain VH: Amino acid sequence: CDR2 VITVKS DNYGANFAESVKG	SEQ ID NO: 126
	37A3 heavy chain VH: Amino acid sequence: FR3 RFTISRDDSKSSVYLQMNRLREEDTATYYC	SEQ ID NO: 127
	37A3 heavy chain VH: Amino acid sequence: CDR3 SRGSGPGFAY	SEQ ID NO: 128
	37A3 heavy chain VH: Amino acid sequence: FR4 WGQGTLLTVS	SEQ ID NO: 129
	37A3 light chain VL: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 130
	atgggtcctaagatggagtcacagacitcaggctcctcctctgtctgttctgttggtatctgtaccctgtgggacattgtgatcacacagtc tccatccctccctgagtgatgcagcaggagagaaggtcacatgagcgtcgaagtcacagtcagtcgtgttaaacacagtggaatac aagaactacttggcctgtgtaaccagcagaaaccaggcagccctcctaaacitgtgatctacggggcattccacttagggaatctggg gtccctgatcgcttcacagcagtgatctggaaccgatttcactcttaccatcagcagtgagcgtgaagacctggcagtttattact gtcagaatgatcatagttatccattcacgttcggtcgggacaaagtggaaataaaa	SEQ ID NO: 131
	37A3 light chain VL: DNA sequence: CDR1 aagtcagtcagagtcgtttaaacagtggaatacaaaactacttggcc	SEQ ID NO: 132
	37A3 light chain VL: DNA sequence: CDR2 ggggcatccactagggaatct	SEQ ID NO: 133
	37A3 light chain VL: DNA sequence: CDR3 cagaatgatcatagttatccattcacg	

Clone	Sequence	SEQ ID NO.
	37A3 light chain VL: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MGFKMESQTQVLISLLFWVSGTCGGDIVMTQSPSSLSVSAGEKVTMSCKSSQSLLNSGNQKNY LAWYQQKPGQPPLLIYGASTRESGVDPDRFTGSGSGTDFTLTISVQAEDLAVYYCQNDHSY PFTFGSGTKLEIK	SEQ ID NO: 134
	37A3 light chain VL: Amino acid sequence: FR1 DIVMTQSPSSLSVSAGEKVTMSC	SEQ ID NO: 135
	37A3 light chain VL: Amino acid sequence: CDR1 KSSQSLLNSGNQKNYLA	SEQ ID NO: 136
	37A3 light chain VL: Amino acid sequence: FR2 WYQQKPGQPPLLIY	SEQ ID NO: 137
	37A3 light chain VL: Amino acid sequence: CDR2 GASTRES	SEQ ID NO: 138
	37A3 light chain VL: Amino acid sequence: FR3 GVDPDRFTGSGSGTDFTLTISVQAEDLAVYYC	SEQ ID NO: 139
	37A3 light chain VL: Amino acid sequence: CDR3 QNDHSYPFT	SEQ ID NO: 140
	37A3 light chain VL: Amino acid sequence: FR4 FGSGTKLEIK	SEQ ID NO: 141
	12A10 heavy chain VH: DNA sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tgggaattccatggaatgagctgggttttctctctctgtaataactacacaggtgtccactccaggcttatctacagcagctctggg gctgagctgtgaggtctgggcccagtgagatgctctgcaagctcttctggtacacattaccagttacataatgacttggttaa agcagacacctggacagggccctggaatgattggaatatattttcttggagatggtggtactaactacaatcagaagtccaaggg caaggccacattgactgcagacacatctccagcacagctacatgcagcagcctgacatctgaagactctgcggtctatttc tgtgcaagatcgggctactatggttaactacgaaaggtttgtcttacttggggcccaaggagctctggtcacgtctctgcag	SEQ ID NO: 142
	12A10 heavy chain VH: DNA sequence: CDR1 ggctacacatttaccagttacaatatgcac	SEQ ID NO: 143

Clone	Sequence	SEQ ID NO.
	12A10 heavy chain VH: DNA sequence: CDR2 tatattttcctgagatggtgtactactacaatcagaagtcaagggc	SEQ ID NO: 144
	12A10 heavy chain VH: DNA sequence: CDR3 gcaagatcgggctactatgtactacgaagggttgcttac	SEQ ID NO: 145
	12A10 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MEWSWVFLFLSITTTGVHSQAYLQQSGAELVRSGASVKMSCKASGYTFTSYNMHWVKQTPG <u>QGLEWIG YIFPGDGGTNYNQKFKGKATLTADTSSSTAYMQISLTSEDSAVYFCARSGYYGN</u> <u>YEGFAYWGQGLTVSA</u>	SEQ ID NO: 146
	12A10 heavy chain VH: Amino acids sequence: FR1 QAYLQQSGAELVRSGASVKMSCKAS	SEQ ID NO: 147
	12A10 heavy chain VH: Amino acid sequence: CDR1 GYTFTSYNMH	SEQ ID NO: 148
	12A10 heavy chain VH: Amino acid sequence: FR2 WVKQTPGQGLEWIG	SEQ ID NO: 149
	12A10 heavy chain VH: Amino acid sequence: CDR2 YIFPGDGGTNYNQKFKG	SEQ ID NO: 150
	12A10 heavy chain VH: Amino acid sequence: FR3 KATLTADTSSSTAYMQISLTSEDSAVYFC	SEQ ID NO: 151
	12A10 heavy chain VH: Amino acid sequence: CDR3 ARSGYYGNYEGFAY	SEQ ID NO: 152
	12A10 heavy chain VH: Amino acid sequence: FR4 WGQGLTVSA	SEQ ID NO: 153

Clone	Sequence	SEQ ID NO.
	12A10 light chain VL: DNA sequence: <u>FR1</u>–<u>CDR1</u>–<u>FR2</u>–<u>CDR2</u>–<u>FR3</u>–<u>CDR3</u>–<u>FR4</u>	SEQ ID NO: 154
	cttcacatgatcatctctaggagagagagatcactatcacttgcaagggcagtcaggacattaatagctatttaagctggtccagca gaaaccagggaatctctaagaccctgatatctatcgtgcaaacagattggtagatgagggtcccatc-aaggttcagtggcagtgga ctggcaagattattctcaccatcagcagcctggaatatgaagatatgggaatttattattgtctacattatgctgaggttcctgacac gttcgaggggggaccacagctggaaataaaacgggctg	
	12A10 light chain VL: DNA sequence: CDR1	SEQ ID NO: 155
	aagcgagtcaggacattaatagctatttaagc	
	12A10 light chain VL: DNA sequence: CDR2	SEQ ID NO: 156
	cgtgcaaacacagattgtagat	
	12A10 light chain VL: DNA sequence: CDR3	SEQ ID NO: 157
	ctacattatgctgagttccgtacacg	
	12A10 light chain VL: Amino acid sequence: <u>FR1</u>–<u>CDR1</u>–<u>FR2</u>–<u>CDR2</u>–<u>FR3</u>–<u>CDR3</u>–<u>FR4</u>	SEQ ID NO: 158
	<u>SMYASLGERVTITCKASQDINSYLSWFQQKPGKSPKTLIYRANRLVDGVPSRFSGSGSGGQDY</u> <u>SLTISSLEYEDMGIYYCLHYAEFPYTFGGGTLKLEIKRA</u>	
	12A10 light chain VL: Amino acid sequence: FR1	SEQ ID NO: 159
	SMYASLGERVTITC	
	12A10 light chain VL: Amino acid sequence: CDR1	SEQ ID NO: 160
	KASQDINSYLS	
	12A10 light chain VL: Amino acid sequence: FR2	SEQ ID NO: 161
	WFQQKPGKSPKTLIY	
	12A10 light chain VL: Amino acid sequence: CDR2	SEQ ID NO: 162
	RANRLVD	
	12A10 light chain VL: Amino acid sequence: FR3	SEQ ID NO: 163
	GVPSRFSGSGGQDYSLTISSLEYEDMGIYYC	
	12A10 light chain VL: Amino acid sequence: CDR3	SEQ ID NO: 164
	IHYAEFPYT	

Clone	Sequence	SEQ ID NO.
	12A10 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRA	SEQ ID NO: 165
3B7	3B7 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tactagtgcacatgggagcgctgatactgtcttctctggtagcaacagctacaggtgtgcactcccaggctccagctgcagcagctgtg ggcctgaggtgtgagcctggggtcctcagtgaaagattctctgcaaggttcc ggctacacattcagtgattatactatgcac tgggt gaagcagatcgtcaaaagctagatgtgattgga gttattagctactgacaatgtgtaatacaaacataaccagaagtttaag ggc aagggcccaatgactgtagacaaactctccagcactgcctatatgtgaactggcagattgacatctgaggattctgccatctatta ctgt gc aag ggaggccgggactacggtagctatctctgttggactact tgggggtcaaggaaacctcagtcacccgtctctcag 3B7 heavy chain VH: DNA sequence: CDR1 ggctacacattcagttattactatgcac 3B7 heavy chain VH: DNA sequence: CDR2 gttattagctacgaatggttaatacaaaactataaccagaagttaagggc 3B7 heavy chain VH: DNA sequence: CDR3 gcaaggaggccgggactacggtagctatctatgtcttggactac 3B7 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MGWSCIMFFLVATATGVHSHQVQLQQSGPEVVRPGVSVKISKCKSGYTFSDYTMHWVKQSHA K SL E W I G V I S T D N G N T N Y N Q K F G K A T M T V D K S S T A Y M E L A R L T S E D S A I Y C A R E A R D Y G S I Y A L D Y W G Q T S V T S Q 3B7 heavy chain VH: Amino acids sequence: FR1 QVQLQQSGPEVVRPGVSVKISKCKGS 3B7 heavy chain VH: Amino acid sequence: CDR1 GYTFSDYTMH 3B7 heavy chain VH: Amino acid sequence: FR2 WVKQSHAKSLEWIG 3B7 heavy chain VH: Amino acid sequence: CDR2 VISTDNGNTNYNQKFKG	SEQ ID NO: 166
	3B7 heavy chain VH: DNA sequence: CDR1 ggctacacattcagttattactatgcac	SEQ ID NO: 167
	3B7 heavy chain VH: DNA sequence: CDR2 gttattagctacgaatggttaatacaaaactataaccagaagttaagggc	SEQ ID NO: 168
	3B7 heavy chain VH: DNA sequence: CDR3 gcaaggaggccgggactacggtagctatctatgtcttggactac	SEQ ID NO: 169
	3B7 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 170
	MGWSCIMFFLVATATGVHSHQVQLQQSGPEVVRPGVSVKISKCKSGYTFSDYTMHWVKQSHA K SL E W I G V I S T D N G N T N Y N Q K F G K A T M T V D K S S T A Y M E L A R L T S E D S A I Y C A R E A R D Y G S I Y A L D Y W G Q T S V T S Q	SEQ ID NO: 171
	3B7 heavy chain VH: Amino acids sequence: FR1 QVQLQQSGPEVVRPGVSVKISKCKGS	SEQ ID NO: 172
	3B7 heavy chain VH: Amino acid sequence: CDR1 GYTFSDYTMH	SEQ ID NO: 173
	3B7 heavy chain VH: Amino acid sequence: FR2 WVKQSHAKSLEWIG	SEQ ID NO: 174

Clone	Sequence	SEQ ID NO.
	3B7 heavy chain VH: Amino acid sequence: FR3 KATMTVDKSSSTAYMELARLTSEDSAIYYC	SEQ ID NO: 175
	3B7 heavy chain VH: Amino acid sequence: CDR3 AREARDYGSYALDY	SEQ ID NO: 176
	3B7 heavy chain VH: Amino acid sequence: FR4 WGQGTSTVTS	SEQ ID NO: 177
	3B7 light chain VL: DNA sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> tattactagtcacatggtcttattgttgctgctgctatggtccagatgacatccagatgactcagtcctccctatc tgcattctgtggagaaactgtcaccatcatgtc <u>gagcaagtggaataattcac</u> aattatttagcatgtatcagcagaaacaggg aaaatctctcagctcctggtctata <u>aatgcaaaaaaccccttagcagat</u> gtggtgcccacatcaagggttcagtggtgagatcaggaacaca atattctcaagatcaacaacctgcagccaggagattttgggaattattactgt <u>caacattttggagtagtaccctg</u> ggacgtggtg aggcaccacagctggaaatcaaacgggctgatgctgca	SEQ ID NO: 178
	3B7 light chain VL: DNA sequence: CDR1 cgagcaagtggaatttcacaattat	SEQ ID NO: 179
	3B7 light chain VL: DNA sequence: CDR2 aatgcaaaaacccttagcagat	SEQ ID NO: 180
	3B7 light chain VL: DNA sequence: CDR3 caacattttggagtactcctgggacg	SEQ ID NO: 181
	3B7 light chain VL: Amino acid sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> MVLMLLLWLTGARC <u>DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQKSPQLL</u> <u>VYNAKTLADGVPSRFSGSGSGTQYSLKINNLQPEDFGNYCQHFWS</u> TPWTFGGG <u>TKLEIKRA</u> <u>DAA</u>	SEQ ID NO: 182
	3B7 light chain VL: Amino acid sequence: FR1 DIQMTQSPASLSASVGETVTITC	SEQ ID NO: 183
	3B7 light chain VL: Amino acid sequence: CDR1 RASGNIHNY	SEQ ID NO: 184

Clone	Sequence	SEQ ID NO.
11G8	3B7 light chain VL: Amino acid sequence: FR2 LAWYQQKQKSPQLLVY	SEQ ID NO: 185
	3B7 light chain VL: Amino acid sequence: CDR2 NAKTLAD	SEQ ID NO: 186
	3B7 light chain VL: Amino acid sequence: FR3 GVPSRFGSGSGTQYSLKINLQPEDFGNYVC	SEQ ID NO: 187
	3B7 light chain VL: Amino acid sequence: CDR3 QHEWSTPWT	SEQ ID NO: 188
	3B7 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADAA	SEQ ID NO: 189
	11G8 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 190
	tactagtgaatgggatggagctgtatcatgtcttcttggtgagtacagctacaggtgtgcactccaggctccagctgcagcagctctggg cctgacctgtgagccctgggtctcagtgaaagtctctgcaaggttccc ggctacacattcactgattatgctatgcactg gggttaa agcagagtcagcaaaagagctgagtgattggag gttattagctgactctgggtactacaaacacagagaagttta aggg caaggccaatgactgtagacaatactccagctacagcctatattggaccttgccagattgacatctgaggattctgccatctattactgt gcaagagacagctcgtactacgtgcgatttcttact ctggggccaaggaaactctggtcacgtctctgcag	SEQ ID NO: 191
	11G8 heavy chain VH: DNA sequence: CDR1 ggctacacattcactgattatgctatgcac	SEQ ID NO: 192
	11G8 heavy chain VH: DNA sequence: CDR2 gttattagctgactcgtgtactacaaactacaaaccagaagttt	SEQ ID NO: 193
	11G8 heavy chain VH: DNA sequence: CDR3 gcaagagacagctgctactacgtgcgatttcttac	SEQ ID NO: 194
	11G8 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	
	MGWSCIMFFLVATATGVHSHV QVQLQQSGPDLVRPGVSVKISCKGSGYTF TDYAMHWNVKQ SHA KSLEWIGVIS TDSGTTN YNQKFKGKATMTVDKSSSTAYMDLARLTSEDS AIY CCARDSSYYVR FSYWGGQGLVT VS A	

Clone	Sequence	SEQ ID NO.
	11G8 heavy chain VH: Amino acids sequence: FR1 QVQLQQSGPDLVRPGSVKISKGS	SEQ ID NO: 195
	11G8 heavy chain VH: Amino acid sequence: CDR1 GYFTDYAMH	SEQ ID NO: 196
	11G8 heavy chain VH: Amino acid sequence: FR2 WVKQSHAKSLEWIG	SEQ ID NO: 197
	11G8 heavy chain VH: Amino acid sequence: CDR2 VISTDSGTTNYNQKF	SEQ ID NO: 198
	11G8 heavy chain VH: Amino acid sequence: FR3 KGKATMTVDKSSSTAYMDLRLTSEDSAIYYC	SEQ ID NO: 199
	11G8 heavy chain VH: Amino acid sequence: CDR3 ARDSSYYVRFYSY	SEQ ID NO: 200
	11G8 heavy chain VH: Amino acid sequence: FR4 WGQGTLTVSA	SEQ ID NO: 201
	11G8 light chain VL: DNA sequence: Leader sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4	SEQ ID NO: 202
	tactagttgatattggtcctaagatggagtcacagaccaggctcttcgtattctactctgtgtgtctgtgtgtctcatgggagattgtgat gaccagactcccaaatctcgtgtttcagtaggagacagggttaccataaacctgt aaggccagtcagagtgtagtaatgatgt agcttggtaccacaagaagccaggcagctctctaaactgtaata ctatgcatccaatcgcacac ctgtagtcctgatcgcttc actggcagtggtataggacggattcacttccaccatcagcacctgtaggcgaagaccctggcagtttattctctgcagcaggattata gtttctcgtggagcgttcggtggagccaccagctggaaatcaaacgggctgatctgca	
	11G8 light chain VL: DNA sequence: CDR1 aaggccagtcagagtgtgagtaatgat	SEQ ID NO: 203
	11G8 light chain VL: DNA sequence: CDR2 tatgcatccaatcgctacact	SEQ ID NO: 204
	11G8 light chain VL: DNA sequence: CDR3 agttctccgtggacg	SEQ ID NO: 205

Clone	Sequence	SEQ ID NO.
	11G8 light chain VL: Amino acid sequence: Leader sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3</u> - <u>FR4</u> MESQTQVFVFLLCVSGAHG <u>SIVMTQTPKFL</u> LVSGDRVITTC <u>KASQSVSND</u> VAWYQQKPGQ <u>SPKLLIY</u> <u>YASNRYT</u> <u>GVDPDRFTGSGYGTDF</u> FTISTVQAEDLAVYFCQQDYSSPWTFGGG <u>TKLEIKRADAA</u>	SEQ ID NO: 206
	11G8 light chain VL: Amino acid sequence: FR1 SIVMTQTPKFLLVSGDRVITTC	SEQ ID NO: 207
	11G8 light chain VL: Amino acid sequence: CDR1 KASQSVSND	SEQ ID NO: 208
	11G8 light chain VL: Amino acid sequence: FR2 VAWYQQKPGQSPKLLIY	SEQ ID NO: 209
	11G8 light chain VL: Amino acid sequence: CDR2 YASNRYT	SEQ ID NO: 210
	11G8 light chain VL: Amino acid sequence: FR3 GVDPDRFTGSGYGTDFFTISTVQAEDLAVYFC	SEQ ID NO: 211
	11G8 light chain VL: Amino acid sequence: CDR3 QQDYSSPWT	SEQ ID NO: 212
	11G8 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADAA	SEQ ID NO: 213
	14F8 heavy chain VH: DNA sequence: Leader sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3</u> - <u>FR4</u> tacttgcacatgggatggagctgtatcatgttcttcttgtagcaacagctacaggtgtgtgcactcccaggtccagctgcagcagctctgg gcctgaggtggtaggcctgggtctcagtagaagatttcctgcaaggttccggctacacattcactgattatatactatgcacttgggtg aagcagagtcattgcaaaagagictagagtggttgga <u>gttattagttacttaaatggtaata</u> taca <u>aactaca</u> aaccagagacttggagg gcaaggccacaatgactgtagacaaatccctccagcacagccctataggaaactgtccagattgacatctgaggattctgccaatcttattac tgt <u>gcaagagagagagggggggggtgtgttactacagtgctgtgggactact</u> tggtggggtcaagggaacctcagtcacgcgtctctcag	SEQ ID NO: 214

Clone	Sequence	SEQ ID NO.
	14F8 heavy chain VH: DNA sequence: CDR1 ggctacacattcactgattatactatgcac	SEQ ID NO: 215
	14F8 heavy chain VH: DNA sequence: CDR2 gttatgtactactacaatgtaatacaactacaaccagaaacttggaggc	SEQ ID NO: 216
	14F8 heavy chain VH: DNA sequence: CDR3 gcaagagagagggggggatggttactacagtgctgtggactac	SEQ ID NO: 217
	14F8 heavy chain VH: Amino acid sequence: Leader sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 MGWSCIMFFLVATATGVHSSQVQLQQSGPEVVRPGVSVKISCKGSGYTFTDYTMHWVKQSHA <u>KSLEWIGVISTYNGNTNYNQNFEGKATMTVDKSSSTAYMELARLTSED</u> SAIYYC <u>ARERGGDG</u> <u>YYS</u> AVD <u>YWGQ</u> TSVTVSQ	SEQ ID NO: 218
	14F8 heavy chain VH: Amino acids sequence: FR1 QVQLQQSGPEVVRPGVSVKISCKGS	SEQ ID NO: 219
	14F8 heavy chain VH: Amino acid sequence: CDR1 GYTFTDYTMH	SEQ ID NO: 220
	14F8 heavy chain VH: Amino acid sequence: FR2 WVKQSHAKSLEWIG	SEQ ID NO: 221
	14F8 heavy chain VH: Amino acid sequence: CDR2 VISTYNGNTNYNQNFEG	SEQ ID NO: 222
	14F8 heavy chain VH: Amino acid sequence: FR3 KATMTVDKSSSTAYMELARLTSED	SEQ ID NO: 223
	14F8 heavy chain VH: Amino acid sequence: CDR3 ARERGGDGYYSVDY	SEQ ID NO: 224
	14F8 heavy chain VH: Amino acid sequence: FR4 WGQGTSTVTVS	SEQ ID NO: 225

Clone	Sequence	SEQ ID NO.
	14F8 light chain VL: DNA sequence: <u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> ccaaattctgttatacagcaggagacaggggtaccataacctgcaagggccagtcagagtggtgattaatgatgtagcttggtacc aacagaagccaggcagttctctaaactgctgatatatactatgcatccaatcgtacacactggagtcctctgacgcttcaactggtgacgtg gatatggacggatttccatccatcagcactgtgcaggctgaagacctggcagttatttctgctcagcaggattatagctctcgt acacgttcggaggaggaccagctggaaataaaacgggctgctgctgc	SEQ ID NO: 226
	14F8 light chain VL: DNA sequence: CDR1 aaggccagtcagagtggtgattaatgat	SEQ ID NO: 227
	14F8 light chain VL: DNA sequence: CDR2 tatgcatccaatcgtctacact	SEQ ID NO: 228
	14F8 light chain VL: DNA sequence: CDR3 cagcaggattatagctctccgtacacg	SEQ ID NO: 229
	14F8 light chain VL: Amino acid sequence: <u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> KFLLVSAGDRVTITCKASQSVINDVAWYQQKPGQSPKLLIYYASNRYTGVDPDRFTGSGYGTDF TFTISTVQAEDLAVYFCQQDYSSPYTFGGGTKLEIKRADA	SEQ ID NO: 230
	14F8 light chain VL: Amino acid sequence: FR1 KFLLVSAGDRVTITC	SEQ ID NO: 231
	14F8 light chain VL: Amino acid sequence: CDR1 KASQSVIND	SEQ ID NO: 232
	14F8 light chain VL: Amino acid sequence: FR2 VAWYQQKPGQSPKLLIY	SEQ ID NO: 233
	14F8 light chain VL: Amino acid sequence: CDR2 YASNRYT	SEQ ID NO: 234
	14F8 light chain VL: Amino acid sequence: FR3 GVDPDRFTGSGYGTDFITFTISTVQAEDLAVYFC	SEQ ID NO: 235
	14F8 light chain VL: Amino acid sequence: CDR3 QQDYSSPYT	SEQ ID NO: 236
	14F8 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADA	SEQ ID NO: 237

Clone	Sequence	SEQ ID NO.
15D2	15D2 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tggggaattcattgagttgggttcagcttcttctgcttcttctttaaagggtgtccagtgtaagtgatgctggtggagtcctggggga ggcttagtaagccctggagggtccctgaaactctctctgtgcagcctctggattcaccttcagtaactatgccatgtctctgtgggttgccca gactccggagaagaggtgagtggtgcgaaccctctcttagtgggtgtaattacaccctactatccagacagctgtgaaggggc gattcaccatctccagagacaatgccaaagagcaccctgtaccctgcaaatgagcagctcgtgaggtctgaggacacggcccatgtattactg tgtaatcccccaaggtagtagtctttgactattggggccaaggcaccactctcacagtcctcag 15D2 heavy chain VH: DNA sequence: CDR1 ggattcaccttcagtaactatgccatgct 15D2 heavy chain VH: DNA sequence: CDR2 acctctcttagtgggtgtaattacaccctactatccagacagtgtaagggg 15D2 heavy chain VH: DNA sequence: CDR3 gtaatcccccaaggtagtagtcttcttgactat 15D2 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MELGFSLIFLVVLKGVQCEVMLVESGGGLVKPGGSLKLSCAASGFTFSNYAMSWVRQTPEK <u>RLEWVATSLSGGNYYTPDSVKGRFTISRDN</u>AKSTLYLQMSSLRSEDTAMYYC<u>VIPQGS</u>SPF <u>DYWGQG</u>TTLTVS 15D2 heavy chain VH: Amino acids sequence: FR1 EVMLVESGGGLVKPGGSLKLSCAAS 15D2 heavy chain VH: Amino acid sequence: CDR1 GFTFSNYAMS 15D2 heavy chain VH: Amino acid sequence: FR2 WVRQTPEKRLWWA 15D2 heavy chain VH: Amino acid sequence: CDR2 TSLSGGNYYTPDSVKG 15D2 heavy chain VH: Amino acid sequence: FR3 RFTISRDN	SEQ ID NO: 238 SEQ ID NO: 239 SEQ ID NO: 240 SEQ ID NO: 241 SEQ ID NO: 242 SEQ ID NO: 243 SEQ ID NO: 244 SEQ ID NO: 245 SEQ ID NO: 246 SEQ ID NO: 247

Clone	Sequence	SEQ ID NO.
15D2	heavy chain VH: Amino acid sequence: CDR3 VIPQGSSPFYD	SEQ ID NO: 248
	heavy chain VH: Amino acid sequence: FR4 WGQGTTTLTVS	SEQ ID NO: 249
	light chain VL: DNA sequence: Leader sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3</u> - <u>FR4</u> tactagtcacatggccttcaagatggagtcacagattcaggcttttggtatttttactctctgtgtgtgtggtcattggtgagtagtattgtgatg accagactcccaaatccctattgttcagtaggagacagggttaccataacctgtaaggccagtcagagtgtagaaataatgatgta gcatgtaccacaagaagccaggcagtcctgtgtaaatgttaatatattatgcatgcaatcgtctacacgggagtccttgatcgcttc actgcagtggaatgtgacggatttcactttccaccatccaccactgtgcaggctgaagacctggcagtttactttttgtcagcaggatcata gttatccgtggacgttcggtgctgggaccacagctggagctgaaacgggctgatgctg	SEQ ID NO: 251
	light chain VL: DNA sequence: CDR1 aagccagtcagagtgtaaaaaatgatgtagca	SEQ ID NO: 252
	light chain VL: DNA sequence: CDR2 tatgcatgcaatgcgtacacg	SEQ ID NO: 253
	light chain VL: DNA sequence: CDR3 cagcaggatcatgattatcgcgtgacg	SEQ ID NO: 254
	light chain VL: Amino acid sequence: Leader sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3</u> - <u>FR4</u> MGFKMESQIQVLVFLLLCVCGGHGSIVMTQTTPKFPIVSVGDRVTTITC.KASQSVKNDVVAWYQQK <u>PGQSGKMLIYACNRYTGVLDRFTVSGYVTDFTFTTTVQAEDLAVVFCQQDHSYPWTFGAG</u> <u>TKLELK</u>	
	light chain VL: Amino acid sequence: FR1 SIVMTQTTPKFPIVSVGDRVTTIC	SEQ ID NO: 255
	light chain VL: Amino acid sequence: CDR1 KASQSVKNDVA	SEQ ID NO: 256
	light chain VL: Amino acid sequence: FR2 WYQQKPGQSGKMLIY	SEQ ID NO: 257

Clone	Sequence	SEQ ID NO.
	15D2 light chain VL: Amino acid sequence: CDR2 YACNRYT	SEQ ID NO: 258
	15D2 light chain VL: Amino acid sequence: FR3 GVLDRTVSGYVTDFTFTTTVQAEDLAVYFC	SEQ ID NO: 259
	15D2 light chain VL: Amino acid sequence: CDR3 QQDHSYPWT	SEQ ID NO: 260
	15D2 light chain VL: Amino acid sequence: FR4 FGAGTKLELK	SEQ ID NO: 261
	29H7 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tattactagtcgcatgggatgagctgtatcatgttcttctggtagcaacagctacaggtgtgcactcccaggtccagctgcagcagtc tggccctgaggtgtgaggcctgggtctcagtgagatttctctgcaaggttcc ggctacacattcactgtattatgtatgcactgg gtgaagcagagtcagtgaaagagctagatggattgg gttattagtacttacaatggttaataacaactacaaccagaaagttaa agggcaaggcccaatgactgtagacaaatcctccagcacagcctataggaaactgcccagattgacatctgaggattctgccaatcta ttactgt gcaagagagaggggggggtgtgttactacagtgctatggactact tggggtcaaggaaacdcagtcaccgtctctctc ag	SEQ ID NO: 262
29H47	29H7 heavy chain VH: DNA sequence: CDR1 ggctacacattcactgtattgtatgcac	SEQ ID NO: 263
	29H7 heavy chain VH: DNA sequence: CDR2 gttattagtactacaatggttaatacaactacaaccagaagttaagggc	SEQ ID NO: 264
	29H7 heavy chain VH: DNA sequence: CDR3 gcaagagagaggggggggtgtgttactacagtgctatggactac	SEQ ID NO: 265
	29H7 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> MGWSCIMFFLVATATGVHSGVQLQQSGPEVVRPGVSVKISKCKSGGYTFTDYVMHWVKQSHG KSLEWIGVISTYNGNTNYNQKFKGKATMTVDKSSSTAYMELARLTSEDSAIYYCARERGGDG YYSAMDYWGQGTSTVTVSS	SEQ ID NO: 266

Clone	Sequence	SEQ ID NO.
	29H7 heavy chain VH: Amino acids sequence: FR1 QVQLQQSGPEVVRPGVSVKISKGS	SEQ ID NO: 267
	29H7 heavy chain VH: Amino acid sequence: CDR1 GYFTDYVMH	SEQ ID NO: 268
	29H7 heavy chain VH: Amino acid sequence: FR2 WVKQSHGKSLEWIG	SEQ ID NO: 269
	29H7 heavy chain VH: Amino acid sequence: CDR2 VISTYNGNTNYNQKFKG	SEQ ID NO: 270
	29H7 heavy chain VH: Amino acid sequence: FR3 KATMTVDKSSSTAYMELARLTSEDSAIYYC	SEQ ID NO: 271
	29H7 heavy chain VH: Amino acid sequence: CDR3 ARERGGDGYYSAMDY	SEQ ID NO: 272
	29H7 heavy chain VH: Amino acid sequence: FR4 WGQGTSTVTS	SEQ ID NO: 273
	29H7 light chain VL: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 274
	acaggagccgggtgttgatttctactctgtgtgtctgtgtcgtatgtgagtgatgacccagagactcccaaatctctgttttc agcaggagacagggttaccatagcctgc caaggccagtcagagtgtgattataa tgtagcttgtagtaccacaagaagccagggca gtctctgaactgcgtatata tatgcattc caatgcgtctacact ggagtcctgctgacgtctcactgcgcagtgatggacggatttcac tttaccatcaccacgtgcaggcgaagaccgtggcagtttatttc gtcagcaggattatagctctccgtacacg ttcggagggggg accaagctggaaataaaacgggctgctgca	
	29H7 light chain VL: DNA sequence: CDR1 aaggccagtcagagtgtgattaataat	SEQ ID NO: 275
	29H7 light chain VL: DNA sequence: CDR2 tatgcaccaatcgtctacact	SEQ ID NO: 276
	29H7 light chain VL: DNA sequence: CDR3 cagcaggattatagctctccgtacacg	SEQ ID NO: 277

Clone	Sequence	SEQ ID NO.
	29H7 light chain VL: Amino acid sequence: Leader sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3-FR4</u>	SEQ ID NO: 278
	RSRVLVFLLLCVSGAHGSIVMTQTTPKFLLSAGDRVTIACKASQSVINWAWYQQKPGQSPEL <u>LIYYASNRYTGVPDRFTGSGYGTDFTTITTVQAEDLAVYFCQQDYSSPYTFGGGTGLEIKRAD</u> <u>AA</u>	
	29H7 light chain VL: Amino acid sequence: FR1 SIVMTQTPKFLLSAGDRVTIAC	SEQ ID NO: 279
	29H7 light chain VL: Amino acid sequence: CDR1 KASQSVINN	SEQ ID NO: 280
	29H7 light chain VL: Amino acid sequence: FR2 VAWYQQKPGQSPPELLY	SEQ ID NO: 281
	29H7 light chain VL: Amino acid sequence: CDR2 YASNRYT	SEQ ID NO: 282
	29H7 light chain VL: Amino acid sequence: FR3 GVDPRTGSGYGTDFTTITTVQAEDLAVYFC	SEQ ID NO: 283
	29H7 light chain VL: Amino acid sequence: CDR3 QQDYSSPYT	SEQ ID NO: 284
	29H7 light chain VL: Amino acid sequence: FR4 FGGGTKLEIKRADAA	SEQ ID NO: 285
30D10	30D10 heavy chain VH: DNA sequence- <u>FR1</u> - <u>CDR1</u> - <u>FR2</u> - <u>CDR2</u> - <u>FR3</u> - <u>CDR3-FR4</u> tggggaattccaggaaatgagctgggttttcttctcctgatgccagtgggtacagggggtcaattcacaggttcagcagtcagcagtcgtggg gctgagcttgtaggccaggcccttagtcaagttgctgcgaagctctt ggcttc-aactttaagac-tacttatgacctgactggtgaa gcagaggccctgaacaggccctggagtgattggaatg attgatactcgtaaaatgtaatactatatataaaccgaa gttcagg caggccag tataaacagcagacacatctccaacacagccctaccctgcagctcagcagcctgacatctgaggacactgcogtctatta ctgt gcta gaggggggtaggtcactggtacttcgatgtctg ggggcgccagggaccacgggtcacccgtctctcag	SEQ ID NO: 286

Clone	Sequence	SEQ ID NO.
	30D10 heavy chain VH: DNA sequence: CDR1 ggctcaacttaagactacttattgacac	SEQ ID NO: 287
	30D10 heavy chain VH: DNA sequence: CDR2 attgatcctgaaaatgtaatactatatatgaacgaagtccagggc	SEQ ID NO: 288
	30D10 heavy chain VH: DNA sequence: CDR3 gctagagggggtaggtcactgtacttcgatgac	SEQ ID NO: 289
	30D10 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4</u> GEFQEWSWWFLFLMAVVTGVNSEVQLQQSGAELVRPGALVKLSCKASGFNFKDYFMHWWVK <u>QRPEQGLEWIGWIDPENGTIYEKPKFQGGKASITADTSSNTAYLQLSSLTSED</u> <u>TAVYYCARGGV</u> <u>GHWYFDWVGAGTTTVS</u>	SEQ ID NO: 290
	30D10 heavy chain VH: Amino acids sequence: FR1 EVQLQQSGAELVRPGALVKLSCKAS	SEQ ID NO: 291
	30D10 heavy chain VH: Amino acid sequence: CDR1 GFNFKDYFMH	SEQ ID NO: 292
	30D10 heavy chain VH: Amino acid sequence: FR2 WVKQRPEQGLEWIGW	SEQ ID NO: 293
	30D10 heavy chain VH: Amino acid sequence: CDR2 IDPENGTIYEKPKFQG	SEQ ID NO: 294
	30D10 heavy chain VH: Amino acid sequence: FR3 KASITADTSSNTAYLQLSSLTSED	SEQ ID NO: 295
	30D10 heavy chain VH: Amino acid sequence: CDR3 ARGGVGHWFYFDV	SEQ ID NO: 296
	30D10 heavy chain VH: Amino acid sequence: FR4 WGAGTTTVTS	SEQ ID NO: 297

Clone	Sequence	SEQ ID NO.
	30D10 light chain VL: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> tgggaattcatgagacagacacactcgtctatgggtgctgctgtctgttgggtccaggctccactgtgacattgtgctgacccaatctc cagctctttggctgtctctagggcagaggccacatctcttgc aaggccagccaaagtgtgattatggtgtagtata tg aactgtaccacagaaacagagacagccaccccaaacctcctcttatt gttgcattc caaatc taaaatc tgggatccagccaggttt agtgcaagtgggtgggacagacttccctcaacatccatcctctgtggaggaggaggtgtgcaacctattactgt tcagc caaa act aatgaggatccgtggacgttc gtggaggccaccaagctggaatacaaacgggctgctgca	SEQ ID NO: 298
	30D10 light chain VL: DNA sequence: CDR1 aaggccagccaaagtgtgattatggtgtagttat	SEQ ID NO: 299
	30D10 light chain VL: DNA sequence: CDR2 gttgcataatctaaatct	SEQ ID NO: 300
	30D10 light chain VL: DNA sequence: CDR3 cagcaaaactaatgaggatccgtggacg	SEQ ID NO: 301
	30D10 light chain VL: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u> METDTLLWVLLWVPGSTGDIVLTQSPASLAVSLGQRATISCKASQSVVDYDGDSYMNNWYQQ KPGQPPKLLIYVASNLKSGIPARFSGSGCGTDFTLNIHPVEEEDGATYYCQQTNE D P W T F G G G T K L E I K	SEQ ID NO: 302
	30D10 light chain VL: Amino acid sequence: FR1 DIVLTQSPASLAVSLGQRATISC	SEQ ID NO: 303
	30D10 light chain VL: Amino acid sequence: CDR1 KASQSVDDYDGSY	SEQ ID NO: 304
	30D10 light chain VL: Amino acid sequence: FR2 MNNWYQQKPGQPPKLLIY	SEQ ID NO: 305
	30D10 light chain VL: Amino acid sequence: CDR2 VASNLKS	SEQ ID NO: 306
	30D10 light chain VL: Amino acid sequence: FR3 GIPARFSGSGCGTDFTLNIHPVEEEDGATYYC	SEQ ID NO: 307

Clone	Sequence	SEQ ID NO.
51C3	3D10 light chain VL: Amino acid sequence: CDR3 QQTNEPDWT	SEQ ID NO: 308
	3D10 light chain VL: Amino acid sequence: FR4 FGGGTKLEIK	SEQ ID NO: 309
	51C3 heavy chain VH: DNA sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	SEQ ID NO: 310
	tgggaattcaggaaatggagctgggttttctctctcctcaggaactgcagggtgctctctgaggtccagctgcaacagctctggacc tgagctggtaagccctgggttcagtgaaagatatctcgaagacttctggatacacattcactgaatacatcatgcactctgggtgaa acagagccatggaaagagccttgagtgattggaaggtataatccttaataatgggtggtactaacatacaaccagaagtttaaggg caaggccacatgactgtagacacgtctcctcagcatagcctacatggaactccgcagcctgacatcgaagattctgcagctctatttg tgcaagagacgatggttactactacgtaagttcgtcttacttggggccaaggacgtctggtcactgctctgcag	SEQ ID NO: 311
	51C3 heavy chain VH: DNA sequence: CDR1 tctggatacacattcactgaatacatcatgcac	SEQ ID NO: 312
	51C3 heavy chain VH: DNA sequence: CDR2 ggattataatcctaataatgggtgtactactacaaccagaagttaagggc	SEQ ID NO: 313
	51C3 heavy chain VH: DNA sequence: CDR3 gcaagagacgatggttactactacgtataaagttcgcttac	SEQ ID NO: 314
	51C3 heavy chain VH: Amino acid sequence: Leader sequence-<u>FR1</u>-<u>CDR1</u>-<u>FR2</u>-<u>CDR2</u>-<u>FR3</u>-<u>CDR3</u>-<u>FR4</u>	
	WGIQEWSSWVFLFLLSGTAGVLSVQLQQSGPELVKPGASVKISCKTSGYTFTEYIMHWVKQS <u>HGKSLEWIGGINPNNGGTNYNQKFKGKATLTVDTSSSIAYMELRSLTSEDSAVYYCARDG</u> <u>YVKFAYWGQGLTVSA</u>	
	51C3 heavy chain VH: Amino acids sequence: FR1 EVQLQQSGPELVKPGASVKISCKT	SEQ ID NO: 315
	51C3 heavy chain VH: Amino acid sequence: CDR1 SGYTFTEYIMH	SEQ ID NO: 316
	51C3 heavy chain VH: Amino acid sequence: FR2 WVKQSHGKSLEWIG	SEQ ID NO: 317

Clone	Sequence	SEQ ID NO.
	51C3 heavy chain VH: Amino acid sequence: CDR2 GINPNNGGTNYNQFKG	SEQ ID NO: 318
	51C3 heavy chain VH: Amino acid sequence: FR3 KATLTVDTSSTSIAYMELRSLTSEDSAVVYC	SEQ ID NO: 319
	51C3 heavy chain VH: Amino acid sequence: CDR3 ARDDGYYVKFAY	SEQ ID NO: 320
	51C3 heavy chain VH: Amino acid sequence: FR4 WGQGLTVTVSA	SEQ ID NO: 321
	51C3 light chain VL: DNA sequence: Leader sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 tactagttgacatgggctcaagatggagtcacagactcaggcttcgtattctactctctgtgtgtctgctcatgggagattgtgat gaccagactcccaaatctctgtatcagcagagacaggggtaccataacctgc aaggccagtcagagtgatgataatgatg tagcttggtaccaacagaaagccagggcagtcctcctaaactgctgatatata atgacatccaatcgctacac ctggagtcctgacgctt cacggcagtggtatgggacggatttcacttcaccatcagcacgtgcaggctgaagaccggcagttatttctgt cagcaggattia tagctctccattcacg ttcggctcggggacacaaagttggaataaaacgggctgctgctgca	
	51C3 light chain VL: DNA sequence: CDR1 aaggccagtcagagtgatgaatgat	SEQ ID NO: 323
	51C3 light chain VL: DNA sequence: CDR2 tatgcataatcgctacact	SEQ ID NO: 324
	51C3 light chain VL: DNA sequence: CDR3 cagcaggattatagctctccattcacg	SEQ ID NO: 325
	51C3 light chain VL: Amino acid sequence: Leader sequence-FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 MGFKMESQTQVFVFLLCVSGAHG SIVMTQTTPKFL LV SAGDRVTITCKASQSVINDV AWY QQK PGQSPKLLIYASNRYTGVPDRFTGSGYGTDFTFTISTVQAEDLAVYFCQQDYSSPFTFGSGT KLEIKRADAA	SEQ ID NO: 326
	51C3 light chain VL: Amino acid sequence: FR1 SIVMTQTTPKFLLV SAGDRVTITC	SEQ ID NO: 327

Clone	Sequence	SEQ ID NO.
	51C3 light chain VL: Amino acid sequence: CDR1 KASQSVIND	SEQ ID NO: 328
	51C3 light chain VL: Amino acid sequence: FR2 VAWYQQKPGQSPKLLIY	SEQ ID NO: 329
	51C3 light chain VL: Amino acid sequence: CDR2 YASNRYT	SEQ ID NO: 330
	51C3 light chain VL: Amino acid sequence: FR3 GVPDRFTGSGYGTDFTFTISTVQAEDLAVYFC	SEQ ID NO: 331
	51C3 light chain VL: Amino acid sequence: mCDR3 QQDYSSPFT	SEQ ID NO: 332
	51C3 light chain VL: Amino acid sequence: FR4 FGSGTKLEIKRADAA	SEQ ID NO: 333

[0072] In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical (e.g., at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identical) to one or more complementarily-determining regions (CDRs) (e.g., CDR1, CDR2, or CDR3) listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to one or more VH CDRs listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to two or more VH CDRs listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to three VH CDRs listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to one or more VL CDRs listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to two or more VL CDRs listed in **Table 4**. In some embodiments, provided antibodies or immunogenic fragments thereof comprise a sequence that is at least 80% identical to three VL CDRs listed in **Table 4**.

[0073] In some embodiments, an antibody is or comprises a humanized antibody. A "humanized" form of a non-human (e.g., rodent) antibody is a chimeric antibody including a sequence derived from a non-human antibody. In many cases, a humanized antibody is a human immunoglobulin in which a residue in a hypervariable domain of a subject species is substituted with a residue in a hypervariable domain of a non-human species (donor antibody) having a desired specificity, affinity and ability, for example, a mouse, a rat, a rabbit or a non-human primate. In some cases, a residue in a framework region (FR) of the human immunoglobulin is substituted with a corresponding non-human residue. In addition, a humanized antibody may include a residue that is not found in a recipient or donor antibody. In some embodiments, such modification may be performed to further improve antibody performance. Generally, a humanized antibody may include substantially at least one, or generally, both of the two variable domains, and here, all or substantially all hypervariable loops correspond to hypervariable loops of a non-human immunoglobulin, and all or substantially all FRs to FRs of a human immunoglobulin sequence. In addition, a humanized antibody may optionally include at least a part of an immunoglobulin constant domain (Fc), or generally, a human immunoglobulin constant domain. Techniques used to humanize a

monoclonal antibody are well known to one of skill in the art and have been described previously. See, e.g., U.S. Patent Nos. 4,816,567; 5,807,715; 5,866,692; 6,331,415; 5,530,101; 5,693,761; 5,693,762; 5,585,089; and 6,180,370; Jones 1986; Riechmann 1988; Vaswani & Hamilton 1998; Harris 1995; Hurle & Gross 1994. In certain aspects, the present technology provides a nucleic acid encoding a humanized antibody. Such a nucleic acid provided herein may be present in a cell, a cell lysate, in an isolated form, a partially purified form, or a substantially purified form. The nucleic acid is "isolated," "partially purified," or "substantially purified" when being separated from different cell components or other cell components, for example, nucleic acids or proteins of different cells by techniques known to one of skill in the art including, but not limited to, alkali/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis, or any other suitable technique. A nucleic acid according to the present technology may be, for example, DNA or RNA, and may or may not include an intron sequence.

Nucleic Acids

[0074] The present technology includes nucleic acids comprising one or more nucleotide sequences encoding one or more heavy chains, heavy chain variable domains, heavy chain framework regions, heavy chain CDRs, heavy chain constant domains, light chains, light chain variable domains, light chain framework regions, light chain CDRs, light chain constant domains, or other immunoglobulin-like sequences, antibodies, or binding molecules disclosed herein. In some embodiments, such nucleotide sequences may be present in a vector (e.g., a plasmid or a viral vector). In some embodiments, such nucleotides may be present in the genome of a cell (e.g., a cell of a subject in need of treatment) or a cell for production of an antibody (e.g., a mammalian cell) for production of an antibody.

KIR3DL3 protein expression and binding

[0075] Using Fluorescence-Activated Cell Sorting (FACS) analysis of PBMC using anti-KIR3DL3 mAbs provided herein, KIR3DL3 protein was shown to be widely expressed on the cells surface of innate immune cells (NK cells, NKT cells, $\gamma\delta$ T cells) and adaptive immune cells (CD8 T cells and CD4 T cells) (FIG. 1). In CD8 T cells, KIR3DL3 is mainly expressed on terminally differentiated effector CD8 T cells.

[0076] Previous studies discovered HHLA2 as the newest member of the B7 family and demonstrate that it is able to inhibit T cell proliferation and function (Zhao 2013; U.S. Patent No. 10,093,737). Subsequent studies reported that HHLA2 is over-expressed in various types of human cancers (Cheng 2018; Cheng 2017; Koirala 2016; Janakiram 2015). To test the binding of HHLA2 to KIR3DL1, KIR3DL2, and KIR3DL3, 3T3 cell lines stable expressing cell surface KIR3DL1, KIR3DL2, or KIR3DL3 were generated. FACS assay results demonstrated that HHLA2 protein bound to KIR3DL3-expressing 3T3 cells, but not KIR3DL1-expressed or KIR3DL2-expressed 3T3 cells (FIG. 2A). Further, the intercellular conjugate assay shows that 3T3 cell line expressing HHLA2 bound to 3T3 cell line expressing KIR3DL3, but not the control 3T3 cell line (FIG. 2B). These results demonstrate HHLA2 binds KIR3DL3, but not its closet homologues KIR3DL1 and KIR3DL2.

[0077] Results provided herein further demonstrate that the D0 domain and the whole extracellular part of KIR3DL3 bind HHLA2 (FIG. 2C), suggesting the D0 domain of KIR3DL3 is the functional domain in the interaction between KIR3DL3 and HHLA2.

[0078] As HHLA2 can bind both KIR3DL3 and/or TMIGD2, competitive assays were performed with FACS and demonstrate that TMIGD2 could not inhibit the binding of KIR3DL3 to HHLA2 (FIG. 3A) and that KIR3DL3 could not inhibit the binding of TMIGD2 to HHLA2 (FIG. 3B), suggesting KIR3DL3 and TMIGD2 bind non-overlapping sites in HHLA2.

KIR3DL3 inhibits functions of human immune cells and anti-KIR3DL3 blocking mAbs neutralize KIR3DL3-induced immune suppression

[0079] In contrast to KIR3DL1 and KIR3DL2 that bind HLA-A and/or HLA-B, KIR3DL3 binds HHLA2, but the function of KIR3DL3 was previously unknown (Beziat 2017). To elucidate the function of KIR3DL3, experiments were performed using FACS to sort the human NK cell line NK92 into the KIR3DL3 positive population (KIR3DL3⁺ NK92) and the KIR3DL3 negative population (KIR3DL3⁻ NK92) for NK-mediated killing function. Results indicate that KIR3DL3⁻ NK92 cells equally killed both HHLA2 positive K562 cells (HHLA2⁺ K562) and HHLA2 negative K562 cells (HHLA2⁻ K562) (FIG. 4A), but KIR3DL3⁺ NK92 cells killed HHLA2⁻ K562 cells much more efficiently than HHLA2⁺ K562 cells (FIG. 4A). Next, FACS was used to sort out KIR3DL3⁺CD8⁺ T cells (terminally differentiated effector cells) and expand those cells with anti-CD3/CD28, IL-

2, and feeder cells *in vitro* to produce enough cells. Next, a CD8 T cell-mediated killing assay was performed which demonstrated that KIR3DL3⁺ CD8 T cells killed K562 cells much more efficiently than HHLA2⁺ K562 cells (FIG. 4B). These results demonstrate KIR3DL3 inhibits functions of immune cells when bound by HHLA2.

[0080] After demonstrating that KIR3DL3 induces immune suppression (FIGS. 4A–4B), experiments were performed to determine whether anti-KIR3DL3 mAbs (such as those provided herein) are able to block the function of KIR3DL3. To test this, KIR3DL3⁺ NK92 cells were pre-incubated with either anti-KIR3DL3 mAbs or negative control mouse IgG1 antibodies. As proof of principle, four anti-KIR3DL3 mAbs were examined (26E10, 34B10, 30D10, 8G7). Following pre-incubation, cells were subjected to the NK cell-mediated killing assay employed in FIG. 4A. Following a cytotoxicity assay, cells pre-incubated with mouse IgG1 did not show an effect, whereas the cells pre-incubated with anti-KIR3DL3 mAbs (26E10, 34B10, 30D10, 8G7) exhibited significantly enhanced KIR3DL3⁺ NK92 cell-mediated killing of targeted HHLA2⁺ K562 cells (FIGS. 5A, 5B).

[0081] The extracellular portion of HHLA2 includes IgV1, IgC, and IgV2 domains (Zhao 2013). In previous work, an anti-HHLA2 mAb that recognizes IgCIgV2 parts was generated (566.1) (Zhao 2013). Subsequently, two additional anti-HHLA2 mAbs (A3H11 and B5B5) were generated. These two antibodies recognize the IgV1 domain. Here, a binding competitive assay revealed that A3H11 and B5B5, not 566.1, blocked the binding of KIR3DL3 protein to HHLA2 (FIG. 6A). Additionally, the A3H11 and B5B5 mAbs, but not 566.1, neutralized KIR3DL3-induced immune suppression in NK cell killing assays (FIG. 6B). These results demonstrate that the IgV1 domain of HHLA2 can bind to KIR3DL3, leading to the inhibition of immune cells and that mAbs against the IgV1 domain of HHLA2 are able to block the binding of HHLA2 to KIR3DL3 and neutralize KIR3DL3-induced immune suppression.

[0082] The different expression patterns between KIR3DL3 and TMIGD2 are unknown. Therefore, experiments were performed with FACS to examine the expression of these two receptors on human immune cells in PBMC. These experiments showed that KIR3DL3 positive CD8 and CD4 T cells are TMIGD2 negative, whereas NK cells can be KIR3DL3⁺/TMIGD2⁺, KIR3DL3⁺/TMIGD2⁻, KIR3DL3⁻

/TMIGD2⁺, or KIR3DL3⁺/TMIGD2⁻ (FIG. 7). These results indicate that, although both are receptors for HHLA2, TMIGD2 and KIR3DL3 have different expression patterns.

[0083] To examine the binding of TMIGD2 to HHLA2, 3T3 cell lines expressing TMIGD2 were stained with a HHLA2 EC-Ig-Fc fusion polypeptide, a HHLA-2-IgV1-hlgG fusion polypeptide, or Ig (control) (FIG. 8). These results show that the IgV1 domain and the whole extracellular part of HHLA2 bound TMIGD2 (FIG. 8), suggesting the IgV1 domain of HHLA2 is the function domain in the interaction between HHLA2 and TMIGD2.

KIR3DL3 inhibits functions of human immune cells by recruiting SHP1/2 through the ITIM motif

[0084] To further explore the mechanism through which KIR3DL3 mediates immune cell suppression, Y381F, a mutant of KIR3DL3, was generated by replacing the tyrosine (Y) residue at position 381 located at the YAQL sequence within the ITIM motif with the phenylalanine (F) residue (FIG. 10A). KIR3DL3-negative (KIR3DL3⁻) NK92 cells were transduced with WT KIR3DL3 or Y381F mutant constructs and examined for KIR3DL3 expression by flow cytometry. Expression of KIR3DL3 WT and Y381F was detected in the cells transduced with the respective construct (FIG. 10A). Next, tyrosine phosphorylation of KIR3DL3 WT and Y381F mutant was examined. Briefly, transfected NK92 cells were cultured in the presence (+) or absence (-) of pervanadate (VO₄, 1 mM) for 5 minutes at 37°C. Pervanadate is an inhibitor of the protein tyrosine phosphatase and functions to promote phosphorylation of proteins on tyrosine residues. Cell lysates were immunoprecipitated with anti-KIR3DL3 antibodies and examined for tyrosine phosphorylation by immunoblots using KIR3DL3 antibody and phosphorylated tyrosine antibody (4G10). Results for both whole-cell lysates (WCL) and immunoprecipitation (IP) samples are shown (FIG. 10B). As expected, tyrosine phosphorylation was detected in WT KIR3DL3, but not Y381F.

[0085] Next, cytotoxicity assays were performed by incubating NK92 cells expressing KIR3DL3 WT or Y381F with K562 cells or Raji cells expressing HHLA2 or control, at different effector to target (E:T) ratios (FIG. 10C). The percentage of specific lysis was calculated and plotted in function of the E:T ratio. As shown, in both K562 cells and Raji cells, a significant difference in cytotoxicity was detected in NK92 cells expressing KIR3DL3 WT incubated with HHLA2-expressing cells compared with

control, consistent with the results observed before. However, no difference in cytotoxicity was observed in NK92 cells expressing KIR3DL3 Y381F, suggesting that the HHLA2-induced KIR3DL3 suppression of immune cell function acts through the ITIM motif of KIR3DL3.

[0086] Finally, considering the importance of the tyrosine phosphorylation of the ITIM motif in KIR3DL3 functioning, and the role of protein tyrosine phosphatases SHP-1/SHP-2 play in immune cells, it was tested whether KIR3DL3 interacted with SHP-1 or SHP-2. Briefly, primary KIR3DL3+ NK Cells (35×10^6 cells) were treated with (+) or without (-) pervanadate (VO_4 , 1 mM) for 5 minutes at 37°C. Anti-KIR3DL3 (lane 2, 4) or mIgG1 (lane 1, 3) immunoprecipitates (IP) and whole-cell lysates (WCL) were analyzed sequentially for KIR3DL3, SHP-1, and SHP-2 by Western blotting. As shown in FIG. 10D, co-immunoprecipitation experiments demonstrated that KIR3DL3 interacted with both SHP-1 and SHP-2, suggesting that KIR3DL3 inhibits functions of human immune cells by recruiting SHP1/2 through its ITIM motif.

Expression of KIR3DL3 in cancer

[0087] To examine KIR3DL3 mRNA expression levels in human tumors, Applicant searched 1,425 human tumor lines. The top 40 tumor lines expressing the highest levels of KIR3DL3 mRNA are shown in FIG. 9. Of the top 40 tumors examined (those exhibiting the highest KIR3DL3 mRNA levels), many tumor lines are human hematologic malignancies, suggesting a particular role for targeting KIR3DL3 in treating these conditions.

[0088] KIR3DL3 expression at the protein level was also examined in human tumors, and it was found that KIR3DL3 is expressed on tumor-infiltrating immune cells in various human cancers, including kidney, gastric, lung, gallbladder, and pancreatic cancer (FIG. 11). Together, these data suggest that the KIR3DL3 pathway represents a novel immunosuppressive mechanism within the tumor microenvironment and an attractive target for human cancer therapy.

Compositions

[0089] In some aspects, the present technology provides compositions comprising an antibody, a fusion polypeptide, a nucleic acid, or a small molecule according to an embodiment disclosed and described herein.

[0090] In some embodiments, the composition further comprises a pharmaceutically acceptable excipient. Non-limiting examples of pharmaceutically acceptable excipients include, for example, those described in "Remington: The Science and Practice of Pharmacy", 19th ed. (1995), or latest edition, Mack Publishing Co; A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy", 20th ed., Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery Systems (1999) H. C. Ansel et al., eds., 7th ed., Lippincott, Williams, & Wilkins; and Handbook of Pharmaceutical Excipients (2000) A. H. Kibbe et al., eds., 3rd ed. Amer. Pharmaceutical Assoc. In some embodiments, the composition is suitable for administration to a subject, for example, a sterile composition. In some embodiments, the composition is suitable for administration to a human subject, for example, the composition is sterile and is free of detectable pyrogens and/or other toxins.

[0091] In some embodiments, the composition comprises other components, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. In some embodiments, the compositions comprise a pharmaceutically acceptable auxiliary substance as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, hydrochloride, sulfate salts, solvates (e.g., mixed ionic salts, water, organics), hydrates (e.g., water), and the like.

[0092] In some embodiments, the compositions are in an aqueous solution, powder form, granules, tablets, pills, suppositories, capsules, suspensions, sprays, and the like. The composition may comprise a pharmaceutically acceptable excipient, a pharmaceutically acceptable salt, diluents, carriers, vehicles, and such other inactive agents well known to the skilled artisan. Vehicles and excipients commonly employed in pharmaceutical preparations include, for example, talc, gum Arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerine, and the like. Parenteral compositions may be prepared using conventional techniques that may include sterile isotonic saline, water, 1,3-butanediol, ethanol, 1,2-propylene glycol,

polyglycols mixed with water, Ringer's solution, etc. In one aspect, a coloring agent is added to facilitate in locating and properly placing the composition to the intended treatment site.

[0093] Compositions may include a preservative and/or a stabilizer. Non-limiting examples of preservatives include methyl-, ethyl-, propyl- parabens, sodium benzoate, benzoic acid, sorbic acid, potassium sorbate, propionic acid, benzalkonium chloride, benzyl alcohol, thimerosal, phenylmercurate salts, chlorhexidine, phenol, 3-cresol, quaternary ammonium compounds (QACs), chlorbutanol, 2-ethoxyethanol, and imidurea.

[0094] To control tonicity, the composition can comprise a physiological salt, such as a sodium salt. Sodium chloride (NaCl) is preferred, which may be present at between 1 and 20 mg/ml. Other salts that may be present include potassium chloride, potassium dihydrogen phosphate, disodium phosphate dehydrate, magnesium chloride and calcium chloride.

[0095] Compositions may include one or more buffers. Typical buffers include: a phosphate buffer; a Tris buffer; a borate buffer; a succinate buffer; a histidine buffer; or a citrate buffer. Buffers will typically be included at a concentration in the 5-20 mM range. The pH of a composition will generally be between 5 and 8, and more typically between 6 and 8, *e.g.*, between 6.5 and 7.5, or between 7.0 and 7.8.

[0096] The composition can be administered by any appropriate route, which will be apparent to the skilled person depending on the disease or condition to be treated. Typical routes of administration include intravenous, intra-arterial, intramuscular, subcutaneous, intracranial, intranasal, or intraperitoneal.

[0097] In some embodiments, the composition may include a cryoprotectant agent. Non-limiting examples of cryoprotectant agents include a glycol (*e.g.*, ethylene glycol, propylene glycol, and glycerol), dimethyl sulfoxide (DMSO), formamide, sucrose, trehalose, dextrose, and any combinations thereof.

[0098] The composition can comprise a pharmaceutically acceptable excipient, a pharmaceutically acceptable salt, diluents, carriers, vehicles, and such other inactive agents well known to the skilled artisan. Vehicles and excipients commonly employed in pharmaceutical preparations include, for example, talc, gum Arabic, lactose, starch,

magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerine, and the like. Parenteral compositions may be prepared using conventional techniques that may include sterile isotonic saline, water, 1,3-butanediol, ethanol, 1,2-propylene glycol, polyglycols mixed with water, Ringer's solution, etc. In one aspect, a coloring agent is added to facilitate in locating and properly placing the composition to the intended treatment site.

[0099] In certain aspects, a nucleic acid molecule encoding antibodies or immunogenic fragments thereof are provided herein.

[0100] In one aspect, a vector encoding a nucleic acid molecule described herein is provided. In certain aspects, a host cell comprising a nucleic acid molecule described herein or a vector described herein is provided.

[0101] In certain embodiments, the antibody is humanized.

[0102] In one aspect, a kit of parts is provided comprising the above-mentioned composition. The kit may further comprise a document or instruction manual that describes a protocol for preparing the antibodies, fusion polypeptide, nucleic acids, and/or small molecules, and/or administering to a subject in need thereof.

Methods of use and treatment

[0103] Provided herein are methods of use and treatment of a subject in need thereof. In some embodiments, provided herein are antibodies, fusion polypeptide, nucleic acid, and/or small molecules for use in therapy. In other embodiments, provided herein are antibodies, fusion polypeptide, nucleic acids, and/or small molecules for use in the production of a medicament.

[0104] Also provided herein are methods of treating a subject, comprising administering to the subject a therapeutically effective amount of an antibody, a fusion polypeptide, a nucleic acid, and/or a small molecule according to an embodiment disclosed and described herein.

[0105] Also provided herein are compositions comprising an antibody, an immunogenic fragment thereof, a fusion polypeptide, or a combination thereof (e.g., in

a chimeric antigen receptor and/or antibody-drug conjugate) according to embodiments disclosed and described herein for use in treating a subject having a condition.

[0106] In certain embodiments, administration of an antibody as described herein is achieved by administering to a subject a nucleic acid encoding the antibody. Nucleic acids encoding an antibody described herein can be incorporated into a gene construct to be used as a part of a gene therapy protocol to deliver nucleic acids that can be used to express and produce antibody within cells. Expression constructs of such components may be administered in any therapeutically effective carrier, for example, any formulation or composition capable of effectively delivering the component gene to cells *in vivo*. Approaches include insertion of a nucleic acid encoding an antibody described herein into viral vectors including recombinant retroviruses, adenovirus, adeno-associated virus, lentivirus, herpes simplex virus-1 (HSV-1), or recombinant bacterial or eukaryotic plasmids. Viral vectors can transfect cells directly; plasmid DNA can be delivered with the help of, for example, cationic liposomes (e.g., Lipofectin®), derivatization, polylysine conjugates, gramicidin S, artificial viral envelopes or other suitable intracellular carriers, direct injection, or CaPO₄ precipitation (see, e.g., WO04/060407). Examples of suitable retroviruses include, but are not limited to, pLJ, pZIP, pWE, and pEM which are known to those skilled in the art (see, e.g., Eglitis 1985; Danos & Mulligan 1988; Wilson 1988; Armentano 1990; Huber 1991; Ferry 1991; Chowdhury 1991; van Beusechem 1992; Kay 1992; Dai 1992; Hwu 1993; U.S. Patent Nos. 4,868,116 and 4,980,286; and PCT Publ. Nos. WO89/07136; WO89/02468; WO89/05345; and WO92/07573). Another viral gene delivery system that may be used to deliver an antibody or a nucleic acid encoding an antibody according to the present technology utilizes adenovirus-derived vectors (see, e.g., Berkner 1988; Rosenfeld 1991; Rosenfeld 1992). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7, etc.) are known to those skilled in the art. Yet another viral vector system that may be used to deliver an antibody or a nucleic acid encoding an antibody according to the present technology is the adeno-associated virus (AAV). See, e.g., Flotte 1992; Samulski 1989; and McLaughlin 1988.

[0107] In some embodiments, the subject has a condition that would benefit from an enhanced immune response, such as an infection, a disease, or cancer. In these embodiments, compositions provided herein (including antibodies, fusion polypeptides,

nucleic acids, and/or small molecules) may be used to block the function of KIR3DL3. In other embodiments, the subject has a condition that would benefit from suppressing an immune response, such as an autoimmune disease or transplant. In these embodiments, compositions provided herein (including antibodies, fusion polypeptides, nucleic acids, and/or small molecules) may be used to stimulate the function of KIR3DL3.

[0108] In some embodiments, the cancer is chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), T-cell lymphoma, B-cell lymphoma, chronic myelogenous leukemia (CML), acute myelogenous leukemia, B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell follicular lymphoma, large cell follicular lymphoma, malignant lymphoproliferative conditions, mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, or preleukemia.

[0109] In some embodiments, the cancer is a human hematologic malignancy. For example, in certain embodiments the human hematologic malignancy may be selected from myeloid neoplasm, acute myeloid leukemia (AML), AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, acute leukemias of ambiguous lineage, myeloproliferative neoplasm, essential thrombocythemia, polycythemia vera, myelofibrosis (MF), primary myelofibrosis, systemic mastocytosis, myelodysplastic syndromes (MDS), myeloproliferative/myelodysplastic syndromes, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, myelodysplastic syndromes (MDS), refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (type 1), refractory anemia with excess blasts (type 2), MDS with isolated del (5q), unclassifiable MDS, myeloproliferative/myelodysplastic syndromes, chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, unclassifiable myeloproliferative/myelodysplastic syndromes, lymphoid neoplasms, precursor

lymphoid neoplasms, B lymphoblastic leukemia, B lymphoblastic lymphoma, T lymphoblastic leukemia, T lymphoblastic lymphoma, mature B-cell neoplasms, diffuse large B-cell lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, Burkitt's lymphoma/leukemia, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, marginal zone lymphomas, post-transplant lymphoproliferative disorders, HIV-associated lymphomas, primary effusion lymphoma, intravascular large B-cell lymphoma, primary cutaneous B-cell lymphoma, hairy cell leukemia, multiple myeloma, monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma, or solitary plasmacytomas (solitary bone and extramedullary).

[0110] In some embodiments, the cancer is Adrenal Cancer, Anal Cancer, Basal and Squamous Cell Skin Cancer, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain and Spinal Cord Tumors, Breast Cancer, Cervical Cancer, Colorectal Cancer, Endometrial Cancer, Esophagus Cancer, Ewing Family of Tumors, Eye Cancer (Ocular Melanoma), Gallbladder Cancer, Gastric Cancer, Gastrointestinal Neuroendocrine (Carcinoid) Tumors, Gastrointestinal Stromal Tumor (GIST), Gestational Trophoblastic Disease, Kaposi Sarcoma, Kidney Cancer, Laryngeal and Hypopharyngeal Cancer, Liver Cancer, Lung Cancer, Lung Carcinoid Tumor, Malignant Mesothelioma, Melanoma Skin Cancer, Merkel Cell Skin Cancer, Nasal Cavity and Paranasal Sinuses Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Small Cell Lung Cancer, neoplasm of the central nervous system (CNS), Oral Cavity and Oropharyngeal Cancer, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer, Pancreatic Neuroendocrine Tumor (NET), Penile Cancer, Pituitary Tumors, Prostate Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Stomach Cancer, Testicular Cancer, Thymus Cancer, Thyroid Cancer, Uterine Sarcoma, Vaginal Cancer, Vulvar Cancer, Waldenström Macroglobulinemia, Wilms Tumor, squamous cell cancer, environmentally induced cancers, combinations of the cancers, and metastatic lesions of the cancers. In some embodiments, the cancer is leukemia or lymphoma, for example, lymphoblastic lymphoma or B-cell Non-Hodgkin's lymphoma. In some embodiments, the cancer is a metastatic cancer.

[0111] In some embodiments, the methods of treating a subject having cancer comprise administering to the subject a therapeutically effective amount of an antibody, a fusion polypeptide, a nucleic acid, and/or a small molecule according to an embodiment disclosed and described herein, in combination with one or more additional cancer therapies targeting a specific type of the cancer over an extended period of time to obtain improved or synergistic therapeutic effects. In some embodiments, the one or more additional cancer therapies are selected from chemotherapy, radiation therapy, immunotherapy, surgery, and a combination thereof. For example, the antibody, fusion polypeptide, nucleic acid, small molecule, and/or composition thereof can be administered in combination with one or more additional chemotherapy agents. For another example, the antibody, fusion polypeptide, nucleic acid, small molecule, and/or composition thereof can be administered in combination with one or more additional immunotherapy agents. Such methods may be used to treat any cancer or tumor type where KIR3DL3 plays a role in regulating the immune cell functions, including, but not limited to, primary, recurrent, and metastatic cancers as listed above.

[0112] A "therapeutically effective amount" of an antibody, a fusion polypeptide, a nucleic acid, and/or a small molecule as used herein is an amount of the antibody, fusion polypeptide, nucleic acid, and/or small molecule that produces a desired effect in a subject for treating and/or preventing a condition, *e.g.*, a therapeutic effect. In certain embodiments, the therapeutically effective amount is an amount of the antibody, fusion polypeptide, nucleic acid, and/or small molecule that yields maximum therapeutic effect. In other embodiments, the therapeutically effective amount yields a therapeutic effect that is less than the maximum therapeutic effect. For example, a therapeutically effective amount may be an amount that produces a therapeutic effect while avoiding one or more side effects associated with a dosage that yields maximum therapeutic effect. A therapeutically effective amount for a particular composition will vary based on a variety of factors, including, but not limited to, the characteristics of the therapeutic composition (*e.g.*, activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (*e.g.*, age, body weight, sex, disease type and stage, medical history, general physical condition, responsiveness to a given dosage, and other present medications), the nature of any pharmaceutically acceptable carriers, excipients, and preservatives in the composition, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically

effective amount through routine experimentation, namely, by monitoring a subject's response to administration of the antibody, fusion polypeptide, nucleic acid, and/or small molecule and adjusting the dosage accordingly. For additional guidance, see, for example, Remington: The Science and Practice of Pharmacy, 22nd ed., Pharmaceutical Press, London, 2012, and Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed., McGraw-Hill, New York, NY, 2011, the entire disclosures of which are incorporated by reference herein.

[0113] In some embodiments, a therapeutically effective amount of the antibody, fusion polypeptide, nucleic acid, and/or small molecule disclosed herein is in the range from about 10 mg/kg to about 150 mg/kg, from 30 mg/kg to about 120 mg/kg, from 60 mg/kg to about 90 mg/kg. In some embodiments, a therapeutically effective amount of the antibody, fusion polypeptide, nucleic acid, and/or small molecule disclosed herein is about 15 mg/kg, about 30 mg/kg, about 45 mg/kg, about 60 mg/kg, about 75 mg/kg, about 90 mg/kg, about 105 mg/kg, about 120 mg/kg, about 135 mg/kg, or about 150 mg/kg. A single dose or multiple doses of the antibody, fusion polypeptide, nucleic acid, and/or small molecule may be administered to a subject. In some embodiments, the antibody, fusion polypeptide, nucleic acid, and/or small molecule is administered once or multiple times a day.

[0114] Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be systemic or local. In some embodiments, administration may be enteral or parenteral. Further, it is within the purview of one of ordinary skill in the art to select a suitable administration route, such as oral administration, subcutaneous administration, intravenous administration, intramuscular administration, intradermal administration, intrathecal administration, or intraperitoneal administration. For treating a subject in need thereof, the antibody, fusion polypeptide, nucleic acid, and/or small molecule can be administered continuously or intermittently, for an immediate release, controlled release, or sustained release. Additionally, the antibody, fusion polypeptide, nucleic acid, and/or small molecule can be administered once a day, twice a day, three times a day, or four times a day for a period of 3 days, 5 days, 7 days, 10 days, 2 weeks, 3 weeks, 4 weeks, 8 weeks, or 12 weeks. In certain embodiments, the antibody, fusion polypeptide, nucleic acid, and/or small molecule can be administered every day, every

other day, every third day, weekly, biweekly (*i.e.*, every other week), every third week, monthly, every other month, or every third month. The antibody, fusion polypeptide, nucleic acid, and/or small molecule may be administered over a pre-determined time period. Alternatively, the antibody, fusion polypeptide, nucleic acid, and/or small molecule may be administered until a particular therapeutic benchmark is reached. In certain embodiments, the methods provided herein include a step of evaluating one or more therapeutic benchmarks, such as, but not limited to, the level of certain biomarkers in a biological sample, such as blood circulating tumor cells, a biopsy sample, or urine to determine whether to continue administration of the antibody, fusion polypeptide, nucleic acid, and/or small molecule. In certain embodiments involving cancer, the antibody, fusion polypeptide, nucleic acid, and/or small molecule may be administered until tumor growth is arrested or reversed, until one or more tumors are eliminated, or until the number of cancer cells are reduced to a specific level.

[0115] As demonstrated in the working examples, KIR3DL3 blockade using antibodies promotes anti-tumor immunity and suppress tumor growth in mouse models of lung adenocarcinoma. As standard of care, treatment of early stages of lung cancer, including non-small cell lung cancer (NSCLC), includes surgery, photodynamic therapy, laser therapy, brachytherapy, chemotherapy, and radiation therapy, and/or any combination thereof. For more advanced stages of lung cancer, the standard treatment includes chemotherapy, radiation therapy, immunotherapy, and/or any combination thereof. In certain embodiments, the chemotherapeutic agents for lung cancer include, but are not limited to, cisplatin (Platinol), carboplatin (Paraplatin), docetaxel (Taxotere), gemcitabine (Gemzar), paclitaxel (Taxol), vinorelbine (Navelbine), pemetrexed (Alimta), albumin-bound paclitaxel (Abraxane), etoposide (VePesid or Etopophos), doxorubicin (Adriamycin), ifosfamide (Ifex), irinotecan (Camptosar), topotecan (Hycamtin), vinblastine (Oncovir) and vincristine (Oncovin). In certain embodiments, the immunotherapy agents for lung cancer include, but are not limited to, pembrolizumab (Keytruda), nivolumab (Opdivo), ipilimumab (Yervoy), bevacizumab (Avastin), atezolizumab (Tecentriq) and necitumumab (Portrazza).

[0116] In some embodiments, the infection is caused by a pathogen. In certain embodiments, the pathogen may be a virus, a bacterium, a prion, a fungus, or a parasite. Non-limiting examples of viruses amenable to the present technology include human immunodeficiency viruses (HIV) (*e.g.*, HIV-1 and HIV-2), influenza viruses (*e.g.*,

influenza A, B, and C viruses), papillomaviruses, coronaviruses (e.g., human respiratory coronavirus), hepatitis viruses (e.g., hepatitis viruses A–G), or herpesviruses (e.g., HSV 1–9), West Nile virus, Zika virus, Encephalomyocarditis virus, Dengue virus, or Ebolavirus. Non-limiting examples of bacterium amenable to the present technology include *Mycobacterium tuberculosis*, *Campylobacter jejuni*, *Staphylococcus aureus*, *Borrelia burgdorferi*, *Helicobacter pylori*, *Salmonella enterica*, *E. coli*, *Streptococcus pyogenes*, multiple drug resistant *S. aureus*, *Chlamydia pneumoniae*, *Clostridium botulinum*, *Vibrio vulnificus*, *Parachlamydia*, *Corynebacterium amycolatum*, *Klebsiella pneumoniae*, *Linezolid-resistant enterococci* (*E. faecalis* and *E. faecium*), and multiple drug resistant *Acinetobacter baumannii*. Non-limiting examples of fungi amenable to the present technology include *Pneumocystis jirovecii* (PJP), *Candida*, *Blastomyces*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Paracoccidioides*, *Aspergillus*, *Talaromyces*, and *Sporothrix*. In certain embodiments, the infection may be HIV, pneumocystis, or mycobacterium tuberculosis.

[0117] In some embodiments, the autoimmune disease is selected from the group consisting of acute disseminated encephalomyelitis (ADEM), alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lipoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticarial, autoimmune uveitis, Behçet's disease, celiac disease, Chagas disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's syndrome, Guillain-Barré syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis.

[0118] In one embodiment, the autoimmune disease treated is adult rheumatoid arthritis.

[0119] In some embodiments, the condition is a transplant. In these embodiments, compositions and methods provided herein may be used to suppress transplant rejection. In certain embodiments, the transplant is a stem cell or bone marrow transplant, for example, in a subject having graft versus host disease. In certain embodiments, the transplant is selected from the group consisting of a kidney transplant, a lung transplant, a heart transplant, a pancreas transplant, a cornea transplant, or a liver transplant.

[0120] In some embodiments, an antibody as described herein may be included in a course of treatment that further includes administration of at least one additional agent to a subject.

[0121] In some embodiments, methods provided herein may be performed in conjunction with an additional therapy, for example, a combination therapy. In certain embodiments, the additional therapy may be a therapy for an immune-associated disorder or condition, including those disclosed herein. For example, a composition disclosed herein may be administered to a subject at the same time, prior to, or after radiation treatment, chemotherapy, hormone therapy, cell therapy, and/or another anti-tumor or anti autoimmune therapy. In some embodiments, the composition can be administered to a subject at the same time, prior to, or after, an organ transplant.

[0122] In some embodiments, an additional agent administered in combination with an antibody as described herein may be administered at the same time as an antibody, on the same day as an antibody, or in the same week as an antibody. In some embodiments, an additional agent administered in combination with an antibody as described herein may be administered in a single formulation. In certain embodiments, an additional agent may be administered in a manner temporally separated from administration of an antibody as described herein, for example, one or more hours before or after, one or more days before or after, one or more weeks before or after, or one or more months before or after administration of a provided antibody. In various embodiments, the administration frequency of one or more additional agents may be the same as, similar to, or different from the administration frequency of an antibody as described herein.

[0123] In some embodiments, a combination therapy may be a treatment regimen that includes administration of two distinct antibodies as described herein and/or a

treatment regimen that includes administration of an antibody as described herein by a plurality of formulations and/or routes of administration.

[0124] In some embodiments, an additional agent may be or comprise one or more drugs. For example, in some embodiments, an additional agent may be or comprise one or more drugs that function to suppress immune responses, for example, to effectively treat patients having autoimmune diseases, or to help prevent transplant rejection. For example, among currently available treatments for rheumatoid arthritis and kidney transplant are Abatacept (Orencia®) and Betacept (Nulojix®), modified antibody fusion polypeptides comprising the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the Fc region of IgG1. Conversely, drugs that activate or inactivate immune responses may be used as additional agents to effectively treat diseases or disorders including cancers or infectious diseases. For example, ipilimumab (Yervoy®) is a monoclonal antibody that activates immune responses by targeting CTLA-4 and can be used to treat melanoma. Pembrolizumab (Keytruda®) is a humanized antibody against human programmed death receptor-1 (PD-1) and is prescribed as an anti-PD-1 immunotherapy against certain cancers. Nivolumab (Opdivo®) is another anti-PD-1 antibody used as an immunotherapy to treat certain cancers.

[0125] From the foregoing, it will be appreciated that specific embodiments of the invention have been described herein for purposes of illustration, but that various modifications may be made without deviating from the scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

EXAMPLE 1

[0126] This working example demonstrates the efficacy of KIR3DL3 blockade using antibodies in promoting anti-tumor immunity and suppressing tumor growth in mouse models of lung adenocarcinoma (FIGS. 12A–12B). An intraperitoneal tumor mouse model was generated by intraperitoneally (i.p.) injecting 4×10^6 HHLA2+ HCC827 cells transduced with luciferase (Luc2-HCC827) into NSG mice (n=6 for each group) (FIG. 12A). Four days later, the mice were allocated to 26E10 (anti-KIR3DL3 mAb) or mIgG1 group based on baseline bioluminescence. Each mouse then received 1×10^7 expanded KIR3DL3+ NK cells together with 1 µg IL-2, 1 µg IL-15 and 200 µg 26E10 (or mIgG1) i.p. every other day (5 times in total). Bioluminescence was measured by IVIS

spectrum Imager (Capiler Perkin Elmer) with imaging beginning 5-10 minutes after i.p. injection of D-Luciferin (150 µg/g body weight) and analyzed with Living Image 3.0 software. Bioluminescence measurement of tumor growth shows that anti-KIR3DL3 monoclonal antibody reduced tumor growth compared with control (FIG. 12B), suggesting that targeting KIR3DL3-mediated immune suppression is an effective approach of cancer therapy through promotion of anti-tumor immunity.

[0127] The efficacy of KIR3DL3 blockade by antibodies was also tested in mouse models of metastatic lung cancer (FIGS. 12C–12D). 5×10^5 Luc2-HCC827 cells were i.v. injected into NSG mice (n=4 for each group). Four days later, the mice were allocated to 26E10 (anti-KIR3DL3) or mIgG1 group based on baseline bioluminescence. Each mouse then received 7×10^6 KIR3DL3+ NK cells together with 1 µg IL-2, 1 µg IL-15 and 200 µg 26E10 (or mIgG1) i.v. every other day (3 times in total). Bioluminescence was measured by IVIS spectrum Imager (Capiler Perkin Elmer) with imaging beginning 10-18 minutes after i.p. injection of D-Luciferin (150 µg/g body weight) and analyzed with Living Image 3.0 software (FIG. 12C). Again, it was observed that anti-KIR3DL3 monoclonal antibody significantly reduced tumor growth compared with control (FIG. 12D), suggesting that inhibition of KIR3DL3-mediated immune suppression and the resulting increase in anti-tumor immunity are effective at treating metastatic cancer as well.

[0128] Finally, the efficacy of KIR3DL3 blockade was confirmed in subcutaneous tumor mouse models (FIGS. 12E–12F). Human lung adenocarcinoma HCC827 cells (3×10^6) were subcutaneously injected into NSG mice. Twelve days later, tumor-bearing mice were randomized to 26E10 or mIgG1 groups (n=4 for each group) and then treated with KIR3DL3+ NK cells (10×10^6 cells), and 26E10 or isotype mIgG1 (200 µg) treated every other day for two weeks (FIG. 12E). Tumor growth was assessment as before. Consistent with prior observations, anti-KIR3DL3 monoclonal antibody significantly reduced tumor growth compared with control (FIG. 12F), confirming that KIR3DL3 is a potential novel target for immunotherapy of cancer treatment.

[0129] An antibody or an immunogenic fragment thereof that specifically binds to KIR3DL3 protein.

[0130] The antibody or the immunogenic fragment thereof of paragraph 129, wherein the antibody or the immunogenic fragment thereof specifically binds to a KIR3DL3 epitope comprising the whole extracellular domain or a portion thereof.

[0131] The antibody or the immunogenic fragment of paragraph 130, wherein the antibody or the immunogenic fragment thereof binds to the KIR3DL3 D0 domain, the KIR3DL3 D1 domain, or KIR3DL3 D2 domain.

[0132] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VH region comprising CDR1, CDR2, and CDR3, having an amino acid sequence of SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0133] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VH region comprising at least one CDR that is 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0134] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VH region comprising at least two CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0135] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VH region comprising at least three CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 31, 33, 35, 54, 56, 76, 78, 80, 100, 102, 104, 124, 126, 128, 148, 150, 152, 172, 174, 176, 196, 198, 200, 220, 222, 224, 244, 246, 248, 268, 270, 272, 292, 294, 296, 316, 318, or 320.

[0136] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VL region comprising CDR1, CDR2, and CDR3, having an amino acid sequence of SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0137] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VL region comprising at least one CDR that is 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0138] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VL region comprising at least two CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0139] The antibody or immunogenic fragment thereof of paragraph 129 or 130, comprising a VL region comprising at least three CDRs that are 80% identical to an amino acid sequence selected from SEQ ID NOs: 19, 21, 23, 43, 45, 47, 64, 66, 68, 88, 90, 92, 112, 114, 116, 136, 138, 140, 160, 162, 164, 184, 186, 188, 208, 210, 212, 232, 234, 236, 256, 258, 260, 280, 282, 284, 304, 306, 308, 328, 330, or 332.

[0140] The antibody of any one of paragraphs 129–139, wherein the antibody is a monoclonal antibody.

[0141] The antibody of any one of paragraphs 129–139, wherein the antibody is a chimeric antibody, a human antibody, or a humanized antibody.

[0142] The antibody or the immunogenic fragment thereof any one of paragraphs 129–139, comprising the amino acid sequence selected from SEQ ID NOs: 7, 9, 11, 19, 21, 23, 31, 33, 35, 43, 45, 47, 54, 56, 64, 66, 68, 76, 78, 80, 88, 90, 92, 100, 102, 104, 112, 114, 116, 124, 126, 128, 136, 138, 140, 148, 150, 152, 160, 162, 164, 172, 174, 176, 184, 186, 188, 196, 198, 200, 208, 210, 212, 220, 222, 224, 232, 234, 236, 244, 246, 248, 256, 258, 260, 268, 270, 272, 280, 282, 284, 292, 294, 296, 304, 306, 308, 316, 318, 320, 328, 330, or 332.

[0143] The antibody of paragraph 140, wherein the antibody is monoclonal 8G7, monoclonal 26E10, monoclonal 26E2, monoclonal 31C4, monoclonal 34B10, monoclonal 37A3, monoclonal 12A10, monoclonal 3B7, monoclonal 11G8, monoclonal 14F8, monoclonal 15D2, monoclonal 29H7, monoclonal 30D10, or monoclonal 51C3.

[0144] The antibody of paragraph 141, wherein the antibody is humanized 8G7, humanized 26E10, humanized 26E2, humanized 31C4, humanized 34B10, humanized 37A3, humanized 12A10, humanized 3B7, humanized 11G8, humanized 14F8, humanized 15D2, humanized 29H7, humanized 30D10, or humanized 51C3.

[0145] A fusion polypeptide comprising the antibody or the immunogenic fragment thereof of any one of paragraphs 129–144.

[0146] A composition comprising the antibody or the immunogenic fragment thereof according to any one of paragraphs 129–144 or the fusion polypeptide of paragraph 145.

[0147] The composition of paragraph 146, further comprising a pharmaceutically acceptable carrier.

[0148] The composition of paragraph 146 or 147, further comprising a pharmaceutically acceptable excipient.

[0149] The antibody or the immunogenic fragment thereof of any one of paragraphs 129–144, the fusion polypeptide of paragraph 145, or the composition of any one of paragraphs 146–148 for use in a therapy.

[0150] The antibody or the immunogenic fragment thereof of any one of paragraphs 129–144, the fusion polypeptide of paragraph 145, or the composition of any one of paragraphs 146–148 for use in the production of a medicament.

[0151] A nucleic acid comprising a nucleic acid encoding an antibody or an immunogenic fragment thereof, wherein the antibody or the immunogenic fragment thereof is the antibody or the immunogenic fragment thereof according to any one of paragraphs 129–144.

[0152] A nucleic acid comprising a nucleic acid encoding a fusion polypeptide, wherein the fusion polypeptide is the fusion polypeptide of paragraph 145.

[0153] A method of treating a subject having a condition, comprising administering to the subject a therapeutically effective amount of the antibody or the immunogenic fragment thereof of any one of paragraphs 129–144, the fusion polypeptide of paragraph 145, or the composition of any one of paragraphs 146–148.

[0154] The method of paragraph 153, wherein the condition is cancer.

[0155] The method of paragraph 154, wherein the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell lymphoma, B-cell lymphoma, T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B-cell prolymphocytic leukemia, T-cell lymphoma, Hodgkin's Disease, B-cell non-Hodgkin's lymphoma, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell follicular lymphoma, large cell follicular lymphoma, malignant lymphoproliferative conditions, mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, or preleukemia.

[0156] The method of paragraph 154, wherein the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, lung cancer, kidney cancer, gastric cancer, gallbladder cancer, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, environmentally induced cancers, combinations of the cancers, and metastatic lesions of the cancers.

[0157] The method of paragraph 154, wherein the cancer is a human hematologic malignancy.

[0158] The method of paragraph 157, wherein the human hematologic malignancy is selected from myeloid neoplasm, acute myeloid leukemia (AML), AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, acute leukemias of ambiguous lineage, myeloproliferative neoplasm, essential thrombocythemia, polycythemia vera, myelofibrosis (MF), primary myelofibrosis, systemic mastocytosis, myelodysplastic syndromes (MDS), myeloproliferative/myelodysplastic syndromes, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, myelodysplastic syndromes (MDS), refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (type 1), refractory anemia with excess blasts (type 2), MDS with isolated del (5q), unclassifiable MDS, myeloproliferative/myelodysplastic syndromes, chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, unclassifiable myeloproliferative/myelodysplastic syndromes, lymphoid neoplasms, precursor lymphoid neoplasms, B lymphoblastic leukemia, B lymphoblastic lymphoma, T lymphoblastic leukemia, T lymphoblastic lymphoma, mature B-cell neoplasms, diffuse large B-cell lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, Burkitt's lymphoma/leukemia, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, marginal zone lymphomas, post-transplant lymphoproliferative disorders, HIV-associated lymphomas, primary effusion lymphoma, intravascular large B-cell lymphoma, primary cutaneous B-cell lymphoma, hairy cell leukemia, multiple myeloma, monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma, or solitary plasmacytomas (solitary bone and extramedullary).

[0159] The method of paragraph 154, wherein the cancer is a metastatic cancer.

[0160] The method of paragraph 154, further comprising subjecting the subject to one or more additional cancer therapies selected from chemotherapy, radiation therapy, immunotherapy, surgery, and a combination thereof.

[0161] The method of paragraph 153, wherein the condition is an infection.

[0162] The method of paragraph 161, wherein the infection is caused by a pathogen.

- [0163]** The method of paragraph 162, wherein the pathogen is a virus.
- [0164]** The method of paragraph 163, wherein the virus is selected from the group consisting of human immunodeficiency viruses, influenza viruses, papillomaviruses, coronaviruses, hepatitis viruses, or herpesviruses.
- [0165]** The method of paragraph 162, wherein the pathogen is a bacterium.
- [0166]** The method of paragraph 165, wherein the bacterium is mycobacterium tuberculosis.
- [0167]** The method of paragraph 162, wherein the pathogen is a prion.
- [0168]** The method of paragraph 162, wherein the pathogen is a fungus.
- [0169]** The method of paragraph 168, wherein the fungus is *Pneumocystis jirovecii* (PJP).
- [0170]** The method of paragraph 162, wherein the pathogen is a parasite.
- [0171]** The method of paragraph 153, wherein the condition is an autoimmune disease or disorder.
- [0172]** The method of paragraph 171, wherein the autoimmune disease or disorder is selected from the group consisting of acute disseminated encephalomyelitis (ADEM), alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lipoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticarial, autoimmune uveitis, Behçet's disease, celiac disease, Chagas disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's syndrome, Guillain-Barré syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis.

[0173] The method of paragraph 171, wherein the autoimmune disease or disorder is adult rheumatoid arthritis.

[0174] The method of paragraph 153, wherein the condition is a transplant.

[0175] The method of paragraph 174, wherein the transplant is selected from a stem cell transplant or a bone marrow transplant.

[0176] The method of paragraph 174, wherein the transplant is selected from the group consisting of a kidney transplant, a lung transplant, a heart transplant, a pancreas transplant, a cornea transplant, or a liver transplant.

[0177] The composition of any one of paragraphs 146–148 for use in a method of treating a subject having a condition.

[0178] The composition of paragraph 177, wherein the condition is cancer.

[0179] The composition of paragraph 178, wherein the cancer is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell lymphoma, B-cell lymphoma, T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B-cell prolymphocytic leukemia, T-cell lymphoma, Hodgkin's Disease, B-cell non-Hodgkin's lymphoma, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell follicular lymphoma, large cell follicular lymphoma, malignant lymphoproliferative conditions, mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenström macroglobulinemia, or preleukemia.

[0180] The composition of paragraph 178, wherein the cancer is selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, lung cancer, kidney cancer, gastric cancer, gallbladder cancer, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the

endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, environmentally induced cancers, combinations of the cancers, and metastatic lesions of the cancers.

[0181] The composition of paragraph 178, wherein the cancer is a human hematologic malignancy.

[0182] The composition of paragraph 181, wherein the human hematologic malignancy is selected from myeloid neoplasm, acute myeloid leukemia (AML), AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, acute leukemias of ambiguous lineage, myeloproliferative neoplasm, essential thrombocythemia, polycythemia vera, myelofibrosis (MF), primary myelofibrosis, systemic mastocytosis, myelodysplastic syndromes (MDS), myeloproliferative/myelodysplastic syndromes, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, myelodysplastic syndromes (MDS), refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (type 1), refractory anemia with excess blasts (type 2), MDS with isolated del (5q), unclassifiable MDS, myeloproliferative/myelodysplastic syndromes, chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, unclassifiable myeloproliferative/myelodysplastic syndromes, lymphoid neoplasms, precursor lymphoid neoplasms, B lymphoblastic leukemia, B lymphoblastic lymphoma, T lymphoblastic leukemia, T lymphoblastic lymphoma, mature B-cell neoplasms, diffuse large B-cell lymphoma, primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, Burkitt's lymphoma/leukemia, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, mantle cell lymphoma, marginal zone lymphomas, post-transplant lymphoproliferative disorders, HIV-associated lymphomas, primary effusion lymphoma, intravascular large B-cell

lymphoma, primary cutaneous B-cell lymphoma, hairy cell leukemia, multiple myeloma, monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma, or solitary plasmacytomas (solitary bone and extramedullary).

[0183] The composition of paragraph 178, wherein the cancer is a metastatic cancer.

[0184] The composition of paragraph 178, wherein the composition is co-administered to the subject with one or more additional cancer therapies selected from chemotherapy, radiation therapy, immunotherapy, surgery, and a combination thereof.

[0185] The composition of paragraph 177, wherein the condition is an infection.

[0186] The composition of paragraph 185, wherein the infection is caused by a pathogen.

[0187] The composition of paragraph 186, wherein the pathogen is a virus.

[0188] The composition of paragraph 187, wherein the virus is selected from the group consisting of human immunodeficiency viruses, influenza viruses, papillomaviruses, coronaviruses, hepatitis viruses, or herpesviruses.

[0189] The composition of paragraph 186, wherein the pathogen is a bacterium.

[0190] The composition of paragraph 189, wherein the bacterium is mycobacterium tuberculosis.

[0191] The composition of paragraph 186, wherein the pathogen is a prion.

[0192] The composition of paragraph 186, wherein the pathogen is a fungus.

[0193] The composition of paragraph 192, wherein the fungus is *Pneumocystis jirovecii* (PJP).

[0194] The composition of paragraph 186, wherein the pathogen is a parasite.

[0195] The composition of paragraph 177, wherein the condition is an autoimmune disease or disorder.

[0196] The composition of paragraph 195, wherein the autoimmune disease or disorder is selected from the group consisting of acute disseminated encephalomyelitis (ADEM), alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease,

autoimmune lipoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticarial, autoimmune uveitis, Behçet's disease, celiac disease, Chagas disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's syndrome, Guillain-Barré syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polymyositis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjögren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis.

[0197] The composition of paragraph 195, wherein the autoimmune disease or disorder is adult rheumatoid arthritis.

[0198] The composition of paragraph 177, wherein the condition is a transplant.

[0199] The composition of paragraph 198, wherein the transplant is selected from a stem cell transplant or a bone marrow transplant.

[0200] The composition of paragraph 198, wherein the transplant is selected from the group consisting of a kidney transplant, a lung transplant, a heart transplant, a pancreas transplant, a cornea transplant, or a liver transplant.

REFERENCES

- Armentano et al. *Proc Natl Acad Sci USA* 87(16):6141-6145 (1990)
- Berkner *Biotechniques* 6(7):616-629 (1988)
- Beziat et al. *Immunology* 150(3):248-264 (2017)
- Cheng et al. *Clin Cancer Res* 24(8):1954-1964 (2018)
- Cheng et al. *Clin Cancer Res* 23(3):825-832 (2017)
- Chowdhury et al. *Science* 254(5039):1802-1805 (1991)
- Dai et al. *Proc Natl Acad Sci USA* 89(22):10892-10895 (1992)
- Danos & Mulligan *Proc Natl Acad Sci USA* 85(17):6460-6464 (1988)
- Eglitis et al. *Science* 230(4732):1395-1398 (1985)
- Ferry et al. *Proc Natl Acad Sci USA* 88(19):8377-8381 (1991)
- Flotte et al. *Am J Respir Cell Mol Biol* 7(3):349-356 (1992)
- Harris *Biochem Soc Trans* 23(4):1035-1038 (1995)
- Huber et al. *Proc Natl Acad Sci USA* 88(18):8039-8043 (1991)
- Hurle & Gross *Curr Opin Biotechnol* 5(4):428-433 (1994)
- Hwu et al. *J Immunol* 150(9):4104-4115 (1993)
- Janakiram et al. *Clin Cancer Res* 21(10):2359-2366 (2015)
- Jones et al. *Nature* 321(6069):522-525 (1986)
- Kay et al. *Hum Gene Ther* 3(6):641-647 (1992)
- Koirala et al. *Sci Rep* 6:31154 (2016)
- McLaughlin et al. *J Virol* 62(6):1963-1973 (1988)
- Presta *Curr Opin Biotechnol* 3(4):394-398 (1992)
- Riechmann et al. *Nature* 332(6162):323-327 (1988)
- Rosenfeld et al. *Science* 252(5004):431-434 (1991)
- Rosenfeld et al. *Cell* 68(1):143-155 (1992)
- Samulski et al. *J Virol* 63(9):3822-3828 (1989)
- van Beusechem et al. *Proc Natl Acad Sci USA* 89(16):7640-7644 (1992)
- Vaswani & Hamilton *Ann Allergy Asthma Immunol* 81(2):105-115 (1998)
- Wilson et al. *Proc Natl Acad Sci USA* 85(9):3014-3018 (1988)
- Zhao et al. *Proc Natl Acad Sci USA* 110(24):9879-9884 (2013)