

ANTI-LY6K ANTIBODIES AND METHODS OF USE**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of and priority to United States Provisional Patent Applications Serial Number 63/605,977, filed December 4, 2023; Serial Number 63/662,231, filed June 20, 2024; and Serial Number 63/686,563, filed August 23, 2024, the contents of which are hereby incorporated by reference in their entirety.

REFERENCE TO SEQUENCE LISTING

[0002] This application contains a sequence listing which has been submitted electronically in ST.26 format and is hereby incorporated by reference in its entirety. Said ST.26 copy, created on December 3, 2024, is named "214967_seqlist.xml" and is 223,249 bytes in size.

FIELD

[0003] The present disclosure relates to antibodies that are specific for human lymphocyte antigen 6 family member K (LY6K), and methods of use thereof.

BACKGROUND

[0004] The lymphocyte antigen 6 (LY6) family is a group of cysteine-rich proteins that share a common structure, are expressed in various tissues, and exhibit a wide variety of cellular functions. LY6 proteins are anchored to the cell membrane via glycosylphosphatidylinositol (GPI) anchor or secreted, and they are involved in cell proliferation, cell migration, cell-cell interactions, immune cell maturation, macrophage activation, and cytokine production. Dysregulated expression of LY6 family members is associated with tumorigenesis and autoimmune diseases, and many LY6 proteins are used as tumor markers and as potential therapeutic targets. Lymphocyte antigen 6 family member K (LY6K) is a cell surface protein that is upregulated in numerous types of cancer, including esophageal squamous cell carcinoma, bladder cancer, and breast cancer, and contributes to cell growth, migration, invasion, and immune escape.

[0005] Thus, there is a need for therapies targeting LY6K.

SUMMARY

[0006] The present disclosure provides antibodies and polypeptides that specifically bind to LY6K (e.g., human LY6K). Also provided are pharmaceutical compositions comprising these antibodies, nucleic acids encoding these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies. The

antibodies provided herein are particularly advantageous because they specifically bind LY6K-expressing cancer cells, allowing targeted delivery of therapeutic and diagnostic agents, and therefore have utility in the treatment and diagnosis of cancer (e.g., LY6K-expressing cancer).

[0007] In one aspect, provided herein is an antibody that specifically binds human LY6K, the antibody comprising a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34 and a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68.

[0008] In certain embodiments, the VH amino acid sequence and VL amino acid sequence are as set forth in: SEQ ID NOs: 1 and 35, 2 and 36, 3 and 37, 4 and 38, 5 and 39, 6 and 40, 7 and 41, 8 and 42, 9 and 43, 10 and 44, 11 and 45, 12 and 46, 13 and 47, 14 and 48, 15 and 49, 16 and 50, 17 and 51, 18 and 52, 19 and 53, 20 and 54, 21 and 55, 22 and 56, 23 and 57, 24 and 58, 25 and 59, 26 and 60, 27 and 61, 28 and 62, 29 and 63, 30 and 64, 31 and 65, 32 and 66, 33 and 67, or 34 and 68, respectively.

[0009] In certain embodiments, the antibody comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in: SEQ ID NOs: 69, 90, and 124; 70, 91, and 125; 71, 92, and 126; 72, 93, and 127; 69, 94, and 124; 73, 95, and 128; 74, 96, and 129; 75, 97, and 130; 74, 98, and 131; 76, 99, and 132; 77, 100, and 133; 78, 101, and 134; 79, 102, and 135; 74, 103, and 136; 80, 104, and 137; 74, 105, and 138; 74, 106, and 139; 81, 107, and 140; 81, 108, and 141; 82, 109, and 142; 83, 110, and 143; 84, 99, and 144; 85, 111, and 145; 81, 112, and 146; 86, 113, and 147; 87, 114, and 148; 74, 115, and 149; 74, 116, and 150; 74, 117, and 151; 88, 118, and 152; 89, 119, and 153; 81, 120, and 154; 74, 121, and 155; 85, 122, and 156; or 86, 123, and 157, respectively.

[0010] In certain embodiments, the antibody comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in: SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs: 174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198; SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs:

178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

[0011] In certain embodiments, the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in: SEQ ID NOs: 69, 90, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 70, 91, 125, 159, WAS, and SEQ ID NO: 199; SEQ ID NOs: 71, 92, 126, 160, STT, and SEQ ID NO: 200; SEQ ID NOs: 72, 93, 127, 161, WAS, and SEQ ID NO: 201; SEQ ID NOs: 69, 94, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 73, 95, 128, 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 74, 96, 129, 163, 185, and 203; SEQ ID NOs: 75, 97, 130, 164, 185, and 204; SEQ ID NOs: 74, 98, 131, 165, 185, and 205; SEQ ID NOs: 76, 99, 132, 166, 186, and 206; SEQ ID NOs: 77, 100, 133, 167, 187, and 207; SEQ ID NOs: 78, 101, 134, 168, 188, and 208; SEQ ID NOs: 79, 102, 135, 169, 186, and 209; SEQ ID NOs: 74, 103, 136, 170, 185, and 198; SEQ ID NOs: 80, 104, 137, 169, 189, and 210; SEQ ID NOs: 74, 105, 138, 170, 185, and 211; SEQ ID NOs: 74, 106, 139, 171, 187, and 212; SEQ ID NOs: 81, 107, 140, 172, 187, and 213; SEQ ID NOs: 81, 108, 141, 173, 190, and 214; SEQ ID NOs: 82, 109, 142, 174, 191, and 215; SEQ ID NOs: 83, 110, 143, 175, 186, and 216; SEQ ID NOs: 84, 99, 144, 176, 186, and 217; SEQ ID NOs: 85, 111, 145, 170, 192, and 198; SEQ ID NOs: 81, 112, 146, 171, 193, and 218; SEQ ID NOs: 86, 113, 147, 177, 187, and 219; SEQ ID NOs: 87, 114, 148, 178, 189, and 220; SEQ ID NOs: 74, 115, 149, 179, 187, and 221; SEQ ID NOs: 74, 116, 150, 165, 185, and 222; SEQ ID NOs: 74, 117, 151, 180, 187, and 223; SEQ ID NOs: 88, 118, 152, 181, 194, and 224; SEQ ID NOs: 89, 119, 153, 182, 195, and 199; SEQ ID NOs: 81, 120, 154, 172, 187, and 225; SEQ ID NOs: 74, 121, 155, 165, 185, and 222; SEQ ID NOs: 85, 122, 156, 183, 196, and 226; or SEQ ID NOs: 86, 123, 157, 184, 197, and 227, respectively.

[0012] In certain embodiments, the antibody comprises the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34. In certain embodiments, the antibody comprises a heavy chain constant region, optionally selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. In certain embodiments, the antibody comprises a heavy chain constant region that is a variant of a wild-type heavy chain constant region, wherein the variant heavy chain constant region binds to an FcγR with lower affinity than the wild-type heavy chain constant region binds to the FcγR. In certain embodiments, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 228 or 229.

[0013] In certain embodiments, the antibody comprises the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 230 or 231.

[0014] In certain embodiments, the VH and VL comprise the amino acid sequences set forth in: SEQ ID NOs: 1 and 35, 2 and 36, 3 and 37, 4 and 38, 5 and 39, 6 and 40, 7 and 41, 8 and 42, 9 and 43, 10 and 44, 11 and 45, 12 and 46, 13 and 47, 14 and 48, 15 and 49, 16 and 50, 17 and 51, 18 and 52, 19 and 53, 20 and 54, 21 and 55, 22 and 56, 23 and 57, 24 and 58, 25 and 59, 26 and 60, 27 and 61, 28 and 62, 29 and 63, 30 and 64, 31 and 65, 32 and 66, 33 and 67, or 34 and 68, respectively.

[0015] In another aspect, provided herein is an antibody that specifically binds to an amino acid sequence selected from the group consisting of SEQ ID NOs: 233-238. In another aspect, provided herein is an antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 233 and 239. In another aspect, provided herein is an antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 234 and 240. In another aspect, provided herein is an antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 237 and 247.

[0016] In certain embodiments, an antibody provided herein is a multispecific antibody comprising a CD3-binding region, optionally wherein the CD3-binding region comprises a single-chain fragment variable (scFv) that specifically binds to CD3, optionally human CD3.

[0017] In another aspect, provided herein is a polypeptide comprising a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34. In certain embodiments, the VH comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 69, 90, and 124; 70, 91, and 125; 71, 92, and 126; 72, 93, and 127; 69, 94, and 124; 73, 95, and 128; 74, 96, and 129; 75, 97, and 130; 74, 98, and 131; 76, 99, and 132; 77, 100, and 133; 78, 101, and 134; 79, 102, and 135; 74, 103, and 136; 80, 104, and 137; 74, 105, and 138; 74, 106, and 139; 81, 107, and 140; 81, 108, and 141; 82, 109, and 142; 83, 110, and 143; 84, 99, and 144; 85, 111, and 145; 81, 112, and 146; 86, 113, and 147; 87, 114, and 148; 74, 115, and 149; 74, 116, and 150; 74, 117, and 151; 88, 118, and 152; 89, 119, and 153; 81, 120, and 154; 74, 121, and 155; 85, 122, and 156; or 86, 123, and 157, respectively.

[0018] Also provided herein is a polypeptide comprising a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the VL comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ

ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs: 174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198; SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs: 178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

[0019] Also provided herein is a polypeptide comprising the amino acid sequence set forth in any one of SEQ ID NOs: 1-68.

[0020] In certain embodiments, an antibody or polypeptide provided herein is conjugated to a cytotoxic agent, cytostatic agent, toxin, radionuclide, or detectable label.

[0021] In another aspect, provided herein is a polynucleotide encoding: a VH, a VL, a heavy chain, and/or a light chain of an antibody or a polypeptide described herein. Also provided is a vector comprising a polynucleotide described herein. Also provided is a recombinant host cell comprising a polynucleotide described herein; a vector described herein; a polynucleotide encoding a heavy chain variable region or a heavy chain of an antibody described herein and a second polynucleotide encoding a light chain variable region or a light chain of an antibody described herein; and/or a first vector comprising a first polynucleotide encoding a heavy chain variable region or a heavy chain of an antibody described herein and a second vector comprising a second polynucleotide encoding a light chain variable region or a light chain of an antibody described herein.

[0022] In another aspect provided herein is a composition comprising an antibody, a polypeptide, a polynucleotide, a vector, and/or a host cell described herein and a pharmaceutically acceptable carrier or excipient.

[0023] In another aspect, provided herein is a method of producing an antibody, the method comprising culturing a host cell described herein under suitable conditions such that a polynucleotide is expressed, and the antibody is produced.

[0024] Also provided herein is a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of: an antibody described herein;

a polypeptide described herein; a polynucleotide described herein; a vector described herein; a host cell described herein; and/or a composition described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] **FIG. 1** shows that exemplary anti-LY6K antibodies provided herein selectively bind LY6K, according to aspects of the present disclosure. Depicted are the plate reading results of ELISA assays measuring the binding of the indicated anti-LY6K antibodies to LY6K, LY6E, LY6D, LY6H, and BSA (negative control).

[0026] **FIG. 2** shows that exemplary anti-LY6K antibodies provided herein detect LY6K, according to aspects of the present disclosure. Depicted in the left panel are the results of a capture ELISA measuring the sensitivity of the indicated anti-LY6K antibodies, as well as positive control commercially available anti-LY6K antibodies from R&D Systems and Abcam, for detecting LY6K. The table in the right panel indicates the sensitivity and half maximal effective concentration (EC50) for each of the indicated antibodies.

[0027] **FIG. 3** shows that an anti-LY6K antibody provided herein is internalized into cells, according to aspects of the present disclosure. Depicted is a representative fluorescence plot for anti-LY6K antibody 3082 labeled with pH-sensitive dye. Upon internalization into OVCAR-8 cells, the antibody is endocytosed and releases fluorescent signal. Also depicted are results for negative control hulgG1 and positive control trastuzumab, a known commercially available internalizer.

[0028] **FIG. 4** shows that an anti-LY6K antibody provided herein detects LY6K, according to aspects of the present disclosure. Depicted are representative IHC images showing detection of LY6K in OVCAR-8 cells, 293 LY6K cells, and 293 cells (negative control) by anti-LY6K antibody 2660, a commercially available positive control anti-LY6K antibody (Abcam), and IgG negative control.

[0029] **FIG. 5** shows that anti-LY6K bispecific T cell engagers provided herein kill tumor cells, according to aspects of the present disclosure. Depicted is a plot showing percent killing of OVCAR-8 tumor cells by addition of increasing concentrations of L2K formatted anti-LY6K bispecific T cell engagers based on the indicated anti-LY6K antibodies (3785, 3520, 2660, 3741) and of a 4D5-based 1+1 T cell engager against Her2 as a comparison.

DETAILED DESCRIPTION

[0030] The instant disclosure provides anti-LY6K antibodies and polypeptides. Also provided are pharmaceutical compositions comprising these antibodies, nucleic acids encoding

these antibodies, expression vectors and host cells for making these antibodies, and methods of treating a subject using these antibodies. The antibodies disclosed herein are particularly useful for diagnosing and/or treating cancer in a subject.

Definitions

[0031] As used herein, the term “LY6K” refers to lymphocyte antigen 6 family member K, a membrane-anchored protein that is highly expressed in cancer cells and tissues. As used herein, the term “human LY6K” refers to a protein encoded by a wild-type human LY6K gene (e.g., the gene set forth in NM_017527.4). The amino acid sequence of an exemplary human LY6K protein (as set forth in RefSeq NP_059997.3) is

MALLALLLVVALPRVWTDANLTARQRDPEDSQRTDEGDNRVWCHVCERENT
FECQNPRRCKWTEPYCVIAAVKIFPRFFMVAKQCSAGCAAMERPKPEEKRFLL
EEMPFFYLKCKKIRYCNLEGPPINSSVFKEYAGSMGESCGGLWLAILLLLASIA
AGLSLS (SEQ ID NO: 232).

[0032] As used herein, the terms “antibody” and “antibodies” include full-length antibodies, antigen-binding fragments of full-length antibodies, and molecules comprising antibody CDRs, VH regions, and/or VL regions. Examples of antibodies include, without limitation, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain-antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, bispecific T cell engagers (BiTEs), chimeric antigen receptors, single domain antibodies, monovalent antibodies, single-chain antibodies or single-chain Fvs (scFv), camelized antibodies, affibodies, Fab fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-anti-Id antibodies), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, or IgY), any class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, or IgA₂), or any subclass (e.g., IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (e.g., human IgG₁ or IgG₄) or subclass thereof. In a specific embodiment, the antibody is a humanized monoclonal antibody. In another specific embodiment, the antibody is a human monoclonal antibody.

[0033] “Multispecific antibodies” are antibodies (*e.g.*, bispecific antibodies) that specifically bind to two or more different antigens or two or more different regions of the same antigen. Multispecific antibodies include bispecific antibodies that contain two different antigen-binding sites (exclusive of the Fc region). Multispecific antibodies can include, for example, recombinantly produced antibodies, human antibodies, humanized antibodies, resurfaced antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, heteroconjugate antibodies, linked single-chain antibodies or linked-single-chain Fvs (scFv), camelized antibodies, affybodies, linked Fab fragments, F(ab')₂ fragments, chemically-linked Fvs, and disulfide-linked Fvs (sdFv). Multispecific antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, or IgY), any class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, or IgA₂), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, multispecific antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG₁, IgG₂, or IgG₄) or subclass thereof.

[0034] As used herein, the term “CDR” or “complementarity determining region” means the noncontiguous antigen combining sites found within the variable regions of heavy and light chain polypeptides. These particular regions have been described by, for example, Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest. (1991), by Chothia *et al.*, J. Mol. Biol. 196: 901-917 (1987), and by MacCallum *et al.*, J. Mol. Biol. 262: 732-745 (1996), all of which are herein incorporated by reference in their entireties, where the definitions include overlapping or subsets of amino acid residues when compared against each other. In certain embodiments, the term “CDR” is a CDR as defined by MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996) and Martin A. “Protein Sequence and Structure Analysis of Antibody Variable Domains,” in *Antibody Engineering*, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In certain embodiments, the term “CDR” is a CDR as defined by Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest. (1991). In certain embodiments, heavy chain CDRs and light chain CDRs of an antibody are defined using different conventions. In certain embodiments, heavy chain CDRs and/or light chain CDRs are defined by performing structural analysis of an antibody and identifying residues in the variable region(s) predicted to make contact with an epitope region of a target molecule (*e.g.*, human LY6K). CDRH1, CDRH2, and CDRH3 denote the heavy chain CDRs, and CDRL1, CDRL2, and CDRL3 denote the light chain CDRs.

[0035] As used herein, the terms “variable region” and “variable domain” are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids or 110 to 125 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable region are called framework regions (FRs). Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In certain embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[0036] As used herein, the terms “VH” and “VL” refer to antibody heavy and light chain variable regions, respectively, as described in Kabat *et al.*, (1991) Sequences of Proteins of Immunological Interest (NIH Publication No. 91-3242, Bethesda), which is herein incorporated by reference in its entirety.

[0037] As used herein, the term “constant region” is common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain, which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with an Fc receptor (*e.g.*, Fc gamma receptor).

[0038] As used herein, the term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ), based on the amino acid sequence of the constant region, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG₁, IgG₂, IgG₃, and IgG₄.

[0039] As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ), based on the amino acid sequence of the constant region. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0040] As used herein, the term “specifically binds” refers to the specificity of a binding molecule (e.g., an antibody) for an antigen, as is understood by one skilled in the art. Binding molecules that specifically bind to an antigen typically bind to the antigen with an equilibrium dissociation constant (KD) of less than 1×10^{-6} M, as measured by, e.g., ELISA assay, surface plasmon resonance, or other suitable assays known in the art. The skilled worker will appreciate that, in certain embodiments, a binding molecule can specifically bind to different antigens, e.g., different antigens that share a common epitope that is recognized by the binding molecule.

[0041] As used herein, the term “affinity” refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (KD). Affinity can be measured by common methods known in the art, including those described herein.

[0042] As used herein, the term “EU numbering system” refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman, G.M. *et al.*, Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat *et al.*, Sequences of Proteins of Immunological Interest, U.S. Dept. Health and Human Services, 5th edition, 1991, each of which is herein incorporated by reference in its entirety.

[0043] As used herein, the term “treat,” “treating,” and “treatment” refer to therapeutic or preventative measures described herein. The methods of “treatment” employ administration of an antibody to a subject having a disease or disorder, or predisposed to having such a disease or disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disease or disorder or recurring disease or disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

[0044] As used herein, the term “pharmaceutically active substance” refers to a molecule or moiety that is used to achieve a beneficial outcome in a subject. Beneficial outcomes include, but are not limited to, diagnosis, prognosis, treatment, cure and prevention (prophylaxis) of diseases and/or symptoms and/or health problems.

[0045] As used herein, the term “effective amount” in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect.

[0046] As used herein, the term “subject” includes any human or non-human animal. In certain embodiments, the subject is a human or non-human mammal. In certain embodiments, the subject is a human.

[0047] As used herein with respect to an antibody, polypeptide, or polynucleotide, the term “isolated” refers to an antibody, polypeptide, or polynucleotide that is separated from one or more contaminants (*e.g.*, polypeptides, polynucleotides, lipids, or carbohydrates, etc.) which are present in a natural source (*e.g.*, in a mouse or a human) of the antibody, polypeptide, or polynucleotide. Moreover, an “isolated” antibody, polypeptide, or polynucleotide can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. For example, the language “substantially free” includes preparations of antibody, polypeptide, or polynucleotide having less than about 15%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (in particular less than about 10%) of other material, *e.g.*, cellular material, culture medium, other nucleic acid molecules, chemical precursors, and/or other chemicals. All instances of “isolated antibodies” described herein are additionally contemplated as antibodies that may be, but need not be, isolated. All instances of “isolated polypeptides” described herein are additionally contemplated as polypeptides that may be, but need not be, isolated. All instances of “isolated polynucleotides” described herein are additionally contemplated as polynucleotides that may be, but need not be, isolated. All instances of “antibodies” described herein are additionally contemplated as antibodies that may be, but need not be, isolated. All instances of “polypeptides” described herein are additionally contemplated as polypeptides that may be, but need not be, isolated. All instances of “polynucleotides” described herein are additionally contemplated as polynucleotides that may be, but need not be, isolated.

[0048] The determination of “percent identity” between two sequences (*e.g.*, amino acid sequences or nucleic acid sequences) can be accomplished using a mathematical algorithm. A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87: 2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90: 5873-5877, each of which is herein incorporated by reference in its entirety. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul SF *et al.*, (1990) J Mol Biol 215: 403, which is herein incorporated by reference in its entirety. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecule described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score 50, wordlength=3

to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul SF *et al.*, (1997) Nuc Acids Res 25: 3389-3402, which is herein incorporated by reference in its entirety. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (*see, e.g.*, National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another specific, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4: 11-17, which is herein incorporated by reference in its entirety. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[0049] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

Anti-LY6K Antibodies

[0050] In one aspect, the instant disclosure provides antibodies that specifically bind to LY6K (*e.g.*, human LY6K). The VH, VL, CDRH and CDRL amino acid sequences of exemplary antibodies are set forth in **Tables 1-4**, respectively.

Table 1. VH amino acid sequences of exemplary anti-LY6K antibodies.

Ab	VH Amino Acid Sequence	SEQ ID
2659	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWKS GIIGYADSVKGRFTISRDNKNSLYLQMNSLRAEDTALYYCAKDSRTGLDYWGQGT LVTVSS	1
2660	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDVWMSWVRQAPGKGLEWVGRIKSKTDG GRIDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTVPYSDYWGQGT LVTVSS	2
3035	EVQLVESGGGLVQPGGSLKLSCAASGFTFSDSTLHWVRQASGKGLEWVGRI RSKANSYATAYAASVKGRFTISRDDSKNTAYLQMNSLKTEDTAVYYCHNWSYGYW GQGTLVTVSS	3
3047	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSGINWNGGS TGYADSVKGRFTISRDNKNSLYLQMNSLRAEDTALYYCARGRLFDYWGQGT LVTVSS	4
3048	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGITWKS GTIGYADSVKGRFTISRDNKNSLYLQMNSLRAEDTALYYCAKDSRTGLDYWGQGA LVTVSS	5

3055	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDFAMHWVRQAPGKGLEWVSGISWNTGT IGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCAKDGGTTGFDYWGQGT TVSS	6
3056	EVQLVESGGGLVQPGRSLRLSCAASGFTYDDYAMHWVRQVPGKGLEWVSGITWKKSI IGYADSVRGRFTVSRDSAKNSLYLQMNSLRAEDTALCYCAKDSTDGLDYWGQGT TVSS	7
3063	EVQLVESGGGLVKPGRSLRLSCAASGFTFDDFAMHWVRQAPGKGLEWVSGLSWKGHT LGYADSVKGRFTFSRDSAKNSLYLQMNSLRAEDTALYYCAKDTRSGLDYWGQGT TVSS	8
3074	EVQLVESGGGLVHPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWKT NKIDYADSVKGRFTISRDNANKNSLYLQMNSLRTEDTAFYYCAKDRREMTFDI WGQGTMTVTVSS	9
3075	QVQLVQSGSELKRPASVKVSCASGYTFIRYAMNWVRQAPGQGLEWMGWINTNTGN PTYAQGFTGRFVLSVDTSVSTAYLQISSLKVEDTAVYYCGRPGISSFEYWGQGT TVSS	10
3082	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSSSMNWVRQAPGKGLEWVSSISRSSYY IYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCAKIGSSSEGVEDY YYYYYMDVWGKGTTVTVSS	11
3090	QVQLQESGPGGLVKPSGTLSTCAVSGGSISRNSWWSVVRQTPGKGLDWIGKIYHSGS TNYNPSLKSRTISVDKSKNRFSLNLSSVTAADTAVYYCASSGSHYYNYMEVWGK GTTVTVSS	12
3096	QVQLVQSGAEVKKPGASVRVSCASGYTFTGYYIHWVRQAPGQGLEWMGWINPNSGG TNYAQKFQDRVTMTRDTSISTVYMELSLRLSDDTAVFFCAREASNFWGQGT LTVTVSS	13
3101	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWVSGITWKS GNIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCAKDTEAGLDYWGQGT LTVTVSS	14
3102	QVQLVQSGAEVKKPGASVKVSCASGYTFTGYYIHWVRQAPGQGLEWMGWINPNSGG TNYAQNFQGRVTMTRDTSINTAYMELSLRLSDDTAVYYCAKESGSPWGQGT LTVTVSS	15
3481	EVQLVESGGGLVQSGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGITWKDVT IGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCAKDTSDGLDYWGQGT LTVTVSS	16
3501	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGT IDYADSVKGRFTISRDNANKNSLYLQVNSLRAEDTALYYCAKDSPQKDYYYMDVWGK GTTVTVSS	17
3503	EVQLVESGGGLVKPGGSLRLSCAASGFISSSYMNWVRQAPGKGLEWVSSISSSSSY IYYADSEKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARQSTTVVTS DYYYYYYMDVWGKGTTVTVSS	18
3507	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSSYMNWVRQAPGKGLEWVSSISSSSDY IYYADSVKGRFTISRDDAKNSLYLQMNSLRAEDTAVYYCARGLEPNYYYYYMDVWGK GTTVTVSS	19
3514	QVQLVQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQATGQGLEWMGWMNPNSGN TGGAQKFQGRVTMTRNTSISTAYMELSSLRSEDVAVYYCRAAGYYYYYYYMDVWGK GTTVTVSS	20
3518	EVQLVESGGGLVQPGGSLKLSAASGFTFSGSAMNWVRQASGKGLEWVGRIRSKANS YATAYAASLKGRTISRDDSKNTAYLQMNSLKTEDTAVYYCTVTPFDYWGQGT LTVTVSS	21
3520	QVQLVQSGSELKKPGASVKVSCASGYTFTLYAMNWVRQAPGQGLEWMGWINTNTGN PTYAQGFTGRFVFLDTSVSTAYLQISSLKAEDTAVYYCARTNWNWSWGQGT MTVTVSS	22
3522	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAANNWIRQSPSRGLEWLGR TYYSRWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARECSG SYRFPDWGQGT LTVTVSS	23
3527	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSSYMNWVRQAPGKGLEWVSSISSTSSY IYYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARSDYYDSGSYK NYYYYYMDVWGKGTTVTVSS	24

3529	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGS TGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARENILTGYYNLYYYYMD VWGKGTITVTVSS	25
3553	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYMHVVRQAPGTGLDWMGWISPNSSG TNYAQKFQGRVTMTRDTSISTVYMEISRLRSDDTALYYCAREVGNVWGQGLTVTVSS	26
3704	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWKIIT IGYADSVKGRFTISRDNVKNLSLYLQMNSLRAEDTALYYCAKDSRTGLDYWGQGLTV VSS	27
3705	EVQLVESGGGLVHPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWKNKG IDYADSVKGRFTISRDNANKNSLYLQMNSLRTEDTALYYCAKDRIEMTFDIWGQGTMT VTVSS	28
3719	EVQLVESGGGLVQPGRSLRLSCTASGFTFNDYAMHWVRQAPGKGLEWVSGISWNSNN IDYADSVKGRFTISRDNANKNSLYMQMNSLRAEDTALYYCAKDGPPTNDADFIDWGQ TMVTVSS	29
3724	QLQLQESGPGLVKPSSETLSLTCTVSGGSINSKSYWDRQPPGKGLEWIGNIYYSG STYYNPSLKSRTISVDTSKNQFSLKLSSVTATDTAVYYCARHRGVTVTYTYWYFDLW GRGTLTVTVSS	30
3728	EVQLVESGGGLVKGPGGSLRLSCAASGFTFSDVWMSWVRQAPGKGLEWVGRIKSKTDG GRIDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTPYSDYWGQGLTV VSS	2
3741	EVQLVESGGGLVKGPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSNY IYYVDSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARQEATGNNYYYYYMDVW GKGTITVTVSS	31
3743	EVQLVESGGGLVHPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWKSGR IDYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCAKDRRELTDFDIWGQGTMT VTVSS	32
3746	EVQLVESGGGLVKGPGGSLRLSCAASGFISSYSMNWVRQAPGKGLEWVSSISSSSSY IYYADSEKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARQSTVVTSDYYYYYMDV WGKGTITVTVSS	18
3785	QVQLQQSGPGLVKPSQTLSTCAISGDSVSSNSAAWNWRQSPSRGLEWLGRITYFRS KWNNDYTLNVKNRITINPDTSKNHFSQLNSVTPEDTAVYYCAGGGYCNRTYCPDVF DIWGQGTMTVTVSS	33
3815	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGS TGYVDSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARMFYGAFDIWGQGTMT VSS	34

Table 2. VL amino acid sequences of exemplary anti-LY6K antibodies.

Ab	VL Amino Acid Sequence	SEQ ID
2659	DIVMTQTPLSSPVTGLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFPYTFGQGTKEIK	35
2660	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSDNENYLAWYQQKPGQPPKLLIYWA SSRESGVDPDRFSGSGSGTDFTLTISLQAEDVAVYYCHQYNTPTWTFGQGTKEIK	36
3035	QTVVTQEPSTLVSPPGTVTLTCASSTGAVTSYYPNWFQKPGQAPRTVIYSTTNKH SWTPARFSGSLGGAALTLGVLPEDEADYYCLLFYGGAYVFGTGKVTVL	37
3047	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWA STRESGVDPDRFSGSGSGTDFTLTISLQAEDVAVYYCQYYSTPSYTFGQGTKEIK	38
3048	DIVMTQSPPLSSPVTGLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFPYTFGQGTKEIK	39
3055	DIQMTQSPSSVSASVGDRTITCRASQGISRWLVWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQANSPRTFGQGTKEIK	40
3056	DIVMTQTPLSSPVTGLGQPASISCRSSQSLHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEGEDVGVYYCMQATEFPYTFGQGTKEIK	41

3063	DIVMTQTPLSSPVTLGQPASISCRSSQSLEHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGNGAGTDFTLKISRVEAEDVGIYYCMQATEFPFTFGGGTKVEIK	42
3074	DIVMTQTPLSSPVTLGQPASISCRSSQSLEHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGIYYCMQATQFPLTFGGGTKEIK	43
3075	DIQMTQSPSSLSASVGDRVAITCRATQDISNYLDWYQQKPGKAPKLLIYDASNLETG VPSRFGSGSGTDFTFTINSLOPEDFATYYCQYDNLPLTFGGGTKEIK	44
3082	DIQMTQSPSSLSASVGDRVTITCRASQINISYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFGSGSGTDFTLTISLQPEDFATYYCHQSYSTPLTFGGGTKEIK	45
3090	EIVLTQSPGTLSLSPGERATLSCRASQTVSSSYLVWYQQKPGQAPRLLIYGASGRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVFCQHYGSSPYTFGGGTKEIK	46
3096	DIQMTQSPSSLSASIGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETG VPSRFGSGSGSGTDFTFTISLQPEDFATYYCQYQESLPFNFGGGTKVEIK	47
3101	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSNGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVIYYCMQATQFPYTFGGGTKEIK	48
3102	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLERG VPSRFGSGSGSGTDFTFTISLQPEDFATYHCQEYDSLPTFGPGTKVDIK	49
3481	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSNGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEDVGIYYCMQAIQFPYTFGGGTKEIK	50
3501	DIQMTQSPSSLSASVGDRVTITCRTSQSISYLNWYQQKPGKAPNLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQSYITPITFGQGTREIK	51
3503	DIQMTQSPSSLSASVGDRVTITCRASQISYLNWYQQKPGKAPNLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQSYSPITFGQGTREIK	52
3507	EIVMTQSPGTLSVSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASTRAT GIPARFSGSGSGTEFTLTISLQSEDFAVYCCQYNNWPLTFGGGTKEIK	53
3514	DIVMTQSPLSLPVTGPGEASISCRSSQSLVHSNGNYLDWYLLQKPGQSPQLLIYLG NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVIYYCMQALQYTFGGGTKEIK	54
3518	DIQMTQSPSSLSASVGDRVTITCQASQDISNHLNWYQQKPGKAPKLLINDASNLETG VPSRFGSGSGSGTDFTFTISLQPEDFATYYCQYDNVPTFGGTKEIK	55
3520	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLHWYQQKPGKAPKLLIYDASNLETG VPSRFGSGSGSGTDFTFTIFSLQPEDFATYYCQHYDNLPLTFGGGTKEIK	56
3522	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSNGNTYLSWLQQRPGQPPRLLIYKIS HRFSGVPDRFSGSGAGTDFTLKIRVEAEDVGVIYYCMQATQFPYTFGGGTKEIK	57
3527	DIQMTQSPSSLSASVGDRVTITCRTSQSISYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGGGTKEIK	58
3529	DIQMTQSPSSLSASVGDRVTITCRASQISYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQSYSTSHGGGTKEIK	59
3553	DIQMTQSPTSLSTSVGDRVTITCQASQDIYNYLNWYQLKPGKAPKLLIYDASNLERG VTSRFGSGSGSGTDFTFTISLQPEDFATYYCQYDSLPTFGQGTREIK	60
3704	DIQMTQSPSSLSASVGDRVTITCRASQTISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQTYTAPLTFGPGTKEIK	61
3705	DIVMTQSPLSSPVTLGQPASISCRSSQSLEHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVIYYCMQTTQFPLTFGGGTKEIK	62
3719	DIQMTQSPSSLSASVGDRVTITCRASHSISYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCHQGYSTPLTFGGGTKEIK	63
3724	EIVLTQSPDFQSVTPKEKVTITCRASQSIGNSLHWYQQKSDQSPKLLIKYVSQSFSG VPSRFGSGSGSGTDFTLTINSLEAEDAATYYCHQSSDFPHTFGGTKEIK	64
3728	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSDNENYLAWYQQKPGQPPKLLIYWA SSRESGVPDRFSGSGSGTDFTLTISLQAEADVAVYYCHQYNTPTWTFGGGTKEIK	36
3741	DIQMTQSPSSLSASVGDRVTITCRASQISYLNWYQQNLGKAPKLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQTYSTPITFGQGTREIK	65
3743	DIVMTQTPLSSPVTLGQPASISCRSSQSLEHSDGNTYLSWLQQRPGQPPRLLIYKIS NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVIYYCMQTTQFPLTFGGGTKEIK	66
3746	DIQMTQSPSSLSASVGDRVTITCRASQISYLNWYQQKPGKAPNLLIYAASSLQSG VPSRFGSGSGSGTDFTLTISLQPEDFATYYCQSYSPITFGQGTREIK	52

3785	DIQMTQSPSSLSASVGDRTFTCRSSQSISSYLNWYQQKPGKAPNLLIYVASTLQSG VPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSYSLPLTFGGGTKVEIK	67
3815	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPFTFGQGTKVDIK	68

Table 3. CDRH amino acid sequences of exemplary anti-LY6K antibodies.

Ab	CDRH1 amino acid sequence	SEQ ID	CDRH2 amino acid sequence	SEQ ID	CDRH3 amino acid sequence	SEQ ID
2659	GFTFDDYA	69	ISWKSGLI	90	AKDSRTGLDY	124
2660	GFTFSDVW	70	IKSKTDGGRI	91	TTVPYSYD	125
3035	GFTFSDST	71	IRSKANSYAT	92	HNWSYGY	126
3047	GFTFSSYS	72	INWNGGST	93	ARGRLFDY	127
3048	GFTFDDYA	69	ITWKSGLI	94	AKDSRTGLDY	124
3055	GFTFDDFA	73	ISWNTGTI	95	AKDKGTTGFDY	128
3056	DYAMH	74	GITWKKSIIGYADSVRG	96	DSTDGLDY	129
3063	DFAMH	75	GLSWKGHTLGYADSVKG	97	DTRSGLDY	130
3074	DYAMH	74	GISWKTNKIDYADSVKG	98	DRREMTFDI	131
3075	RYAMN	76	WINTNTGNPTYAQGFTG	99	PGISSFEY	132
3082	SSSMN	77	SISRSSYYIYYADSVEG	100	IGSSSEGVEDY YMDV	133
3090	RSNWS	78	KIYHSGSTNYPNLSKS	101	SGSHYYNYMEV	134
3096	GYIYH	79	WINPNSSGGTNYAQKFQD	102	EASNF	135
3101	DYAMH	74	GITWKSIGNIYADSVKG	103	DTEAGLDY	136
3102	GYIYH	80	WINPNSSGGTNYAQNFQG	104	ESGSP	137
3481	DYAMH	74	GITWKDVTIGYADSVKG	105	DTSDGLDY	138
3501	DYAMH	74	GISWNSGTIDYADSVKG	106	DSPQKDYMDV	139
3503	SYSMN	81	SISSSSYIYYADSEKG	107	QSTVVTSDY YMDV	140
3507	SYSMN	81	SISSSSDYIYYADSVKG	108	GLEPNYYYMDV	141
3514	SYGIS	82	WMNPNSGNTGYAQKFQG	109	AGYYYYYYYMDV	142
3518	GSAMN	83	RIRSKANSYATAYASLKG	110	TPFDY	143
3520	LYAMN	84	WINTNTGNPTYAQGFTG	99	TNWS	144
3522	SNSAAWN	85	RTYYRSKWYNDYAVSVKS	111	ECSGSYYRFPD	145
3527	SYSMN	81	SISSTSSYIYYADSVKG	112	SDYYDSGSYKNYYY YMDV	146
3529	DYGMS	86	GINWNGGSTGYADSVKG	113	ENILTGYYNLYYYY MDV	147

3553	GYMH	87	WISPNSSGGTNYAQKFQG	114	EVGNY	148
3704	DYAMH	74	GISWKIITIGYADSVKG	115	DSRTGLDY	149
3705	DYAMH	74	GISWKNGKIDYADSVKG	116	DRIEMTFDI	150
3719	DYAMH	74	GISWNSNNIDYADSVKG	117	DGPGTTNDAFDI	151
3724	SKSYWD	88	NIYYSGSTYYNPSLKS	118	HRGVTVTTYWYFDL	152
3728	DVWMS	89	RIKSKTDGGRIDYAAPVKG	119	VPYSDY	153
3741	SYSMN	81	SISSSSNYYIYVDSVKG	120	QEATGNYYYYYMD V	154
3743	DYAMH	74	GISWKSGRIDYADSVKG	121	DRRELTFDI	155
3746	SYSMN	81	SISSSSYIYYADSEKG	107	QSTVVTSDYYYYYM DV	140
3785	SNSAAWN	85	RTYFRSKWNNDYTLVKVN	122	GGYCNRTYCPDVFD I	156
3815	DYGMS	86	GINWNNGGSTGYVDSVKG	123	MFYGAFDI	157

Table 4. CDRL amino acid sequences of exemplary anti-LY6K antibodies.

Ab	CDRL1 amino acid sequence	SEQ ID	CDRL2 amino acid sequence	SEQ ID	CDRL3 amino acid sequence	SEQ ID
2659	QSLVHSDGNTY	158	KIS	--	MQATQFPYT	198
2660	QSVLYSSDNENY	159	WAS	--	HQYYNTPWT	199
3035	TGAVTSYYY	160	STT	--	LLFYGGAYV	200
3047	QSVLYSSNNKNY	161	WAS	--	QQYYSTPSYT	201
3048	QSLVHSDGNTY	158	KIS	--	MQATQFPYT	198
3055	QGISRW	162	AAS	--	QQANSFPRT	202
3056	RSSQSLHSNGNTYLS	163	KISNRFS	185	MQATEFPYT	203
3063	RSSQSLEHSDGNTYLS	164	KISNRFS	185	MQATEFPFT	204
3074	RSSQSLEHSDGNTYLS	165	KISNRFS	185	MQATQFPLT	205
3075	RATQDISNYLD	166	DASNLET	186	QQYDNLPLT	206
3082	RASQNINSYLN	167	AASSLQS	187	HQSYSTPLT	207
3090	RASQTVSSSYLV	168	GASGRAT	188	QHYGSSPYT	208
3096	QASQDISNYLN	169	DASNLET	186	QQYESLPFN	209
3101	RSSQSLVHSNGNTYLS	170	KISNRFS	185	MQATQFPYT	198
3102	QASQDISNYLN	169	DASNLER	189	QEYDSLPT	210
3481	RSSQSLVHSNGNTYLS	170	KISNRFS	185	MQAIQFPYT	211
3501	RTSQSISSYLN	171	AASSLQS	187	QQSYITPIT	212
3503	RASQISNYLN	172	AASSLQS	187	QQSYSPIT	213

3507	RASQSVSSSYLA	173	GASTRAT	190	QQYNNWPLT	214
3514	RSSQSLHLSNGYNYLD	174	LGSNRAS	191	MQALQTYT	215
3518	QASQDISNHLN	175	DASNLET	186	QQYDNVPYT	216
3520	QASQDISNYLH	176	DASNLET	186	QHYDNLPLT	217
3522	RSSQSLVHSNGNTYLS	170	KISHRFS	192	MQATQFPYT	198
3527	RTSQSISSYLN	171	AASSLQR	193	QQSYSTPLT	218
3529	RASQSISSYLN	177	AASSLQS	187	QQSYSTS	219
3553	QASQDIYNYLN	178	DASNLER	189	QQYDSLPIIT	220
3704	RASQTISSYLN	179	AASSLQS	187	QQTYTAPLT	221
3705	RSSQSLEHSNGNTYLS	165	KISNRFS	185	MQTTQFPLT	222
3719	RASHSISSYLN	180	AASSLQS	187	HQGYSTPLT	223
3724	RASQSIGNSLH	181	YVSQSFS	194	HQSSDFPHT	224
3728	KSSQSVLYSSDNENYLA	182	WASSRES	195	HQYYNTPWT	199
3741	RASQSISSYLN	172	AASSLQS	187	QQTYSTPIT	225
3743	RSSQSLEHSNGNTYLS	165	KISNRFS	185	MQTTQFPLT	222
3746	RASQSISSYLN	172	AASSLQS	187	QQSYSPPIIT	213
3785	RSSQSISSYLN	183	VASTLQS	196	QQSYSIPLT	226
3815	RASQSVSSNYLA	184	GASSRAT	197	QQYGSSPFT	227

[0051] The individual CDRs of an antibody disclosed herein can be determined according to any CDR numbering scheme known in the art.

[0052] In certain embodiments, one or more of the CDRs of an antibody disclosed herein can be determined according to Kabat *et al.*, J. Biol. Chem. 252, 6609-6616 (1977) and Kabat *et al.*, Sequences of protein of immunological interest (1991), each of which is herein incorporated by reference in its entirety.

[0053] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the Kabat numbering scheme. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the Kabat numbering scheme.

[0054] In certain embodiments, one or more of the CDRs of an antibody disclosed herein can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (*see, e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol

Biol 227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226, all of which are herein incorporated by reference in their entireties).

[0055] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the Chothia numbering system. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the Chothia numbering system.

[0056] In certain embodiments, one or more of the CDRs of an antibody disclosed herein can be determined according to MacCallum RM *et al.*, (1996) J Mol Biol 262: 732-745, herein incorporated by reference in its entirety. *See also*, e.g., Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in *Antibody Engineering*, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001), herein incorporated by reference in its entirety.

[0057] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the MacCallum numbering system. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the MacCallum numbering system.

[0058] In certain embodiments, the CDRs of an antibody disclosed herein can be determined according to the IMGT numbering system as described in: Lefranc M-P, (1999) The Immunologist 7: 132-136; Lefranc M-P *et al.*, (1999) Nucleic Acids Res 27: 209-212, each of which is herein incorporated by reference in its entirety; and Lefranc M-P *et al.*, (2009) Nucleic Acids Res 37: D1006-D1012.

[0059] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the IMGT numbering system. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the IMGT numbering system.

[0060] In certain embodiments, the CDRs of an antibody disclosed herein can be determined according to the AbM numbering scheme, which refers to AbM hypervariable regions, which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.), herein incorporated by reference in its entirety.

[0061] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the AbM numbering scheme. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the AbM numbering scheme.

[0062] In certain embodiments, the CDRs of an antibody disclosed herein can be determined according to the AHO numbering system, as described in Honegger and Plückthun, A., J. Mol. Biol. 309:657-670 (2001), herein incorporated by reference in its entirety.

[0063] In certain embodiments, an antibody provided herein comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any of SEQ ID NOs: 1-34 as determined by the AHO numbering system. In certain embodiments, an antibody provided herein comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any of SEQ ID NOs: 35-68 as determined by the AHO numbering system.

[0064] In certain embodiments, the individual CDRs of an antibody disclosed herein are each independently determined according to one of the Kabat, Chothia, MacCallum, IMGT, AHO, or AbM numbering schemes, or by structural analysis of the multispecific molecule, wherein the structural analysis identifies residues in the variable region(s) predicted to make contact with an epitope region of LY6K.

[0065] In certain embodiments, the instant disclosure provides an antibody that specifically binds LY6K (*e.g.*, human LY6K) comprising a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of a VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of a VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68, wherein each CDR is independently determined according to one of the Kabat, Chothia, MacCallum, IMGT, AHO, or AbM numbering schemes, or by structural analysis of the multispecific molecule, wherein the structural analysis identifies residues in the variable region(s) predicted to make contact with an epitope region of LY6K (*e.g.*, human LY6K).

[0066] In certain embodiments, the instant disclosure provides an antibody that specifically binds LY6K (*e.g.*, human LY6K) comprising a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of a VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of a VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68, wherein the VH amino acid sequence and the VL amino acid sequence are from the same antibody (*i.e.*, as shown in **Tables 1** and **2**), and wherein each CDR is independently determined according to one of the

Kabat, Chothia, MacCallum, IMGT, AHO, or AbM numbering schemes, or by structural analysis of the multispecific molecule, wherein the structural analysis identifies residues in the variable region(s) predicted to make contact with an epitope region of LY6K (*e.g.*, human LY6K).

[0067] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences of the VH and VL amino acid sequences set forth in SEQ ID NOs: 1 and 35; SEQ ID NOs: 2 and 36; SEQ ID NOs: 3 and 37; SEQ ID NOs: 4 and 38; SEQ ID NOs: 5 and 39; SEQ ID NOs: 6 and 40; SEQ ID NOs: 7 and 41; SEQ ID NOs: 8 and 42; SEQ ID NOs: 9 and 43; SEQ ID NOs: 10 and 44; SEQ ID NOs: 11 and 45; SEQ ID NOs: 12 and 46; SEQ ID NOs: 13 and 47; SEQ ID NOs: 14 and 48; SEQ ID NOs: 15 and 49; SEQ ID NOs: 16 and 50; SEQ ID NOs: 17 and 51; SEQ ID NOs: 18 and 52; SEQ ID NOs: 19 and 53; SEQ ID NOs: 20 and 54; SEQ ID NOs: 21 and 55; SEQ ID NOs: 22 and 56; SEQ ID NOs: 23 and 57; SEQ ID NOs: 24 and 58; SEQ ID NOs: 25 and 59; SEQ ID NOs: 26 and 60; SEQ ID NOs: 27 and 61; SEQ ID NOs: 28 and 62; SEQ ID NOs: 29 and 63; SEQ ID NOs: 30 and 64; SEQ ID NOs: 31 and 65; SEQ ID NOs: 32 and 66; SEQ ID NOs: 33 and 67; or SEQ ID NOs: 34 and 68, respectively.

[0068] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VH comprising a CDRH1, CDRH2, and/or CDRH3 amino acid sequence set forth in **Table 3**. In certain embodiments, the antibody comprises a VH comprising a CDRH1 amino acid sequence set forth in any one of SEQ ID NOs: 69-89. In certain embodiments, the antibody comprises a VH comprising a CDRH2 amino acid sequence set forth in any one of SEQ ID NOs: 90-123. In certain embodiments, the antibody comprises a VH comprising a CDRH3 amino acid sequence set forth in any one of SEQ ID NOs: 124-157.

[0069] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of any of the antibodies in **Table 3**. In certain embodiments, the antibody comprises a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 69, 90, and 124; SEQ ID NOs: 70, 91, and 125; SEQ ID NOs: 71, 92, and 126; SEQ ID NOs: 72, 93, and 127; SEQ ID NOs: 69, 94, and 124; SEQ ID NOs: 73, 95, and 128; SEQ ID NOs: 74, 96, and 129; SEQ ID NOs: 75, 97, and 130; SEQ ID NOs: 74, 98, and 131; SEQ ID NOs: 76, 99, and 132; SEQ ID NOs: 77, 100, and 133; SEQ ID NOs: 78, 101, and 134; SEQ ID NOs: 79, 102, and 135; SEQ ID NOs:

74, 103, and 136; SEQ ID NOs: 80, 104, and 137; SEQ ID NOs: 74, 105, and 138; SEQ ID NOs: 74, 106, and 139; SEQ ID NOs: 81, 107, and 140; SEQ ID NOs: 81, 108, and 141; SEQ ID NOs: 82, 109, and 142; SEQ ID NOs: 83, 110, and 143; SEQ ID NOs: 84, 99, and 144; SEQ ID NOs: 85, 111, and 145; SEQ ID NOs: 81, 112, and 146; SEQ ID NOs: 86, 113, and 147; SEQ ID NOs: 87, 114, and 148; SEQ ID NOs: 74, 115, and 149; SEQ ID NOs: 74, 116, and 150; SEQ ID NOs: 74, 117, and 151; SEQ ID NOs: 88, 118, and 152; SEQ ID NOs: 89, 119, and 153; SEQ ID NOs: 81, 120, and 154; SEQ ID NOs: 74, 121, and 155; SEQ ID NOs: 85, 122, and 156; or SEQ ID NOs: 86, 123, and 157; respectively.

[0070] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VL comprising a CDRL1, CDRL2, and/or CDRL3 amino acid sequence set forth in **Table 4**. In certain embodiments, the antibody comprises a VL comprising a CDRL1 amino acid sequence set forth in any one of SEQ ID NOs: 158-184. In certain embodiments, the antibody comprises a VL comprising a CDRL2 amino acid sequence set forth in any one of KIS, WAS, STT, AAS, and SEQ ID NOs: 185-197. In certain embodiments, the antibody comprises a VL comprising a CDRL3 amino acid sequence set forth in any one of SEQ ID NOs: 198-227.

[0071] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of any of the antibodies in **Table 4**. In certain embodiments, the antibody comprises a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs: 174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198; SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs: 178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

[0072] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VH comprising a CDRH1, CDRH2, and/or CDRH3 amino acid sequence set forth in **Table 3** and a VL comprising a CDRL1, CDRL2, and/or CDRL3 amino acid sequence set forth in **Table 4**, wherein 2, 3, 4, 5, or 6 of the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences are from the same antibody (*i.e.*, as shown in **Tables 3** and **4**). In certain embodiments, the antibody comprises a VH comprising CDRH1, CDRH2, and CDRH3 regions, and a VL comprising CDRL1, CDRL2, and CDRL3 regions, wherein the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 regions comprise the amino acid sequences set forth in SEQ ID NOs: 69, 90, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 70, 91, 125, 159, WAS, and SEQ ID NO: 199; SEQ ID NOs: 71, 92, 126, 160, STT, and SEQ ID NO: 200; SEQ ID NOs: 72, 93, 127, 161, WAS, and SEQ ID NO: 201; SEQ ID NOs: 69, 94, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 73, 95, 128, 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 74, 96, 129, 163, 185, and 203; SEQ ID NOs: 75, 97, 130, 164, 185, and 204; SEQ ID NOs: 74, 98, 131, 165, 185, and 205; SEQ ID NOs: 76, 99, 132, 166, 186, and 206; SEQ ID NOs: 77, 100, 133, 167, 187, and 207; SEQ ID NOs: 78, 101, 134, 168, 188, and 208; SEQ ID NOs: 79, 102, 135, 169, 186, and 209; SEQ ID NOs: 74, 103, 136, 170, 185, and 198; SEQ ID NOs: 80, 104, 137, 169, 189, and 210; SEQ ID NOs: 74, 105, 138, 170, 185, and 211; SEQ ID NOs: 74, 106, 139, 171, 187, and 212; SEQ ID NOs: 81, 107, 140, 172, 187, and 213; SEQ ID NOs: 81, 108, 141, 173, 190, and 214; SEQ ID NOs: 82, 109, 142, 174, 191, and 215; SEQ ID NOs: 83, 110, 143, 175, 186, and 216; SEQ ID NOs: 84, 99, 144, 176, 186, and 217; SEQ ID NOs: 85, 111, 145, 170, 192, and 198; SEQ ID NOs: 81, 112, 146, 171, 193, and 218; SEQ ID NOs: 86, 113, 147, 177, 187, and 219; SEQ ID NOs: 87, 114, 148, 178, 189, and 220; SEQ ID NOs: 74, 115, 149, 179, 187, and 221; SEQ ID NOs: 74, 116, 150, 165, 185, and 222; SEQ ID NOs: 74, 117, 151, 180, 187, and 223; SEQ ID NOs: 88, 118, 152, 181, 194, and 224; SEQ ID NOs: 89, 119, 153, 182, 195, and 199; SEQ ID NOs: 81, 120, 154, 172, 187, and 225; SEQ ID NOs: 74, 121, 155, 165, 185, and 222; SEQ ID NOs: 85, 122, 156, 183, 196, and 226; or SEQ ID NOs: 86, 123, 157, 184, 197, and 227, respectively.

[0073] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K) comprising a VH comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) identical to the amino acid sequence set forth in any one of SEQ ID NOs: 1-34. In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VH comprising an amino acid sequence set

forth in any one of SEQ ID NOs: 1-34. In certain embodiments, the amino acid sequence of the VH consists of the amino acid sequence set forth in any one of SEQ ID NOs: 1-34.

[0074] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VL comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) identical to the amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VL comprising an amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the amino acid sequence of the VL consists of the amino acid sequence set forth in any one of SEQ ID NOs: 35-68.

[0075] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VH comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to the amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and a VL comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) identical to the amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VH comprising an amino acid sequence of any one of SEQ ID NOs: 1-34, and a VL comprising an amino acid sequence of any one of SEQ ID NOs: 35-68. In certain embodiments, the amino acid sequence of the VH consists of the amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and the amino acid sequence of the VL consists of the amino acid sequence set forth in any one of SEQ ID NOs: 35-68.

[0076] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), comprising a VH comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and a VL comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, or 100% (*e.g.*, at least 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) identical to an amino acid sequence set forth in any one of SEQ ID NOs: 35-68, wherein the amino acid sequences set forth in any one of SEQ ID NOs: 1-34 and any one of SEQ ID NOs: 35-68 are from the same antibody (*i.e.*, as shown in **Tables 1 and 2**). In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K),

comprising a VH comprising an amino acid sequence of any one of SEQ ID NOs: 1-34, and a VL comprising an amino acid sequence of any one of SEQ ID NOs: 35-68, wherein the amino acid sequences set forth in any one of SEQ ID NOs: 1-34 and any one of SEQ ID NOs: 35-68 are from the same antibody (*i.e.*, as shown in **Tables 1** and **2**). In certain embodiments, the amino acid sequence of the VH consists of the amino acid sequence set forth in any one of SEQ ID NOs: 1-34, and the amino acid sequence of the VL consists of the amino acid sequence set forth in any one of SEQ ID NOs: 35-68, wherein the amino acid sequences set forth in any one of SEQ ID NOs: 1-34 and any one of SEQ ID NOs: 35-68 are from the same antibody (*i.e.*, as shown in **Tables 1** and **2**).

[0077] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VH and VL comprising the amino acid sequences set forth in SEQ ID NOs: 1 and 35; SEQ ID NOs: 2 and 36; SEQ ID NOs: 3 and 37; SEQ ID NOs: 4 and 38; SEQ ID NOs: 5 and 39; SEQ ID NOs: 6 and 40; SEQ ID NOs: 7 and 41; SEQ ID NOs: 8 and 42; SEQ ID NOs: 9 and 43; SEQ ID NOs: 10 and 44; SEQ ID NOs: 11 and 45; SEQ ID NOs: 12 and 46; SEQ ID NOs: 13 and 47; SEQ ID NOs: 14 and 48; SEQ ID NOs: 15 and 49; SEQ ID NOs: 16 and 50; SEQ ID NOs: 17 and 51; SEQ ID NOs: 18 and 52; SEQ ID NOs: 19 and 53; SEQ ID NOs: 20 and 54; SEQ ID NOs: 21 and 55; SEQ ID NOs: 22 and 56; SEQ ID NOs: 23 and 57; SEQ ID NOs: 24 and 58; SEQ ID NOs: 25 and 59; SEQ ID NOs: 26 and 60; SEQ ID NOs: 27 and 61; SEQ ID NOs: 28 and 62; SEQ ID NOs: 29 and 63; SEQ ID NOs: 30 and 64; SEQ ID NOs: 31 and 65; SEQ ID NOs: 32 and 66; SEQ ID NOs: 33 and 67; or SEQ ID NOs: 34 and 68, respectively.

[0078] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (*e.g.*, human LY6K), wherein the antibody comprises a VH and VL consisting of the amino acid sequences set forth in SEQ ID NOs: 1 and 35; SEQ ID NOs: 2 and 36; SEQ ID NOs: 3 and 37; SEQ ID NOs: 4 and 38; SEQ ID NOs: 5 and 39; SEQ ID NOs: 6 and 40; SEQ ID NOs: 7 and 41; SEQ ID NOs: 8 and 42; SEQ ID NOs: 9 and 43; SEQ ID NOs: 10 and 44; SEQ ID NOs: 11 and 45; SEQ ID NOs: 12 and 46; SEQ ID NOs: 13 and 47; SEQ ID NOs: 14 and 48; SEQ ID NOs: 15 and 49; SEQ ID NOs: 16 and 50; SEQ ID NOs: 17 and 51; SEQ ID NOs: 18 and 52; SEQ ID NOs: 19 and 53; SEQ ID NOs: 20 and 54; SEQ ID NOs: 21 and 55; SEQ ID NOs: 22 and 56; SEQ ID NOs: 23 and 57; SEQ ID NOs: 24 and 58; SEQ ID NOs: 25 and 59; SEQ ID NOs: 26 and 60; SEQ ID NOs: 27 and 61; SEQ ID NOs: 28 and 62; SEQ ID NOs: 29 and 63; SEQ ID NOs: 30 and 64; SEQ ID NOs: 31 and 65; SEQ ID NOs: 32 and 66; SEQ ID NOs: 33 and 67; or SEQ ID NOs: 34 and 68, respectively.

[0079] In certain embodiments, the instant disclosure provides an antibody that cross-competes for binding to LY6K (*e.g.*, human LY6K) with any of the antibodies described above. In certain embodiments, the instant disclosure provides an antibody that binds to the same or an overlapping epitope of LY6K (*e.g.*, an epitope of human LY6K) as an antibody described above.

[0080] In certain embodiments, the epitope of an antibody can be determined by, *e.g.*, NMR spectroscopy, surface plasmon resonance (BIAcore[®]), X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson A (1990) *Eur J Biochem* 189: 1-23; Chayen NE (1997) *Structure* 5: 1269-1274; McPherson A (1976) *J Biol Chem* 251: 6300-6303, all of which are herein incorporated by reference in their entireties). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; *see, e.g.*, *Meth Enzymol* (1985) volumes 114 & 115, eds. Wyckoff HW *et al.*; U.S. Patent Application No. 2004/0014194), and BUSTER (Bricogne G (1993) *Acta Crystallogr D Biol Crystallogr* 49(Pt 1): 37-60; Bricogne G (1997) *Meth Enzymol* 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) *Acta Crystallogr D Biol Crystallogr* 56(Pt 10): 1316-1323, all of which are herein incorporated by reference in their entireties). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.*, (1995) *supra* and Cunningham BC & Wells JA (1989) *supra* for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. In a specific embodiment, the epitope of an antibody is determined using alanine scanning mutagenesis studies. In addition, or antibodies that recognize and bind to the same or overlapping epitopes of LY6K (*e.g.*, human LY6K) can be identified using routine techniques such as an immunoassay, for example, by showing the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competition binding assays also can be used to determine whether two antibodies have similar binding specificity for an epitope. Competitive binding can be determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as LY6K (*e.g.*, human LY6K). Numerous types of competitive binding assays are known, for example: solid phase direct or indirect

radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see* Stahl C *et al.*, (1983) *Methods Enzymol* 9: 242-253); solid phase direct biotin-avidin EIA (*see* Kirkland TN *et al.*, (1986) *J Immunol* 137: 3614-9); solid phase direct labeled assay, solid phase direct labeled sandwich assay (*see* Harlow E & Lane D, (1988) *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (*see* Morel GA *et al.*, (1988) *Mol Immunol* 25(1): 7-15); solid phase direct biotin-avidin EIA (*see* Cheung RC *et al.*, (1990) *Virology* 176: 546-52); and direct labeled RIA (*see* Moldenhauer G *et al.*, (1990) *Scand J Immunol* 32: 77-82), all of which are herein incorporated by reference in their entireties. Typically, such an assay involves the use of purified antigen (*e.g.*, LY6K, such as human LY6K) bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition can be measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually, the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference or antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70%, 70-75%, or more. A competition binding assay can be configured in a large number of different formats using either labeled antigen or labeled antibody. In a common version of this assay, the antigen is immobilized on a 96-well plate. The ability of unlabeled antibodies to block the binding of labeled antibodies to the antigen is then measured using radioactive or enzyme labels. For further details *see. e.g.*, Wagener C *et al.*, (1983) *J Immunol* 130: 2308-2315; Wagener C *et al.*, (1984) *J Immunol Methods* 68: 269-274; Kuroki M *et al.*, (1990) *Cancer Res* 50: 4872-4879; Kuroki M *et al.*, (1992) *Immunol Invest* 21: 523-538; Kuroki M *et al.*, (1992) *Hybridoma* 11: 391-407 and *Antibodies: A Laboratory Manual*, Ed Harlow E & Lane D editors *supra*, pp. 386-389, all of which are herein incorporated by reference in their entireties.

[0081] The anti-LY6K antigen-binding molecules of the present disclosure can be linked to or co-expressed with another functional molecule, *e.g.*, another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association, or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bispecific or a multispecific antibody (*e.g.*, a bispecific T cell engager [BiTE] or a dual-affinity re-targeting antibody [DART]) with a second or additional binding specificity. In some embodiments, the bispecific or multispecific antibody has binding specificity for a molecule on an effector cell (*e.g.*, CD3, CD16, CD137). In some embodiments, an antibody provided herein is a

multispecific antibody. In some embodiments, a multispecific antibody provided herein comprises a CD3-binding region. In some embodiments, the CD3-binding region comprises a sequence from an antibody known to bind CD3 (e.g., OKT3, UTCH1, L2K, TR66, etc.). In some embodiments, the CD3-binding region comprises a sequence from an L2K anti-CD3 antibody. In some embodiments, the CD3-binding region comprises a sequence from a de-immunized L2K anti-CD3 antibody. In some embodiments, the CD3-binding region comprises a single-chain fragment variable (scFv) that specifically binds to CD3. In some embodiments, a multispecific antibody provided herein specifically binds to human CD3.

[0082] In certain embodiments, an antibody disclosed herein is conjugated to a pharmaceutically active substance. Pharmaceutically active substances include, but are not limited to, cytotoxic agents, cytostatic agents, toxins, radionuclides (e.g., radioisotopes), polypeptides, polynucleotides, detectable labels, and combinations thereof. In certain embodiments, pharmaceutically active substance is a cytotoxic agent. In certain embodiments, the cytotoxic agent is able to induce death or destruction of a cell in contact therewith. In certain embodiments, the pharmaceutically active substance is a cytostatic agent. In certain embodiments, the cytostatic agent is able to prevent or substantially reduce proliferation and/or inhibits the activity or function of a cell in contact therewith. In certain embodiments, the cytotoxic agent or cytostatic agent is a chemotherapeutic agent.

[0083] In certain embodiments, the pharmaceutically active substance is a radionuclide. Suitable radionuclides include, but are not limited to, beta emitters, auger emitters, converted electron emitters, alpha emitters, and low photon energy emitters. In certain embodiments, the radionuclide is selected from ^3H , ^{14}C , ^{32}P , ^{35}S , ^{36}Cl , ^{45}Ca , ^{51}Cr , ^{57}Co , ^{58}Co , ^{59}Fe , ^{67}Cu , ^{67}Ga , ^{76}As , ^{77}As , ^{89}Sr , ^{90}Y , ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{111}In , $^{114\text{m}}\text{In}$, ^{117}Lu , ^{121}I , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{149}Tb , ^{153}Sm , ^{161}Tb , ^{166}Ho , ^{177}Lu , ^{198}Au , ^{201}Tl , ^{211}At , ^{212}Pb , ^{213}Bi , ^{225}Ac , ^{186}Re , ^{188}Re , ^{212}Bi , ^{213}Bi , ^{221}At , ^{223}Ac , ^{223}Ra , ^{225}Ac , ^{255}Fm , and combinations thereof.

[0084] In certain embodiments, the pharmaceutically active substance is a detectable label. In certain embodiments, the detectable label comprises a fluorescent moiety, a click chemistry handle, or a combination thereof.

[0085] In certain embodiments, the pharmaceutically active substance is a drug. Suitable drugs include, but are not limited to, anti-cancer agents, anti-inflammatory agents, and anti-infective (e.g., anti-fungal, antibacterial, anti-parasitic, antiviral) agents. Suitable anti-cancer agents include, but are not limited to, alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, photosensitizers, kinase inhibitors, anti-hormonal agents, aromatase inhibitors, anti-androgens, protein kinase

inhibitors, lipid kinase inhibitors, antisense oligonucleotides (*e.g.*, those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation), ribozymes, (*e.g.*, VEGF expression inhibitors and HER2 expression inhibitors), vaccines (*e.g.*, gene therapy vaccines), topoisomerase 1 inhibitors, anti-angiogenic agents, pharmaceutically acceptable salts, acids, solvates and derivatives of any of the above, and any combination thereof.

[0086] In certain embodiments, the pharmaceutically active substance is a toxin. Suitable toxins include, but are not limited to, proteinaceous toxins (*e.g.*, bacterial-derived toxins, and plant-derived toxins), toxins targeting tubulin filaments, toxins targeting DNA, toxins targeting RNA. Examples of proteinaceous toxins include saporin, dianthin, ricin, modeccin, abrin, volkensin, viscumin, shiga toxin, shiga-like toxin, pseudomonas exotoxin (PE, also known as exotoxin A), diphtheria toxin (DT), and cholera toxin. Examples of toxins targeting tubulin filaments include maytansinoids (*e.g.* DM1 and DM4), auristatins (*e.g.*, Monomethyl auristatin E (MMAE) and Monomethyl auristatin F (MMAF)), toxoids, tubulysins, cryptophycins, rhizoxin. Examples of DNA-targeting toxins include calicheamicins: N-Acetyl-γ-calicheamicin, CC-1065 analogs, duocarmycins, doxorubicin, methotrexate, benzodiazepines, camptothecin analogues, and anthracyclines. Examples of RNA-targeting toxins are amanitins, spliceostatsins, and thailanstatins.

[0087] In certain embodiments, the pharmaceutically active substance is a polypeptide. Suitable polypeptides include, but are not limited to, Cas9; toxins (*e.g.*, saporin, dianthin, gelonin, (de)bougainin, agrostin, ricin (toxin A chain); pokeweed antiviral protein, apoptin, diphtheria toxin, pseudomonas exotoxin); metabolic enzymes (*e.g.*, argininosuccinate lyase, argininosuccinate synthetase); enzymes of the coagulation cascade; repairing enzymes; enzymes for cell signaling; cell cycle regulation factors; gene regulating factors (*e.g.*, transcription factors such as NF-KB or gene repressors such as methionine repressor).

[0088] In certain embodiments, the pharmaceutically active substance is a polynucleotide. In certain embodiments, the polynucleotide comprises coding information. In certain embodiments, the polynucleotide is a gene or an open reading frame encoding a protein. In certain embodiments, the polynucleotide comprises regulatory information. In certain embodiments, the polynucleotide is a promoter, a regulatory element binding region, or a sequence encoding a micro RNA. Suitable polynucleotides include natural and artificial nucleic acids. Artificial nucleic acids include, but are not limited to, peptide nucleic acids (PNA), Morpholinos and locked nucleic acids (LNA), glycol nucleic acids (GNA), and threose nucleic acids (TNA). Each of these is distinguished from naturally occurring DNA or RNA by changes

to the backbone of the molecule. Suitable polynucleotides include, but are not limited to, a vector; a gene (e.g., a cell suicide-inducing transgene); single stranded DNA; linear double stranded DNA; circular double stranded DNA (e.g., a plasmid); mini-circle DNA; a DNA aptamer; single stranded RNA; linear double stranded RNA; mRNA; tRNA; rRNA; short interfering RNA (siRNA); microRNA (miRNA); antisense RNA; anti-sense oligonucleotides; peptide nucleic acid (PNA); phosphoramidate morpholino oligomer (PMO); locked nucleic acid (LNA); bridged nucleic acid (BNA); 2'-deoxy-2'-fluoroarabino nucleic acid (FANA); 2'-O-methoxyethyl-RNA (MOE); 2'-0,4'-aminoethylene bridged nucleic acid; 3'-fluoro hexitol nucleic acid (FHNA); an RNA aptamer; and combinations thereof.

[0089] Any immunoglobulin (Ig) constant region can be used in the antibodies disclosed herein. In certain embodiments, the Ig region is a human IgG, IgE, IgM, IgD, IgA, or IgY immunoglobulin molecule, any class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂), or any subclass (e.g., IgG_{2a} and IgG_{2b}) of immunoglobulin molecule.

[0090] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (e.g., human LY6K), the antibody comprising a heavy chain constant region, optionally selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂.

[0091] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (e.g., human LY6K), the antibody comprising a heavy chain constant region that is a variant of a wild-type heavy chain constant region, wherein the variant heavy chain constant region binds to an FcγR with lower affinity than the wild-type heavy chain constant region binds to the FcγR.

[0092] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (e.g., human LY6K), the antibody comprising a heavy chain constant region comprising an amino acid sequence shown in **Table 5**. In certain embodiments, the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 228 or 229. In certain embodiments, the heavy chain constant region consists of the amino acid sequence of SEQ ID NO: 228 or 229.

Table 5. Heavy chain constant region amino acid sequences of exemplary anti-LY6K antibodies.

Description	Amino Acid Sequence	SEQ ID
WT IgG1 heavy chain constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK	228

	EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK	
S228P IgG4 heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVDPKPSNTKVDKRVESKYGPCCPCCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK	229

[0093] In certain embodiments, the instant disclosure provides an antibody that specifically binds to LY6K (e.g., human LY6K), the antibody comprising a light chain constant region comprising an amino acid sequence shown in **Table 6**. In certain embodiments, the heavy chain constant region comprises the amino acid sequence of SEQ ID NO: 230 or 231. In certain embodiments, the heavy chain constant region consists of the amino acid sequence of SEQ ID NO: 230 or 231.

Table 6. Light chain constant region amino acid sequences of exemplary anti-LY6K antibodies.

Description	Amino Acid Sequence	SEQ ID
Kappa light chain constant region	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	230
Lambda light chain constant region	GQPKANPTVTLFPSSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTKPSKQSNKNKYAASSYLSTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	231

[0094] In certain embodiments, one, two, or more mutations (e.g., amino acid substitutions) are introduced into an Fc region (e.g., a CH2 domain (residues 231-340 of human IgG₁) and/or a CH3 domain (residues 341-447 of human IgG₁, numbered according to the EU numbering system) and/or a hinge region (residues 216-230, numbered according to the EU numbering system) of an antibody described herein, to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity.

[0095] In certain embodiments, one, two, or more mutations (e.g., amino acid substitutions) are introduced into the hinge region of an antibody described herein, such that the number of cysteine residues in the hinge region is altered (e.g., increased or decreased) as described in, e.g., U.S. Patent No. 5,677,425, herein incorporated by reference in its entirety.

The number of cysteine residues in the hinge region may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody.

[0096] In a specific embodiment, one, two, or more amino acid mutations (*e.g.*, substitutions, insertions, or deletions) are introduced into an IgG constant region, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc fragment) to alter (*e.g.*, decrease or increase) half-life of the antibody *in vivo*. *See, e.g.*, International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375, and 6,165,745, all of which are herein incorporated by reference in their entireties, for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody *in vivo*. In certain embodiments, one, two or more amino acid mutations (*e.g.*, substitutions, insertions, or deletions) are introduced into an IgG constant region, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc fragment) to decrease the half-life of the antibody *in vivo*. In other embodiments, one, two or more amino acid mutations (*e.g.*, substitutions, insertions, or deletions) are introduced into an IgG constant region, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc fragment) to increase the half-life of the antibody *in vivo*. In a specific embodiment, the antibodies may have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG₁) and/or the third constant (CH3) domain (residues 341-447 of human IgG₁), numbered according to the EU numbering system. In a specific embodiment, the constant region of the IgG₁ of antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU numbering system. *See* U.S. Patent No. 7,658,921, which is herein incorporated by reference in its entirety. This type of mutant IgG, referred to as “YTE mutant” has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (*see* Dall’Acqua WF *et al.*, (2006) J Biol Chem 281: 23514-24, which is herein incorporated by reference in its entirety). In certain embodiments, an antibody comprises an IgG constant region comprising one, two, three, or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU numbering system.

[0097] In certain embodiments, one, two, or more mutations (*e.g.*, amino acid substitutions) are introduced into an Fc region (*e.g.*, a CH2 domain (residues 231-340 of human IgG₁)) and/or a CH3 domain (residues 341-447 of human IgG₁, numbered according to the EU numbering system) and/or a hinge region (residues 216-230, numbered according to the EU numbering system) of an antibody described herein, to increase or decrease the affinity of the

antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, *e.g.*, Smith P *et al.*, (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, all of which are herein incorporated by reference in their entireties.

[0098] In certain embodiments, the antibody comprises a heavy chain constant region that is a variant of a wild-type heavy chain constant region, wherein the variant heavy chain constant region binds to FcγRIIB with higher affinity than the wild-type heavy chain constant region binds to FcγRIIB. In certain embodiments, the variant heavy chain constant region is a variant human heavy chain constant region, *e.g.*, a variant human IgG₁, a variant human IgG₂, or a variant human IgG₄ heavy chain constant region. In certain embodiments, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations, according to the EU numbering system: G236D, P238D, S239D, S267E, L328F, and L328E. In certain embodiments, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S267E and L328F; P238D and L328E; P238D and one or more substitutions selected from the group consisting of E233D, G237D, H268D, P271G, and A330R; P238D, E233D, G237D, H268D, P271G, and A330R; G236D and S267E; S239D and S267E; V262E, S267E, and L328F; and V264E, S267E, and L328F, according to the EU numbering system. In certain embodiments, the FcγRIIB is expressed on a cell selected from the group consisting of macrophages, monocytes, B cells, dendritic cells, endothelial cells, and activated T cells.

[0099] In a further embodiment, one, two, or more amino acid substitutions are introduced into an IgG constant region Fc region to alter the effector function(s) of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 239, 243, 267, 292, 297, 300, 318, 320, 322, 328, 330, 332, and 396, numbered according to the EU numbering system, can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260, each of which is herein incorporated by reference in its entirety. In certain embodiments, the deletion or inactivation (through point mutations or other means)

of a constant region domain may reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. *See, e.g.*, U.S. Patent Nos. 5,585,097 and 8,591,886, each of which is herein incorporated by reference in its entirety, for a description of mutations that delete or inactivate the constant region and thereby increase tumor localization. In certain embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on the Fc region, which may reduce Fc receptor binding (*see, e.g.*, Shields RL *et al.*, (2001) J Biol Chem 276: 6591-604, which is herein incorporated by reference in its entirety). In various embodiments, one or more of the following mutations in the constant region of an antibody described herein may be made: an N297A substitution; an N297Q substitution; an L234A substitution; an L234F substitution; an L235A substitution; an L235F substitution; an L235V substitution; an L237A substitution; an S239D substitution; an E233P substitution; an L234V substitution; a C236 deletion; a P238A substitution; an F243L substitution; a D265A substitution; an S267E substitution; an L328F substitution; an R292P substitution; a Y300L substitution; an A327Q substitution; a P329A substitution; an A330L substitution; an I332E substitution; or a P396L substitution, numbered according to the EU numbering system.

[00100] In certain embodiments, a mutation selected from the group consisting of D265A, P329A, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein. In certain embodiments, a mutation selected from the group consisting of L235A, L237A, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein. In certain embodiments, a mutation selected from the group consisting of S267E, L328F, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein. In certain embodiments, a mutation selected from the group consisting of S239D, I332E, optionally A330L, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein. In certain embodiments, a mutation selected from the group consisting of L235V, F243L, R292P, Y300L, P396L, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein. In certain embodiments, a mutation selected from the group consisting of S267E, L328F, and a combination thereof, numbered according to the EU numbering system, may be made in the constant region of an antibody described herein.

[00101] In a specific embodiment, an antibody described herein comprises the constant region of an IgG₁ with an N297Q or N297A amino acid substitution, numbered according to the EU numbering system. In certain embodiments, an antibody described herein comprises the constant region of an IgG₁ with a mutation selected from the group consisting of D265A, P329A, and a combination thereof, numbered according to the EU numbering system. In another embodiment, an antibody described herein comprises the constant region of an IgG₁ with a mutation selected from the group consisting of L234A, L235A, and a combination thereof, numbered according to the EU numbering system. In another embodiment, an antibody described herein comprises the constant region of an IgG₁ with a mutation selected from the group consisting of L234F, L235F, N297A, and a combination thereof, numbered according to the EU numbering system. In certain embodiments, amino acid residues in the constant region of an antibody described herein in the positions corresponding to positions L234, L235, and D265 in a human IgG₁ heavy chain, numbered according to the EU numbering system, are not L, L, and D, respectively. This approach is described in detail in International Publication No. WO 14/108483, which is herein incorporated by reference in its entirety. In certain embodiments, the amino acids corresponding to positions L234, L235, and D265 in a human IgG₁ heavy chain are F, E, and A; or A, A, and A, respectively, numbered according to the EU numbering system.

[00102] In certain embodiments, one or more amino acids selected from amino acid residues 329, 331, and 322 in the constant region of an antibody described herein, numbered according to the EU numbering system, can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 (Idusogie *et al.*), which is herein incorporated by reference in its entirety. In certain embodiments, one or more amino acid residues within amino acid positions 231 to 238 in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement, numbered according to the EU numbering system. This approach is described further in International Publication No. WO 94/29351, which is herein incorporated by reference in its entirety. In certain embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by mutating one or more amino acids (*e.g.*, introducing amino acid substitutions) at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267,

268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 328, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438, or 439, numbered according to the EU numbering system. This approach is described further in International Publication No. WO 00/42072, which is herein incorporated by reference in its entirety.

[00103] In certain embodiments, an antibody described herein comprises a modified constant region of an IgG₁, wherein the modification increases the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC). In certain embodiments, 0.1, 1, or 10 µg/ml of the antibody is capable of inducing cell death of at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, or 60% of LY6K-expressing cells within 1, 2, or 3 hours, as assessed by methods described herein and/or known to a person of skill in the art. In certain embodiments, the modified constant region of an IgG₁ comprises S239D and I332E substitutions, numbered according to the EU numbering system. In certain embodiments, the modified constant region of an IgG₁ comprises S239D, A330L, and I332E substitutions, numbered according to the EU numbering system. In certain embodiments, the modified constant region of an IgG₁ comprises L235V, F243L, R292P, Y300L, and P396L substitutions, numbered according to the EU numbering system. In certain embodiments, the antibody is capable of inducing cell death in effector T cells and Tregs, wherein the percentage of Tregs that undergo cell death is higher than the percentage of effector T cells that undergo cell death by at least 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 1.6 fold, 1.7 fold, 1.8 fold, 1.9 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, or 5 fold.

[00104] In certain embodiments, an antibody described herein comprises the constant region of an IgG₄ antibody and the serine at amino acid residue 228 of the heavy chain, numbered according to the EU numbering system, is substituted for proline.

[00105] In certain embodiments, any of the constant region mutations or modifications described herein can be introduced into one or both heavy chain constant regions of an antibody described herein having two heavy chain constant regions.

Polypeptides

[00106] In another aspect, provided herein are polypeptides comprising one or more sequences set forth in **Tables 1-4**, above. In certain embodiments, the polypeptide comprises the CDRH1, CDRH2, and/or CDRH3 of a VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34, as determined by any of the methods discussed above. In certain

embodiments, the polypeptide comprises a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34. In certain embodiments, the polypeptide comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 69, 90, and 124; 70, 91, and 125; 71, 92, and 126; 72, 93, and 127; 69, 94, and 124; 73, 95, and 128; 74, 96, and 129; 75, 97, and 130; 74, 98, and 131; 76, 99, and 132; 77, 100, and 133; 78, 101, and 134; 79, 102, and 135; 74, 103, and 136; 80, 104, and 137; 74, 105, and 138; 74, 106, and 139; 81, 107, and 140; 81, 108, and 141; 82, 109, and 142; 83, 110, and 143; 84, 99, and 144; 85, 111, and 145; 81, 112, and 146; 86, 113, and 147; 87, 114, and 148; 74, 115, and 149; 74, 116, and 150; 74, 117, and 151; 88, 118, and 152; 89, 119, and 153; 81, 120, and 154; 74, 121, and 155; 85, 122, and 156; or 86, 123, and 157, respectively.

[00107] In certain embodiments, the polypeptide comprises the CDRL1, CDRL2, and/or CDRL3 of a VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68, as determined by any of the methods discussed above. In certain embodiments, the polypeptide comprises a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain embodiments, the polypeptide comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs: 174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198; SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs: 178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

[00108] In certain embodiments, the polypeptide comprises a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34; and a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68. In certain

embodiments, the polypeptide comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences of the VH and VL amino acid sequences set forth in SEQ ID NOs: 1 and 35, 2 and 36, 3 and 37, 4 and 38, 5 and 39, 6 and 40, 7 and 41, 8 and 42, 9 and 43, 10 and 44, 11 and 45, 12 and 46, 13 and 47, 14 and 48, 15 and 49, 16 and 50, 17 and 51, 18 and 52, 19 and 53, 20 and 54, 21 and 55, 22 and 56, 23 and 57, 24 and 58, 25 and 59, 26 and 60, 27 and 61, 28 and 62, 29 and 63, 30 and 64, 31 and 65, 32 and 66, 33 and 67, or 34 and 68, respectively.

[00109] In certain embodiments, a polypeptide provided herein comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in: SEQ ID NOs: 69, 90, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 70, 91, 125, 159, WAS, and SEQ ID NO: 199; SEQ ID NOs: 71, 92, 126, 160, STT, and SEQ ID NO: 200; SEQ ID NOs: 72, 93, 127, 161, WAS, and SEQ ID NO: 201; SEQ ID NOs: 69, 94, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 73, 95, 128, 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 74, 96, 129, 163, 185, and 203; SEQ ID NOs: 75, 97, 130, 164, 185, and 204; SEQ ID NOs: 74, 98, 131, 165, 185, and 205; SEQ ID NOs: 76, 99, 132, 166, 186, and 206; SEQ ID NOs: 77, 100, 133, 167, 187, and 207; SEQ ID NOs: 78, 101, 134, 168, 188, and 208; SEQ ID NOs: 79, 102, 135, 169, 186, and 209; SEQ ID NOs: 74, 103, 136, 170, 185, and 198; SEQ ID NOs: 80, 104, 137, 169, 189, and 210; SEQ ID NOs: 74, 105, 138, 170, 185, and 211; SEQ ID NOs: 74, 106, 139, 171, 187, and 212; SEQ ID NOs: 81, 107, 140, 172, 187, and 213; SEQ ID NOs: 81, 108, 141, 173, 190, and 214; SEQ ID NOs: 82, 109, 142, 174, 191, and 215; SEQ ID NOs: 83, 110, 143, 175, 186, and 216; SEQ ID NOs: 84, 99, 144, 176, 186, and 217; SEQ ID NOs: 85, 111, 145, 170, 192, and 198; SEQ ID NOs: 81, 112, 146, 171, 193, and 218; SEQ ID NOs: 86, 113, 147, 177, 187, and 219; SEQ ID NOs: 87, 114, 148, 178, 189, and 220; SEQ ID NOs: 74, 115, 149, 179, 187, and 221; SEQ ID NOs: 74, 116, 150, 165, 185, and 222; SEQ ID NOs: 74, 117, 151, 180, 187, and 223; SEQ ID NOs: 88, 118, 152, 181, 194, and 224; SEQ ID NOs: 89, 119, 153, 182, 195, and 199; SEQ ID NOs: 81, 120, 154, 172, 187, and 225; SEQ ID NOs: 74, 121, 155, 165, 185, and 222; SEQ ID NOs: 85, 122, 156, 183, 196, and 226; or SEQ ID NOs: 86, 123, 157, 184, 197, and 227, respectively.

Pharmaceutical Compositions

[00110] Provided herein are compositions comprising an anti-LY6K antibody disclosed herein having the desired degree of purity in a physiologically acceptable carrier, excipient, or stabilizer (*see, e.g.*, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the

dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates, including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose, or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[00111] In a specific embodiment, pharmaceutical compositions comprise an anti-LY6K antibody disclosed herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In a specific embodiment, pharmaceutical compositions comprise an anti-LY6K antibody disclosed herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In certain embodiments, the antibody is the only active ingredient included in the pharmaceutical composition. Pharmaceutical compositions described herein can be useful in decreasing or blocking LY6K (*e.g.*, human LY6K) activity and treating a condition, such as cancer. In certain embodiments, the present disclosure relates to a pharmaceutical composition of the present disclosure comprising an anti-LY6K antibody of the present disclosure for use as a medicament. In another embodiment, the present disclosure relates to a pharmaceutical composition of the present disclosure for use in a method for the treatment of cancer.

[00112] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents, and other pharmaceutically acceptable substances. Examples of aqueous vehicles include Sodium Chloride Injection, Ringer's Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringer's Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil, and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid

esters, thimerosal, benzalkonium chloride, and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN[®] 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol, and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid, or lactic acid for pH adjustment.

[00113] A pharmaceutical composition can be formulated for any route of administration to a subject. Specific examples of routes of administration include intranasal, oral, pulmonary, transdermal, intradermal, and parenteral. Parenteral administration, characterized by either subcutaneous, intramuscular, or intravenous injection, is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions, and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol, or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, and cyclodextrins.

[00114] Preparations for parenteral administration of antibody include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use, and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[00115] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol, and mixtures thereof.

[00116] Topical mixtures comprising an antibody are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions, or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches, or any other formulations suitable for topical administration.

[00117] An anti-LY6K antibody disclosed herein can be formulated as an aerosol for topical application, such as by inhalation (*see, e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma and are herein incorporated by reference in their entireties). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in certain embodiments, have diameters of less than 50 microns, in certain embodiments, less than 10 microns.

[00118] An anti-LY6K antibody disclosed herein can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the antibody alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[00119] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer an antibody. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010,715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957, all of which are herein incorporated by reference in their entireties.

[00120] In certain embodiments, a pharmaceutical composition comprising an antibody described herein is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions, and other mixtures. It may also be reconstituted and formulated as solids or gels. The lyophilized powder is prepared by dissolving an antibody described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In certain embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose, or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate, or other such buffer known to those of skill in the art, at, in certain embodiments, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In certain embodiments, the resulting

solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to room temperature. Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such an amount can be empirically determined.

[00121] The anti-LY6K antibodies disclosed herein and other compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, *see, e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542, and 5,709,874, all of which are herein incorporated by reference in their entireties. In a specific embodiment, an antibody described herein is targeted to a tumor.

[00122] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

Methods of Use and Uses

[00123] In another aspect, the instant disclosure provides a method of treating a subject using the anti-LY6K antibodies disclosed herein. Any disease or disorder in a subject that is characterized by overexpression of LY6K (*e.g.*, human LY6K) can be treated using the anti-LY6K antibodies disclosed herein. In certain embodiments, the disease or disorder is resistant to a checkpoint targeting agent (*e.g.*, an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, or an antagonist anti-PD-1 antibody). In certain embodiments, the disease or disorder is recurrent after treatment with a checkpoint targeting agent (*e.g.*, an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, or an antagonist anti-PD-1 antibody).

[00124] In certain embodiments, the instant disclosure provides a method of treating cancer in a subject, the method comprising administering to the subject an effective amount of the antibody or pharmaceutical composition, as disclosed herein.

[00125] Cancers that can be treated with the anti-LY6K antibodies or pharmaceutical compositions disclosed herein include, without limitation, a solid tumor, a hematological

cancer (*e.g.*, leukemia, lymphoma, myeloma, *e.g.*, multiple myeloma), and a metastatic lesion. In certain embodiments, the cancer is a solid tumor. Examples of solid tumors include malignancies, *e.g.*, sarcomas and carcinomas, *e.g.*, adenocarcinomas of the various organ systems, such as those affecting the lung, breast, ovarian, lymphoid, gastrointestinal (*e.g.*, colon), anal, genitals and genitourinary tract (*e.g.*, renal, urothelial, bladder cells, prostate), pharynx, CNS (*e.g.*, brain, neural or glial cells), head and neck, skin (*e.g.*, melanoma), and pancreas, as well as adenocarcinomas which include malignancies such as colon cancers, rectal cancer, renal-cell carcinoma, liver cancer, lung cancer (*e.g.*, non-small cell lung cancer or small cell lung cancer), cancer of the small intestine, and cancer of the esophagus. The cancer may be at an early, intermediate, late stage, or metastatic cancer. In certain embodiments, the cancer is resistant to a checkpoint targeting agent (*e.g.*, an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, or an antagonist anti-PD-1 antibody). In certain embodiments, the cancer is recurrent after treatment with a checkpoint targeting agent (*e.g.*, an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, or an antagonist anti-PD-1 antibody).

[00126] In certain embodiments, the cancer is chosen from lung cancer (*e.g.*, lung adenocarcinoma or non-small cell lung cancer (NSCLC) (*e.g.*, NSCLC with squamous and/or non-squamous histology, or NSCLC adenocarcinoma)), melanoma (*e.g.*, an advanced melanoma), renal cancer (*e.g.*, a renal cell carcinoma), liver cancer (*e.g.*, hepatocellular carcinoma), myeloma (*e.g.*, a multiple myeloma), a prostate cancer, a breast cancer (*e.g.*, a breast cancer that does not express one, two or all of estrogen receptor, progesterone receptor, or Her2/neu, *e.g.*, a triple negative breast cancer), an ovarian cancer, a colorectal cancer, a pancreatic cancer, a head and neck cancer (*e.g.*, head and neck squamous cell carcinoma (HNSCC)), anal cancer, gastro-esophageal cancer (*e.g.*, esophageal squamous cell carcinoma), mesothelioma, nasopharyngeal cancer, thyroid cancer, cervical cancer, epithelial cancer, peritoneal cancer, or a lymphoproliferative disease (*e.g.*, a post-transplant lymphoproliferative disease).

[00127] In certain embodiments, the cancer is a hematological cancer, for example, a leukemia, a lymphoma, or a myeloma. In certain embodiments, the cancer is a leukemia, for example, acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute myeloblastic leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic lymphocytic leukemia (CLL), or hairy cell leukemia. In certain embodiments, the cancer is a lymphoma, for example, B cell lymphoma, diffuse large B-cell

lymphoma (DLBCL), activated B-cell like (ABC) diffuse large B cell lymphoma, germinal center B cell (GCB) diffuse large B cell lymphoma, mantle cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, relapsed non-Hodgkin lymphoma, refractory non-Hodgkin lymphoma, recurrent follicular non-Hodgkin lymphoma, Burkitt lymphoma, small lymphocytic lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, or extranodal marginal zone lymphoma. In certain embodiments the cancer is a myeloma, for example, multiple myeloma.

[00128] In another embodiment, the cancer is chosen from a carcinoma (*e.g.*, advanced or metastatic carcinoma), melanoma or a lung carcinoma, *e.g.*, a non-small cell lung carcinoma.

[00129] In certain embodiments, the cancer is a lung cancer, *e.g.*, a lung adenocarcinoma, non-small cell lung cancer, or small cell lung cancer.

[00130] In certain embodiments, the cancer is a melanoma, *e.g.*, an advanced melanoma. In certain embodiments, the cancer is an advanced or unresectable melanoma that does not respond to other therapies. In other embodiments, the cancer is a melanoma with a BRAF mutation (*e.g.*, a BRAF V600 mutation). In yet other embodiments, the anti-LY6K antibodies or pharmaceutical composition disclosed herein is administered after treatment with an anti-CTLA-4 antibody (*e.g.*, ipilimumab) with or without a BRAF inhibitor (*e.g.*, vemurafenib or dabrafenib).

[00131] In another embodiment, the cancer is a hepatocarcinoma, *e.g.*, an advanced hepatocarcinoma, with or without a viral infection, *e.g.*, a chronic viral hepatitis.

[00132] In another embodiment, the cancer is a prostate cancer, *e.g.*, an advanced prostate cancer.

[00133] In yet another embodiment, the cancer is a myeloma, *e.g.*, multiple myeloma.

[00134] In yet another embodiment, the cancer is a renal cancer, *e.g.*, a renal cell carcinoma (RCC) (*e.g.*, a metastatic RCC, clear cell renal cell carcinoma (CCRCC) or kidney papillary cell carcinoma).

[00135] In yet another embodiment, the cancer is chosen from a lung cancer, a melanoma, a renal cancer, a breast cancer, a colorectal cancer, a leukemia, or a metastatic lesion of the cancer.

[00136] In certain embodiments, these methods further comprise administering an additional therapeutic agent to the subject. In certain embodiments, the additional therapeutic agent is a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent. In certain embodiments, the chemotherapeutic agent is a hypomethylating agent (*e.g.*, azacitidine). In certain embodiments, the chemotherapeutic agent is a DNA damage-inducing agent (*e.g.*,

gemcitabine). In certain embodiments, the checkpoint targeting agent is selected from the group consisting of an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, an antagonist anti-PD-1 antibody, an antagonist anti-TIM-3 antibody, an antagonist anti-LAG-3 antibody, an antagonist anti-VISTA antibody, an antagonist anti-CD96 antibody, an antagonist anti-CEACAM1 antibody, an agonist anti-CD137 antibody, an agonist anti-GITR antibody, and an agonist anti-OX40 antibody. In certain embodiments, the checkpoint targeting agent is selected from the group consisting of an antagonist anti-CTLA-4 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, and an antagonist anti-PD-1 antibody, wherein the LY6K (*e.g.*, human LY6K) antibodies or pharmaceutical compositions disclosed herein synergize with the checkpoint targeting agent.

[00137] In certain embodiments, the present disclosure relates to an antibody and/or pharmaceutical composition of the present disclosure for use in a method of the present disclosure, wherein the method further comprises administering an additional therapeutic agent to the subject. In certain embodiments, the present disclosure relates to (a) an antibody and/or pharmaceutical composition of the present disclosure and (b) an additional therapeutic agent for use as a medicament. In certain embodiments, the present disclosure relates to (a) an antibody and/or pharmaceutical composition of the present disclosure and (b) an additional therapeutic agent for use in a method for the treatment of cancer. In a further embodiment, the present disclosure relates to a pharmaceutical composition, kit or kit-of-parts comprising (a) an antibody and/or pharmaceutical composition of the present disclosure and (b) an additional therapeutic agent. In certain embodiments, the additional therapeutic agent is a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent.

[00138] In certain embodiments, an anti-PD-1 antibody is used in methods disclosed herein. In certain embodiments, the anti-PD-1 antibody is nivolumab, also known as BMS-936558 or MDX1106, developed by Bristol-Myers Squibb. In certain embodiments, the anti-PD-1 antibody is pembrolizumab, also known as lambrolizumab or MK-3475, developed by Merck & Co. In certain embodiments, the anti-PD-1 antibody is pidilizumab, also known as CT-011, developed by CureTech. In certain embodiments, the anti-PD-1 antibody is MEDI0680, also known as AMP-514, developed by MedImmune. In certain embodiments, the anti-PD-1 antibody is PDR001 developed by Novartis Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is REGN2810 developed by Regeneron Pharmaceuticals. In certain embodiments, the anti-PD-1 antibody is PF-06801591 developed by Pfizer. In certain embodiments, the anti-PD-1 antibody is BGB-A317 developed by BeiGene. In certain

embodiments, the anti-PD-1 antibody is TSR-042 developed by AnaptysBio and Tesaro. In certain embodiments, the anti-PD-1 antibody is SHR-1210 developed by Hengrui.

[00139] Further non-limiting examples of anti-PD-1 antibodies that may be used in treatment methods disclosed herein are disclosed in the following patents and patent applications, all of which are herein incorporated by reference in their entireties for all purposes: U.S. Patent No. 6,808,710; U.S. Patent No. 7,332,582; U.S. Patent No. 7,488,802; U.S. Patent No. 8,008,449; U.S. Patent No. 8,114,845; U.S. Patent No. 8,168,757; U.S. Patent No. 8,354,509; U.S. Patent No. 8,686,119; U.S. Patent No. 8,735,553; U.S. Patent No. 8,747,847; U.S. Patent No. 8,779,105; U.S. Patent No. 8,927,697; U.S. Patent No. 8,993,731; U.S. Patent No. 9,102,727; U.S. Patent No. 9,205,148; U.S. Publication No. US 2013/0202623 A1; U.S. Publication No. US 2013/0291136 A1; U.S. Publication No. US 2014/0044738 A1; U.S. Publication No. US 2014/0356363 A1; U.S. Publication No. US 2016/0075783 A1; PCT Publication No. WO 2013/033091 A1; PCT Publication No. WO 2015/036394 A1; PCT Publication No. WO 2014/179664 A2; PCT Publication No. WO 2014/209804 A1; PCT Publication No. WO 2014/206107 A1; PCT Publication No. WO 2015/058573 A1; PCT Publication No. WO 2015/085847 A1; PCT Publication No. WO 2015/200119 A1; PCT Publication No. WO 2016/015685 A1; and PCT Publication No. WO 2016/020856 A1.

[00140] In certain embodiments, an anti-PD-L1 antibody is used in methods disclosed herein. In certain embodiments, the anti-PD-L1 antibody is atezolizumab developed by Genentech. In certain embodiments, the anti-PD-L1 antibody is durvalumab developed by AstraZeneca, Celgene, and MedImmune. In certain embodiments, the anti-PD-L1 antibody is avelumab, also known as MSB0010718C, developed by Merck Serono and Pfizer. In certain embodiments, the anti-PD-L1 antibody is MDX-1105 developed by Bristol-Myers Squibb. In certain embodiments, the anti-PD-L1 antibody is AMP-224 developed by Amplimmune and GSK.

[00141] Non-limiting examples of anti-PD-L1 antibodies that may be used in treatment methods disclosed herein are disclosed in the following patents and patent applications, all of which are herein incorporated by reference in their entireties for all purposes: U.S. Patent No. 7,943,743; U.S. Patent No. 8,168,179; U.S. Patent No. 8,217,149; U.S. Patent No. 8,552,154; U.S. Patent No. 8,779,108; U.S. Patent No. 8,981,063; U.S. Patent No. 9,175,082; U.S. Publication No. US 2010/0203056 A1; U.S. Publication No. US 2003/0232323 A1; U.S. Publication No. US 2013/0323249 A1; U.S. Publication No. US 2014/0341917 A1; U.S. Publication No. US 2014/0044738 A1; U.S. Publication No. US 2015/0203580 A1; U.S. Publication No. US 2015/0225483 A1; U.S. Publication No. US 2015/0346208 A1; U.S.

Publication No. US 2015/0355184 A1; PCT Publication No. WO 2014/100079 A1; PCT Publication No. WO 2014/022758 A1; PCT Publication No. WO 2014/055897 A2; PCT Publication No. WO 2015/061668 A1; PCT Publication No. WO 2015/109124 A1; PCT Publication No. WO 2015/195163 A1; PCT Publication No. WO 2016/000619 A1; and PCT Publication No. WO 2016/030350 A1.

[00142] In certain embodiments, an anti-CTLA-4 antibody is used in methods disclosed herein. In certain embodiments, the anti-CTLA-4 antibody is ipilimumab developed by Bristol-Myers Squibb.

[00143] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with a compound that targets an immunomodulatory enzyme(s) such as IDO (indoleamine-(2,3)-dioxygenase) and/or TDO (tryptophan 2,3-dioxygenase). Therefore, in certain embodiments, the additional therapeutic agent is a compound that targets an immunomodulatory enzyme(s), such as an inhibitor of indoleamine-(2,3)-dioxygenase (IDO). In certain embodiments, such compound is selected from the group consisting of epacadostat (Incyte Corp; *see, e.g.*, WO 2010/005958 which is herein incorporated by reference in its entirety), F001287 (Flexus Biosciences/Bristol-Myers Squibb), indoximod (NewLink Genetics), and NLG919 (NewLink Genetics). In certain embodiments, the compound is epacadostat. In another embodiment, the compound is F001287. In another embodiment, the compound is indoximod. In another embodiment, the compound is NLG919. In a specific embodiment, an anti-LY6K antibody disclosed herein is administered to a subject in combination with an IDO inhibitor for treating cancer. The IDO inhibitor as described herein for use in treating cancer is present in a solid dosage form of a pharmaceutical composition such as a tablet, a pill, or a capsule, wherein the pharmaceutical composition includes an IDO inhibitor and a pharmaceutically acceptable excipient. As such, the antibody as described herein and the IDO inhibitor as described herein can be administered separately, sequentially, or concurrently as separate dosage forms. In certain embodiments, the antibody is administered parenterally, and the IDO inhibitor is administered orally. In certain embodiments, the inhibitor is selected from the group consisting of epacadostat (Incyte Corporation), F001287 (Flexus Biosciences/Bristol-Myers Squibb), indoximod (NewLink Genetics), and NLG919 (NewLink Genetics). Epacadostat has been described in PCT Publication No. WO 2010/005958, which is herein incorporated by reference in its entirety for all purposes. In certain embodiments, the inhibitor is epacadostat. In another embodiment, the inhibitor is F001287. In another embodiment, the inhibitor is indoximod. In another embodiment, the inhibitor is NLG919.

[00144] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with a vaccine. The vaccine can be, *e.g.*, a peptide vaccine, a DNA vaccine, or an RNA vaccine.

[00145] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with an adjuvant. Various adjuvants can be used depending on the treatment context. Non-limiting examples of appropriate adjuvants include, but not limited to, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), montanide ISA (incomplete Seppic adjuvant), the Ribi adjuvant system (RAS), Titer Max, muramyl peptides, Syntex Adjuvant Formulation (SAF), alum (aluminum hydroxide and/or aluminum phosphate), aluminum salt adjuvants, Gerbu[®] adjuvants, nitrocellulose absorbed antigen, encapsulated or entrapped antigen, 3 De-O-acylated monophosphoryl lipid A (3 D-MPL), immunostimulatory oligonucleotides, toll-like receptor (TLR) ligands, mannan-binding lectin (MBL) ligands, STING agonists, immuno-stimulating complexes such as saponins, Quil A, QS-21, QS-7, ISCOMATRIX, and others. Other adjuvants include CpG oligonucleotides and double stranded RNA molecules, such as poly(A) and poly(U). Combinations of the above adjuvants may also be used. *See, e.g.*, U.S. Patent Nos. 6,645,495; 7,029,678; and 7,858,589, all of which are incorporated herein by reference in their entireties. In certain embodiments, the adjuvant used herein is QS-21 STIMULON.

[00146] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with an additional therapeutic agent comprising a TCR. In certain embodiments, the additional therapeutic agent is a soluble TCR. In certain embodiments, the additional therapeutic agent is a cell expressing a TCR. Therefore, in certain embodiments, the present disclosure relates to an antibody and/or pharmaceutical composition of the present disclosure in combination with an additional therapeutic agent comprising a TCR for use as a medicament and/or for use in a method for the treatment of cancer.

[00147] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with a cell expressing a chimeric antigen receptor (CAR). In certain embodiments, the cell is a T cell.

[00148] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with a TCR mimic antibody. In certain embodiments, the TCR mimic antibody is an antibody that specifically binds to a peptide-MHC complex. For non-limiting examples of TCR mimic antibodies, *see, e.g.*, U.S. Patent No. 9,074,000 and U.S. Publication Nos. US 2009/0304679 A1 and US 2014/0134191 A1, all of which are incorporated herein by reference in their entireties.

[00149] In certain embodiments, an anti-LY6K antibody disclosed herein is administered to a subject in combination with a bispecific T-cell engager (BiTE) (*e.g.*, as described in WO2005061547A2, which is incorporated by reference herein in its entirety) and/or a dual-affinity re-targeting antibody (DART) (*e.g.*, as described in WO2012162067A2, which is incorporated by reference herein in its entirety). In certain embodiments, the BiTE and/or DART specifically binds to a tumor-associated antigen (*e.g.*, a polypeptide overexpressed in a tumor, a polypeptide derived from an oncovirus, a polypeptide comprising a post-translational modification specific to a tumor, a polypeptide specifically mutated in a tumor) and a molecule on an effector cell (*e.g.*, CD3 or CD16). In certain embodiments, the tumor-associated antigen is EGFR (*e.g.*, human EGFR), optionally wherein the BiTE and/or DART comprises the VH and VL sequences of cetuximab. In certain embodiments, the tumor-associated antigen is Her2 (*e.g.*, human Her2), optionally wherein the BiTE and/or DART comprises the VH and VL sequences of trastuzumab. In certain embodiments, the tumor-associated antigen is CD20 (*e.g.*, human CD20).

[00150] The anti-LY6K antibody and the additional therapeutic agent (*e.g.*, chemotherapeutic, radiotherapeutic, checkpoint targeting agent, IDO inhibitor, vaccine, adjuvant, a soluble TCR, a cell expressing a TCR, a cell expressing a chimeric antigen receptor, and/or a TCR mimic antibody) can be administered separately, sequentially, or concurrently as separate dosage forms. In certain embodiments, an anti-LY6K antibody is administered parenterally, and an IDO inhibitor is administered orally.

[00151] An antibody or pharmaceutical composition described herein may be delivered to a subject by a variety of routes. These include, but are not limited to, parenteral, intranasal, intratracheal, oral, intradermal, topical, intramuscular, intraperitoneal, transdermal, intravenous, intratumoral, conjunctival, intra-arterial, and subcutaneous routes. Pulmonary administration can also be employed, *e.g.* by use of an inhaler or nebulizer, and formulation with an aerosolizing agent for use as a spray. In certain embodiments, the antibody or pharmaceutical composition described herein is delivered subcutaneously or intravenously. In certain embodiments, the antibody or pharmaceutical composition described herein is delivered intra-arterially. In certain embodiments, the antibody or pharmaceutical composition described herein is delivered intratumorally. In certain embodiments, the antibody or pharmaceutical composition described herein is delivered into a tumor draining lymph node.

[00152] The amount of an antibody or composition which will be effective in the treatment and/or prevention of a condition will depend on the nature of the disease and can be determined by standard clinical techniques.

[00153] The precise dose to be employed in a composition will also depend on the route of administration, and the seriousness of the infection or disease caused by it and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the patient (including age, body weight, and health), whether the patient is human or an animal, other medications administered, or whether treatment is prophylactic or therapeutic. Usually, the patient is a human, but non-human mammals, including transgenic mammals, can also be treated. Treatment dosages are optimally titrated to optimize safety and efficacy.

[00154] An anti-LY6K antibody described herein can also be used to assay LY6K (*e.g.*, human LY6K) protein levels in a biological sample using classical immunohistological methods known to those of skill in the art, including immunoassays, such as the enzyme linked immunosorbent assay (ELISA), immunoprecipitation, or Western blotting. Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{121}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. Such labels can be used to label an antibody described herein. Alternatively, a second antibody that recognizes an anti-LY6K antibody described herein can be labeled and used in combination with an anti-LY6K antibody to detect LY6K (*e.g.*, human LY6K) protein levels. Therefore, in certain embodiments, the present disclosure relates to the use of an anti-LY6K antibody of the present disclosure for *in vitro* detection of LY6K (*e.g.*, human LY6K) protein in a biological sample. In a further embodiment, the present disclosure relates to the use of an anti-LY6K antibody of the disclosure, for assaying and/or detecting LY6K (*e.g.*, human LY6K) protein levels in a biological sample *in vitro*, optionally wherein the anti-LY6K antibody is conjugated to a radionuclide or detectable label, and/or carries a label described herein, and/or wherein an immunohistological method is used.

[00155] Assaying for the expression level of LY6K (*e.g.*, human LY6K) protein is intended to include qualitatively or quantitatively measuring or estimating the level of LY6K (*e.g.*, human LY6K) protein in a first biological sample either directly (*e.g.*, by determining or estimating absolute protein level) or relatively (*e.g.*, by comparing to the disease associated protein level in a second biological sample). LY6K (*e.g.*, human LY6K) polypeptide expression level in the first biological sample can be measured or estimated and compared to a standard LY6K (*e.g.*, human LY6K) protein level, the standard being taken, for example, from a second biological sample obtained from an individual not having the disorder or being

determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once the “standard” LY6K (*e.g.*, human LY6K) polypeptide level is known, it can be used repeatedly as a standard for comparison. Therefore, in a further embodiment, the present disclosure relates to an *in vitro* method for assaying and/or detecting LY6K protein levels, for example human LY6K protein levels, in a biological sample, comprising qualitatively or quantitatively measuring or estimating the level of LY6K protein, for example of human LY6K protein, in a biological sample, by an immunohistological method.

[00156] As used herein, the term “biological sample” refers to any biological sample obtained from a subject, cell line, tissue, or other source of cells potentially expressing LY6K (*e.g.*, human LY6K). Methods for obtaining tissue biopsies and body fluids from animals (*e.g.*, humans or cynomolgus monkeys) are well known in the art. Biological samples include peripheral blood mononuclear cells (PBMCs).

[00157] An anti-LY6K antibody described herein can be used for prognostic, diagnostic, monitoring, and screening applications, including *in vitro* and *in vivo* applications well known and standard to the skilled artisan and based on the present description. Prognostic, diagnostic, monitoring, and screening assays and kits for *in vitro* assessment and evaluation of immune system status, immune response, and/or cancer (*e.g.*, tumorigenesis) may be utilized to predict, diagnose, and monitor to evaluate patient samples, including those known to have or suspected of having an immune system-dysfunction or cancer, or with regard to an anticipated or desired immune system response, antigen response, or vaccine response. The assessment and evaluation of immune system status, immune response, and/or cancer are also useful in determining the suitability of a patient for a clinical trial of a drug or for the administration of a particular chemotherapeutic agent, a radiotherapeutic agent, or an antibody, including combinations thereof, versus a different agent or antibody. This type of prognostic and diagnostic monitoring and assessment is already in practice utilizing antibodies against the HER2 protein in breast cancer (HercepTest™, Dako) where the assay is also used to evaluate patients for antibody therapy using Herceptin®. *In vivo* applications include directed cell therapy and immune system modulation and radio imaging of immune responses. Therefore, in certain embodiments, the present disclosure relates to an anti-LY6K antibody and/or pharmaceutical composition of the present disclosure for use as a diagnostic. In certain embodiments, the present disclosure relates to an anti-LY6K antibody and/or pharmaceutical composition of the present disclosure for use in a method for the prediction, diagnosis, and/or monitoring of a subject having or suspected to have an immune system-dysfunction, cancer,

and/or with regard to an anticipated or desired immune system response, antigen response, or vaccine response. In another embodiment, the present disclosure relates to the use of an anti-LY6K antibody of the disclosure, for predicting, diagnosing, and/or monitoring of a subject having or suspected to have an immune system-dysfunction, cancer, and/or with regard to an anticipated or desired immune system response, antigen response, or vaccine response by assaying and/or detecting human LY6K protein levels in a biological sample of the subject *in vitro*.

[00158] In certain embodiments, an anti-LY6K antibody can be used in immunohistochemistry of biopsy samples. In certain embodiments, the method is an *in vitro* method. In another embodiment, an anti-LY6K antibody can be used to detect levels of LY6K (*e.g.*, human LY6K), or levels of cells which contain LY6K (*e.g.*, human LY6K) on their membrane surface, the levels of which can then be linked to certain disease symptoms. Anti-LY6K antibodies described herein may carry a detectable or functional label and/or may be conjugated to a radionuclide or detectable label. When fluorescence labels are used, currently available microscopy and fluorescence-activated cell sorter analysis (FACS) or combination of both methods procedures known in the art may be utilized to identify and to quantitate the specific binding members. Anti-LY6K antibodies described herein may carry or may be conjugated to a fluorescence label. Exemplary fluorescence labels include, for example, reactive and conjugated probes, *e.g.*, Aminocoumarin, Fluorescein and Texas red, Alexa Fluor dyes, Cy dyes, and DyLight dyes. An anti-LY6K antibody may carry or may be conjugated to a radioactive label or radionuclide, such as the isotopes ^3H , ^{14}C , ^{32}P , ^{35}S , ^{36}Cl , ^{51}Cr , ^{57}Co , ^{58}Co , ^{59}Fe , ^{67}Cu , ^{90}Y , ^{99}Tc , ^{111}In , ^{117}Lu , ^{121}I , ^{124}I , ^{125}I , ^{131}I , ^{198}Au , ^{211}At , ^{213}Bi , ^{225}Ac , and ^{186}Re . When radioactive labels are used, currently available counting procedures known in the art may be utilized to identify and quantitate the specific binding of an anti-LY6K antibody to LY6K (*e.g.*, human LY6K). In the instance where the label is an enzyme, detection may be accomplished by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric, or gasometric techniques as known in the art. This can be achieved by contacting a sample or a control sample with an anti-LY6K antibody under conditions that allow for the formation of a complex between the anti-LY6K antibody and LY6K (*e.g.*, human LY6K). Any complexes formed between the anti-LY6K antibody and LY6K (*e.g.*, human LY6K), are detected and compared in the sample and the control. In light of the specific binding of the anti-LY6K antibodies described herein for LY6K (*e.g.*, human LY6K), the anti-LY6K antibodies can be used to specifically detect LY6K (*e.g.*, human LY6K). The anti-LY6K antibodies described herein can also be used to purify LY6K (*e.g.*, human LY6K) via

immunoaffinity purification. Also included herein is an assay system which may be prepared in the form of a test kit, kit, or kit-of-parts for the quantitative analysis of the extent of the presence of, for instance, LY6K (*e.g.*, human LY6K)/LY6K (*e.g.*, human LY6K) ligand complexes. The system, test kit, kit, or kit-of-parts may comprise a labeled component, *e.g.*, a labeled antibody, and one or more additional immunochemical reagents.

Polynucleotides, Vectors, and Methods of Producing Antibodies

[00159] In another aspect, provided herein are polynucleotides comprising a nucleotide sequence encoding an antibody, or a portion thereof, described herein or a fragment thereof (*e.g.*, a VL and/or VH; and a light chain and/or heavy chain) that specifically binds to a LY6K (*e.g.*, human LY6K) antigen, and vectors, *e.g.*, vectors comprising such polynucleotides for recombinant expression in host cells (*e.g.*, *E. coli* and mammalian cells). Provided herein are polynucleotides comprising nucleotide sequences encoding a heavy and/or light chain of any of the antibodies provided herein, as well as vectors comprising such polynucleotide sequences, *e.g.*, expression vectors for their efficient expression in host cells, *e.g.*, mammalian cells. In certain embodiments, a nucleic acid molecule(s) encoding an antibody described herein is isolated or purified.

[00160] In particular aspects, provided herein are polynucleotides comprising nucleotide sequences encoding antibodies, which specifically bind to a LY6K (*e.g.*, human LY6K) polypeptide and comprise an amino acid sequence as described herein, as well as antibodies which compete with such antibodies for binding to a LY6K (*e.g.*, human LY6K) polypeptide (*e.g.*, in a dose-dependent manner), or which binds to the same epitope as that of such antibodies.

[00161] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding the light chain or heavy chain of an antibody described herein. The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VL FRs and CDRs of antibodies described herein (*see, e.g.*, **Tables 2 and 4**) or nucleotide sequences encoding a heavy chain comprising the VH FRs and CDRs of antibodies described herein (*see, e.g.*, **Tables 1 and 3**). In certain embodiments, a polynucleotide encodes a VH, VL, heavy chain, and/or light chain of an antibody described herein. In another embodiment, a polynucleotide encodes the first VH and the first VL of an antibody described herein. In another embodiment, a polynucleotide encodes the second VH and the second VL of an antibody described herein. In another embodiment, a polynucleotide encodes the first heavy chain and the first light chain of an antibody described herein. In another embodiment, a polynucleotide

encodes the second heavy chain and the second light chain of an antibody described herein. In another embodiment, a polynucleotide encodes the VH and/or the VL, or the heavy chain and/or the light chain, of an antibody described herein.

[00162] Also provided herein are polynucleotides encoding an anti-LY6K antibody that are optimized, *e.g.*, by codon/RNA optimization, replacement with heterologous signal sequences, and elimination of mRNA instability elements. Methods to generate optimized nucleic acids encoding an anti-LY6K antibody or a fragment thereof (*e.g.*, light chain, heavy chain, VH domain, or VL domain) for recombinant expression by introducing codon changes and/or eliminating inhibitory regions in the mRNA can be carried out by adapting the optimization methods described in, *e.g.*, U.S. Patent Nos. 5,965,726; 6,174,666; 6,291,664; 6,414,132; and 6,794,498, accordingly, all of which are herein incorporated by reference in their entireties. For example, potential splice sites and instability elements (*e.g.*, A/T or A/U rich elements) within the RNA can be mutated without altering the amino acids encoded by the nucleic acid sequences to increase stability of the RNA for recombinant expression. The alterations utilize the degeneracy of the genetic code, *e.g.*, using an alternative codon for an identical amino acid. In certain embodiments, it can be desirable to alter one or more codons to encode a conservative mutation, *e.g.*, a similar amino acid with similar chemical structure and properties and/or function as the original amino acid. Such methods can increase expression of an anti-LY6K antibody or fragment thereof by at least 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold or more relative to the expression of an anti-LY6K antibody encoded by polynucleotides that have not been optimized.

[00163] In certain embodiments, an optimized polynucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof (*e.g.*, VL domain and/or VH domain) can hybridize to an antisense (*e.g.*, complementary) polynucleotide of an unoptimized polynucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof (*e.g.*, VL domain and/or VH domain). In specific embodiments, an optimized nucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof hybridizes under high stringency conditions to antisense polynucleotide of an unoptimized polynucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof. In a specific embodiment, an optimized nucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof hybridizes under high stringency, intermediate or lower stringency hybridization conditions to an antisense polynucleotide of an unoptimized nucleotide sequence encoding an anti-LY6K antibody described herein or a fragment thereof.

Information regarding hybridization conditions has been described, *see, e.g.*, U.S. Patent Application Publication No. US 2005/0048549 (*e.g.*, paragraphs 72-73), which is herein incorporated by reference in its entirety.

[00164] The polynucleotides can be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Nucleotide sequences encoding antibodies described herein, *e.g.*, antibodies described in **Tables 1-4**, and modified versions of these antibodies can be determined using methods known in the art, *i.e.*, nucleotide codons known to encode particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody. Such a polynucleotide encoding the antibody can be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier G *et al.*, (1994), *BioTechniques* 17: 242-6, herein incorporated by reference in its entirety), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[00165] Alternatively, a polynucleotide encoding an antigen-binding region of an antibody described herein can be generated from nucleic acid from a suitable source (*e.g.*, a hybridoma) using methods well known in the art (*e.g.*, PCR and other molecular cloning methods). For example, PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of a known sequence can be performed using genomic DNA obtained from hybridoma cells producing the antibody of interest. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the light chain and/or heavy chain of an antibody. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the variable light chain region and/or the variable heavy chain region of an antibody. The amplified nucleic acids can be cloned into vectors for expression in host cells and for further cloning.

[00166] If a clone containing a nucleic acid encoding a particular antigen-binding region or antibody is not available, but the sequence of the antigen-binding region or antibody molecule is known, a nucleic acid encoding the immunoglobulin can be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library or a cDNA library generated from, or nucleic acid, preferably poly A⁺ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody described herein) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence, or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids

generated by PCR can then be cloned into replicable cloning vectors using any method well known in the art.

[00167] DNA encoding anti-LY6K (*e.g.*, human LY6K) antibodies described herein can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the anti-LY6K (*e.g.*, human LY6K) antibodies). Hybridoma cells can serve as a source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells (*e.g.*, CHO cells from the CHO GS System™ (Lonza)), or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of anti-LY6K antibodies in the recombinant host cells.

[00168] To generate whole antibodies or antigen-binding regions, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a heavy chain constant region, *e.g.*, the human gamma 1 or human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a light chain constant region, *e.g.*, human kappa or lambda constant regions. In certain embodiments, the vectors for expressing the VH or VL domains comprise an EF-1 α promoter, a secretion signal, a cloning site for the variable region, constant regions, and a selection marker such as neomycin. The VH and VL domains can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00169] The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant regions in place of the murine sequences, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

[00170] Also provided are polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides that encode an antibody described herein. In specific embodiments, polynucleotides described herein hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides encoding a VH domain and/or VL domain provided herein.

[00171] Hybridization conditions have been described in the art and are known to one of skill in the art. For example, hybridization under stringent conditions can involve hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45°C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65°C; hybridization under highly stringent conditions can involve hybridization to filter-bound nucleic acid in 6xSSC at about 45°C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68°C. Hybridization under other stringent hybridization conditions are known to those of skill in the art and have been described, *see, e.g.*, Ausubel FM *et al.*, eds., (1989) Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3, which is herein incorporated by reference in its entirety.

[00172] In certain aspects, provided herein are cells (*e.g.*, host cells) expressing (*e.g.*, recombinantly) antibodies described herein which specifically bind to LY6K (*e.g.*, human LY6K), and related polynucleotides and expression vectors. Provided herein are vectors (*e.g.*, expression vectors) comprising polynucleotides comprising nucleotide sequences encoding anti-LY6K antibodies or a fragment for recombinant expression in host cells, preferably in mammalian cells (*e.g.*, CHO cells). Also provided herein are host cells comprising such vectors for recombinantly expressing anti-LY6K antibodies described herein (*e.g.*, human or humanized antibody). In a particular aspect, provided herein are methods for producing an antibody described herein, comprising expressing the antibody from a host cell.

[00173] Recombinant expression of an antibody described herein (*e.g.*, a full-length antigen-binding region or antibody or heavy and/or light chain of an antibody described herein) that specifically binds to LY6K (*e.g.*, human LY6K) generally involves construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule, heavy and/or light chain of an antibody, or a fragment thereof (*e.g.*, heavy and/or light chain variable regions) described herein has been obtained, the vector for the production of the antibody molecule can be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody or antibody fragment (*e.g.*, light chain or heavy chain) encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing an antibody or antibody fragment (*e.g.*, light chain or heavy chain) coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Also provided are replicable vectors comprising a nucleotide sequence

encoding containing an antibody molecule described herein, a heavy or light chain of an antibody, a heavy or light chain variable region of an antibody or a fragment thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors can, for example, include the nucleotide sequence encoding the constant region of the antibody molecule (*see, e.g.*, International Publication Nos. WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464, which are herein incorporated by reference in their entireties) and variable regions of the antibody can be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[00174] In certain embodiments, a vector comprises a polynucleotide encoding a VH, VL, heavy chain, and/or light chain of an antibody described herein. In another embodiment, a vector comprises a polynucleotide encoding the VH and the VL of an antibody described herein. In another embodiment, a vector comprises a polynucleotide encoding the heavy chain and the light chain of an antibody described herein.

[00175] An expression vector can be transferred to a cell (*e.g.*, host cell) by conventional techniques and the resulting cells can then be cultured by conventional techniques to produce cells containing an antibody described herein or a fragment thereof. Thus, provided herein are host cells containing a polynucleotide encoding containing an antibody described herein or fragments thereof, or a heavy or light chain thereof, or fragment thereof, or a single-chain antibody described herein, operably linked to a promoter for expression of such sequences in the host cell.

[00176] In certain embodiments, a host cell comprises a polynucleotide encoding the VH and VL of an antibody described herein. In another embodiment, a host cell comprises a vector comprising a polynucleotide encoding the VH and VL of an antibody described herein. In another embodiment, a host cell comprises a first polynucleotide encoding the VH of an antibody described herein, and a second polynucleotide encoding the VL of an antibody described herein. In another embodiment, a host cell comprises a first vector comprising a first polynucleotide encoding the VH of an antibody described herein, and a second vector comprising a second polynucleotide encoding the VL of an antibody described herein.

[00177] In specific embodiments, a heavy chain/heavy chain variable region expressed by a first cell is associated with a light chain/light chain variable region of a second cell to form an anti-LY6K (*e.g.*, human LY6K) antibody described herein. In certain embodiments, provided herein is a population of host cells comprising such first host cell and such second host cell.

[00178] In certain embodiments, provided herein is a population of vectors comprising a first vector comprising a polynucleotide encoding a light chain/light chain variable region of

an anti-LY6K (*e.g.*, human LY6K) antibody described herein, and a second vector comprising a polynucleotide encoding a heavy chain/heavy chain variable region of an anti-LY6K (*e.g.*, human LY6K) antibody described herein.

[00179] A variety of host-expression vector systems can be utilized to express antibody molecules described herein (*see, e.g.*, U.S. Patent No. 5,807,715, which is herein incorporated by reference in its entirety). Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also represent cells which can, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule described herein *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with, *e.g.*, recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces* and *Pichia*) transformed with, *e.g.*, recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with, *e.g.*, recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems (*e.g.*, green algae such as *Chlamydomonas reinhardtii*) infected with, *e.g.*, recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with, *e.g.*, recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS (*e.g.*, COS1 or COS), CHO, BHK, MDCK, HEK 293, NS0, PER.C6, VERO, CRL7030, HsS78Bst, HeLa, and NIH 3T3, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20 and BMT10 cells) harboring, *e.g.*, recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). In a specific embodiment, cells for expressing antibodies described herein are Chinese hamster ovary (CHO) cells, for example CHO cells from the CHO GS System™ (Lonza). In certain embodiments, the heavy chain and/or light chain of an antibody produced by a CHO cell may have an N-terminal glutamine or glutamate residue replaced by pyroglutamate. In certain embodiments, cells for expressing antibodies described herein are human cells, *e.g.*, human cell lines. In a specific embodiment, a mammalian expression vector is pOptiVEC™ or pcDNA3.3. In certain embodiments, bacterial cells such as *Escherichia coli*, or eukaryotic cells (*e.g.*, mammalian cells), especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as CHO cells, in conjunction with a vector such as the major intermediate early gene promoter element from human

cytomegalovirus, are an effective expression system for antibodies (Foecking MK & Hofstetter H (1986) Gene 45: 101-5; and Cockett MI *et al.*, (1990) Biotechnology 8(7): 662-7, each of which is herein incorporated by reference in its entirety). In certain embodiments, antibodies described herein are produced by CHO cells or NS0 cells. In a specific embodiment, the expression of nucleotide sequences encoding antibodies described herein which specifically bind to LY6K (*e.g.*, human LY6K) is regulated by a constitutive promoter, inducible promoter, or tissue specific promoter.

[00180] In bacterial systems, a number of expression vectors can be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such an antibody is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified can be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruether U & Mueller-Hill B (1983) EMBO J 2: 1791-1794), in which the coding sequence can be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye S & Inouye M (1985) Nuc Acids Res 13: 3101-3109; Van Heeke G & Schuster SM (1989) J Biol Chem 24: 5503-5509); and the like, all of which are herein incorporated by reference in their entireties. For example, pGEX vectors can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[00181] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV), for example, can be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[00182] In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the coding sequence of interest can be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene can then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and

capable of expressing the molecule in infected hosts (*see, e.g.*, Logan J & Shenk T (1984) PNAS 81(12): 3655-9, which is herein incorporated by reference in its entirety). Specific initiation signals can also be required for efficient translation of inserted coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (*see, e.g.*, Bitter G *et al.*, (1987) Methods Enzymol. 153: 516-544, which is herein incorporated by reference in its entirety).

[00183] In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products can be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product can be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, MDCK, HEK 293, NIH 3T3, W138, BT483, Hs578T, HTB2, BT20 and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7030, COS (*e.g.*, COS1 or COS), PER.C6, VERO, HsS78Bst, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20, BMT10, and HsS78Bst cells. In certain embodiments, anti-LY6K (*e.g.*, human LY6K) antibodies described herein are produced in mammalian cells, such as CHO cells.

[00184] In a specific embodiment, the antibodies described herein have reduced fucose content or no fucose content. Such antibodies can be produced using techniques known one skilled in the art. For example, the antibodies can be expressed in cells deficient or lacking the ability to fucosylate. In a specific example, cell lines with a knockout of both alleles of α 1,6-fucosyltransferase can be used to produce antibodies with reduced fucose content. The Potelligent[®] system (Lonza) is an example of such a system that can be used to produce antibodies with reduced fucose content.

[00185] For long-term, high-yield production of recombinant proteins, stable expression cells can be generated. For example, cell lines which stably express an anti-LY6K (*e.g.*, human

LY6K) antibody described herein can be engineered. In specific embodiments, a cell provided herein stably expresses a light chain/light chain variable region and a heavy chain/heavy chain variable region which associate to form an antigen-binding region or an antibody described herein.

[00186] In certain aspects, rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA/polynucleotide, engineered cells can be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express an anti-LY6K (*e.g.*, human LY6K) described herein or a fragment thereof. Such engineered cell lines can be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[00187] A number of selection systems can be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler M *et al.*, (1977) Cell 11(1): 223-32), hypoxanthineguanine phosphoribosyltransferase (Szybalska EH & Szybalski W (1962) PNAS 48(12): 2026-2034), and adenine phosphoribosyltransferase (Lowy I *et al.*, (1980) Cell 22(3): 817-23) genes in tk-, hgp^rt- or ap^rt-cells, respectively, all of which are herein incorporated by reference in their entireties. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler M *et al.*, (1980) PNAS 77(6): 3567-70; O'Hare K *et al.*, (1981) PNAS 78: 1527-31); *gpt*, which confers resistance to mycophenolic acid (Mulligan RC & Berg P (1981) PNAS 78(4): 2072-6); *neo*, which confers resistance to the aminoglycoside G-418 (Wu GY & Wu CH (1991) Biotherapy 3: 87-95; Tolstoshev P (1993) Ann Rev Pharmacol Toxicol 32: 573-596; Mulligan RC (1993) Science 260: 926-932; and Morgan RA & Anderson WF (1993) Ann Rev Biochem 62: 191-217; Nabel GJ & Felgner PL (1993) Trends Biotechnol 11(5): 211-5); and *hygro*, which confers resistance to hygromycin (Santerre RF *et al.*, (1984) Gene 30(1-3): 147-56), all of which are herein incorporated by reference in their entireties. Methods commonly known in the art of recombinant DNA technology can be routinely applied to select the desired recombinant clone and such methods are described, for example, in Ausubel FM *et al.*, (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler M, Gene Transfer and

Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli NC *et al.*, (eds.), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colbère-Garapin F *et al.*, (1981) J Mol Biol 150: 1-14, all of which are herein incorporated by reference in their entirety.

[00188] The expression levels of an antibody molecule can be increased by vector amplification (for a review, *see* Bebbington CR & Hentschel CCG, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3 (Academic Press, New York, 1987), which is herein incorporated by reference in its entirety). When a marker in the vector system is amplifiable, an increase in the level of inhibitor present in culture of the host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the gene of interest, production of the protein will also increase (Crouse GF *et al.*, (1983) Mol Cell Biol 3: 257-66, which is herein incorporated by reference in its entirety).

[00189] The host cell can be co-transfected with two or more expression vectors described herein, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors can contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. The host cells can be co-transfected with different amounts of the two or more expression vectors. For example, host cells can be transfected with any one of the following ratios of a first expression vector and a second expression vector: about 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, or 1:50.

[00190] Alternatively, a single vector can be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot NJ (1986) Nature 322: 562-565; and Köhler G (1980) PNAS 77: 2197-2199, each of which is herein incorporated by reference in its entirety). The coding sequences for the heavy and light chains can comprise cDNA or genomic DNA. The expression vector can be monocistronic or multicistronic. A multicistronic nucleic acid construct can encode 2, 3, 4, 5, 6, 7, 8, 9, 10, or more genes/nucleotide sequences, or in the range of 2-5, 5-10, or 10-20 genes/nucleotide sequences. For example, a bicistronic nucleic acid construct can comprise, in the following order, a promoter, a first gene (*e.g.*, heavy chain of an antibody described herein), and a second gene and (*e.g.*, light chain of an antibody described herein). In such an expression vector, the transcription of both genes can be driven by the promoter, whereas the translation of the mRNA

from the first gene can be by a cap-dependent scanning mechanism and the translation of the mRNA from the second gene can be by a cap-independent mechanism, *e.g.*, by an IRES.

[00191] Once an antibody molecule described herein has been produced by recombinant expression, it can be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies described herein can be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[00192] In specific embodiments, an antibody described herein is isolated or purified. In certain embodiments, an isolated antibody is one that is substantially free of other antibodies with different antigenic specificities than the isolated antibody. For example, in certain embodiments, a preparation of an antibody described herein is substantially free of cellular material and/or chemical precursors. The language “substantially free of cellular material” includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (by dry weight) of heterologous protein (also referred to herein as a “contaminating protein”) and/or variants of an antibody, for example, different post-translational modified forms of an antibody or other different versions of an antibody (*e.g.*, antibody fragments). When the antibody is recombinantly produced, it is also generally substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, 2%, 1%, 0.5%, or 0.1% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is generally substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, or 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a specific embodiment, antibodies described herein are isolated or purified.

[00193] Anti-LY6K (*e.g.*, human LY6K) antibodies or fragments thereof can be produced by any method known in the art for the synthesis of proteins or antibodies, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employ, unless otherwise indicated, conventional techniques in molecular biology,

microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. *See, e.g.*, Maniatis T *et al.*, (1982) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (1989), *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (2001) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons (1987 and annual updates); *Current Protocols in Immunology*, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) *Oligonucleotide Synthesis: A Practical Approach*, IRL Press; Eckstein (ed.) (1991) *Oligonucleotides and Analogues: A Practical Approach*, IRL Press; Birren B *et al.*, (eds.) (1999) *Genome Analysis: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, all of which are herein incorporated by reference in their entireties.

[00194] In a specific embodiment, an antibody described herein is prepared, expressed, created, or isolated by any means that involves creation, *e.g.*, via synthesis, genetic engineering of DNA sequences. In certain embodiments, such an antibody comprises sequences (*e.g.*, DNA sequences or amino acid sequences) that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.*, human) *in vivo*.

[00195] In one aspect, provided herein is a method of making an anti-LY6K (*e.g.*, human LY6K) antibody comprising culturing a cell or host cell described herein. In certain embodiments, the method is performed *in vitro*. In a certain aspect, provided herein is a method of making an anti-LY6K (*e.g.*, human LY6K) antibody comprising expressing (*e.g.*, recombinantly expressing) the antibody using a cell or host cell described herein (*e.g.*, a cell or a host cell comprising polynucleotides encoding an antibody described herein). In certain embodiments, the cell is an isolated cell. In certain embodiments, the exogenous polynucleotides have been introduced into the cell. In certain embodiments, the method further comprises the step of purifying the antibody obtained from the cell or host cell.

[00196] In certain embodiments, an antibody is produced by expressing in a cell a polynucleotide encoding the VH and VL of an antibody described herein under suitable conditions so that the polynucleotides are expressed and the antibody is produced. In another embodiment, an antibody is produced by expressing in a cell a polynucleotide encoding the heavy chain and light chain of an antibody described herein under suitable conditions so that the polynucleotides are expressed and the antibody is produced. In certain embodiments, an

antibody is produced by expressing in a cell a first polynucleotide encoding the VH of an antibody described herein, and a second polynucleotide encoding the VL of an antibody described herein, under suitable conditions so that the polynucleotides are expressed and the antibody is produced. In certain embodiments, an antibody is produced by expressing in a cell a first polynucleotide encoding the heavy chain of an antibody described herein, and a second polynucleotide encoding the light chain of an antibody described herein, under suitable conditions so that the polynucleotides are expressed and the antibody is produced.

[00197] Methods for producing polyclonal antibodies are known in the art (*see, e.g.*, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.*, eds., John Wiley and Sons, New York, which is herein incorporated by reference in its entirety).

[00198] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art, including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques, including those known in the art and taught, for example, in Harlow E & Lane D, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981), each of which is herein incorporated by reference in its entirety. The term “monoclonal antibody” as used herein is not limited to antibodies produced through hybridoma technology. For example, monoclonal antibodies can be produced recombinantly from host cells exogenously expressing an antibody described herein or a fragment thereof, for example, light chain and/or heavy chain of such antibody.

[00199] In specific embodiments, a “monoclonal antibody,” as used herein, is an antibody produced by a single cell (*e.g.*, hybridoma or host cell producing a recombinant antibody), wherein the antibody specifically binds to LY6K (*e.g.*, human LY6K) as determined, *e.g.*, by ELISA or other antigen-binding or competitive binding assay known in the art or in the examples provided herein. In certain embodiments, a monoclonal antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a monoclonal antibody is a monovalent antibody or multivalent (*e.g.*, bivalent) antibody. In certain embodiments, a monoclonal antibody is a monospecific or multispecific antibody (*e.g.*, bispecific antibody). Monoclonal antibodies described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495, which is herein incorporated by reference in its entirety, or can, *e.g.*, be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of

monoclonal antibodies expressed thereby are well known in the art (*see, e.g.*, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.*, *supra*).

[00200] As used herein, an antibody binds to an antigen multivalently (*e.g.*, bivalently) when the antibody comprises at least two (*e.g.*, two or more) monovalent binding regions, each monovalent binding region capable of binding to an epitope on the antigen. Each monovalent binding region can bind to the same or different epitopes on the antigen.

[00201] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. For example, in the hybridoma method, a mouse or other appropriate host animal, such as a sheep, goat, rabbit, rat, hamster, or macaque monkey, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein (*e.g.*, LY6K (*e.g.*, human LY6K)) used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding JW (Ed.), Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986), herein incorporated by reference in its entirety). Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilpatrick KE *et al.*, (1997) Hybridoma 16:381-9, herein incorporated by reference in its entirety).

[00202] In certain embodiments, mice (or other animals, such as rats, monkeys, donkeys, pigs, sheep, hamster, or dogs) can be immunized with an antigen (*e.g.*, LY6K (*e.g.*, human LY6K)), and once an immune response is detected, *e.g.*, antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well-known techniques to any suitable myeloma cells, for example, cells from cell line SP20 available from the American Type Culture Collection (ATCC®) (Manassas, VA), to form hybridomas. Hybridomas are selected and cloned by limited dilution. In certain embodiments, lymph nodes of the immunized mice are harvested and fused with NS0 myeloma cells.

[00203] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00204] Specific embodiments employ myeloma cells that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these myeloma cell lines are murine myeloma lines, such as the NS0 cell line or those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8.653 cells available from the American Type Culture Collection, Rockville, MD, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor D (1984) J Immunol 133: 3001-5; Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987), each of which is herein incorporated by reference in its entirety).

[00205] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against LY6K (*e.g.*, human LY6K). The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by methods known in the art, for example, immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

[00206] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding JW (Ed.), Monoclonal Antibodies: Principles and Practice, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI 1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00207] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00208] Antibodies described herein include, *e.g.*, antibody fragments which recognize LY6K (*e.g.*, human LY6K), and can be generated by any technique known to those of skill in the art. For example, Fab and F(ab')₂ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). A Fab fragment corresponds to one of the two identical arms of an antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A F(ab')₂ fragment contains the two antigen-binding arms of an antibody molecule linked by disulfide bonds in the hinge region.

[00209] Further, the antibodies described herein can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli*, and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage, including fd and M13, and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen-binding region that binds to a particular antigen can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies described herein include those disclosed in Brinkman U *et al.*, (1995) J Immunol Methods 182: 41-50; Ames RS *et al.*, (1995) J Immunol Methods 184: 177-186; Kettleborough CA *et al.*, (1994) Eur J Immunol 24: 952-958; Persic L *et al.*, (1997) Gene 187: 9-18; Burton DR & Barbas CF (1994) Advan Immunol 57: 191-280; PCT Application No. PCT/GB91/001134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO 97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743, and 5,969,108, all of which are herein incorporated by reference in their entireties.

[00210] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen-binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce antibody fragments such as Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax RL *et al.*, (1992) BioTechniques 12(6): 864-9; Sawai H *et al.*, (1995) Am J Reprod Immunol 34: 26-34; and Better M *et al.*, (1988) Science 240: 1041-1043, all of which are herein incorporated by reference in their entireties.

[00211] In certain embodiments, to generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site, can be used to amplify the VH or VL sequences from a template, *e.g.*, scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains

can be cloned into vectors expressing a VH constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. The VH and VL domains can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00212] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. For example, a chimeric antibody can contain a variable region of a mouse or rat monoclonal antibody fused to a constant region of a human antibody. Methods for producing chimeric antibodies are known in the art. *See, e.g.*, Morrison SL (1985) *Science* 229: 1202-7; Oi VT & Morrison SL (1986) *BioTechniques* 4: 214-221; Gillies SD *et al.*, (1989) *J Immunol Methods* 125: 191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415, all of which are herein incorporated by reference in their entireties.

[00213] A humanized antibody is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and CDRs having substantially the amino acid sequence of a non-human immunoglobulin (*e.g.*, a murine immunoglobulin). In certain embodiments, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The antibody also can include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. A humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA, and IgE, and any isotype, including IgG₁, IgG₂, IgG₃, and IgG₄. Humanized antibodies can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592106 and EP 519596; Padlan EA (1991) *Mol Immunol* 28(4/5): 489-498; Studnicka GM *et al.*, (1994) *Prot Engineering* 7(6): 805-814; and Roguska MA *et al.*, (1994) *PNAS* 91: 969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.*, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 93/17105; Tan P *et al.*, (2002) *J Immunol* 169: 1119-25; Caldas C *et al.*, (2000) *Protein Eng.* 13(5): 353-60; Morea V *et al.*, (2000) *Methods* 20(3): 267-79; Baca M *et al.*, (1997) *J Biol Chem* 272(16): 10678-84; Roguska MA *et al.*, (1996) *Protein Eng* 9(10): 895-904; Couto JR *et al.*, (1995) *Cancer Res.* 55 (23 Supp): 5973s-5977s; Couto JR

et al., (1995) *Cancer Res* 55(8): 1717-22; Sandhu JS (1994) *Gene* 150(2): 409-10; and Pedersen JT *et al.*, (1994) *J Mol Biol* 235(3): 959-73, all of which are herein incorporated by reference in their entirety. *See also*, U.S. Application Publication No. US 2005/0042664 A1 (Feb. 24, 2005), which is herein incorporated by reference in its entirety.

[00214] Methods for making multispecific antibodies (*e.g.*, bispecific antibodies) have been described, *see, e.g.*, U.S. Patent Nos. 7,951,917; 7,183,076; 8,227,577; 5,837,242; 5,989,830; 5,869,620; 6,132,992; and 8,586,713, all of which are herein incorporated by reference in their entirety.

[00215] Bispecific, bivalent antibodies, and methods of making them, are described, for instance in U.S. Pat. Nos. 5,731,168; 5,807,706; 5,821,333; and U.S. Appl. Publ. Nos. 2003/020734 and 2002/0155537, each of which is herein incorporated by reference in its entirety. Bispecific tetravalent antibodies, and methods of making them are described, for instance, in Int. Appl. Publ. Nos. WO 02/096948 and WO 00/44788, the disclosures of both of which are herein incorporated by reference in its entirety. *See generally*, Int. Appl. Publ. Nos. WO 93/17715, WO 92/08802, WO 91/00360, and WO 92/05793; Tutt *et al.*, *J. Immunol.* 147:60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; and 5,601,819; and Kostelny *et al.*, *J. Immunol.* 148:1547-1553 (1992); each of which is herein incorporated by reference in its entirety.

[00216] A bispecific antibody as described herein can be generated according to the DuoBody technology platform (Genmab A/S) as described, *e.g.*, in International Publication Nos. WO 2011/131746, WO 2011/147986, WO 2008/119353, and WO 2013/060867, and in Labrijn AF *et al.*, (2013) *PNAS* 110(13): 5145-5150. The DuoBody technology can be used to combine one half of a first monospecific antibody, or first antigen-binding region, containing two heavy and two light chains with one half of a second monospecific antibody, or second antigen-binding region, containing two heavy and two light chains. The resultant heterodimer contains one heavy chain and one light chain from the first antibody, or first antigen-binding region, paired with one heavy chain and one light chain from the second antibody, or second antigen-binding region. When both of the monospecific antibodies, or antigen-binding regions, recognize different epitopes on different antigens, the resultant heterodimer is a bispecific antibody.

[00217] The DuoBody technology requires that each of the monospecific antibodies, or antigen-binding regions, includes a heavy chain constant region with a single point mutation in the CH3 domain. The point mutations allow for a stronger interaction between the CH3 domains in the resultant bispecific antibody than between the CH3 domains in either of the

monospecific antibodies, or antigen-binding regions. The single point mutation in each monospecific antibody, or antigen-binding region, is at residue 366, 368, 370, 399, 405, 407, or 409, numbered according to the EU numbering system, in the CH3 domain of the heavy chain constant region, as described, *e.g.*, in International Publication No. WO 2011/131746. Moreover, the single point mutation is located at a different residue in one monospecific antibody, or antigen-binding region, as compared to the other monospecific antibody, or antigen-binding region. For example, one monospecific antibody, or antigen-binding region, can comprise the mutation F405L (*i.e.*, a mutation from phenylalanine to leucine at residue 405), while the other monospecific antibody, or antigen-binding region, can comprise the mutation K409R (*i.e.*, a mutation from lysine to arginine at residue 409), numbered according to the EU numbering system. The heavy chain constant regions of the monospecific antibodies, or antigen-binding regions, can be an IgG₁, IgG₂, IgG₃, or IgG₄ isotype (*e.g.*, a human IgG₁ isotype), and a bispecific antibody produced by the DuoBody technology can retain Fc-mediated effector functions.

[00218] Another method for generating bispecific antibodies has been termed the “knobs-into-holes” strategy (*see, e.g.*, Intl. Publ. WO2006/028936). The mispairing of Ig heavy chains is reduced in this technology by mutating selected amino acids forming the interface of the CH3 domains in IgG. At positions within the CH3 domain at which the two heavy chains interact directly, an amino acid with a small side chain (hole) is introduced into the sequence of one heavy chain and an amino acid with a large side chain (knob) into the counterpart interacting residue location on the other heavy chain. In certain embodiments, compositions of the disclosure have immunoglobulin chains in which the CH3 domains have been modified by mutating selected amino acids that interact at the interface between two polypeptides so as to preferentially form a bispecific antibody. The bispecific antibodies can be composed of immunoglobulin chains of the same subclass (*e.g.*, IgG₁ or IgG₃) or different subclasses (*e.g.*, IgG₁ and IgG₃, or IgG₃ and IgG₄).

[00219] Bispecific antibodies can, in certain instances contain, IgG₄ and IgG₁, IgG₄ and IgG₂, IgG₄ and IgG₃, or IgG₁ and IgG₃ chain heterodimers. Such heterodimeric heavy chain antibodies can routinely be engineered by, for example, modifying selected amino acids forming the interface of the CH3 domains in human IgG₄ and the IgG₁ or IgG₃, so as to favor heterodimeric heavy chain formation.

[00220] In certain embodiments, an antibody described herein, which binds to the same epitope of LY6K (*e.g.*, human LY6K) as an anti-LY6K (*e.g.*, human LY6K) antibody described herein, is a human antibody. In certain embodiments, an antibody described herein, which

competitively blocks (*e.g.*, in a dose-dependent manner) any one of the antibodies described herein, from binding to LY6K (*e.g.*, human LY6K), is a human antibody. Human antibodies can be produced using any method known in the art. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, can be used. In particular, the human heavy and light chain immunoglobulin gene complexes can be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region can be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes can be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of an antigen (*e.g.*, LY6K (*e.g.*, human LY6K)). Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM, and IgE antibodies. For an overview of this technology for producing human antibodies, *see* Lonberg N & Huszar D (1995) *Int Rev Immunol* 13: 65-93, herein incorporated by reference in its entirety. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, International Publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, all of which are herein incorporated by reference in their entirety. Examples of mice capable of producing human antibodies include the XenoMouseTM (Abgenix, Inc.; U.S. Patent Nos. 6,075,181 and 6,150,184), the HuAb-MouseTM (Medarex, Inc./Gen Pharm; U.S. Patent Nos. 5,545,806 and 5,569, 825), the TransChromo MouseTM (Kirin) and the KM MouseTM (Medarex/Kirin), all of which are herein incorporated by reference in their entirety.

[00221] Human antibodies that specifically bind to LY6K (*e.g.*, human LY6K) can be made by a variety of methods known in the art, including the phage display methods described above

using antibody libraries derived from human immunoglobulin sequences. *See also*, U.S. Patent Nos. 4,444,887, 4,716,111, and 5,885,793; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741, all of which are herein incorporated by reference in their entireties.

[00222] In certain embodiments, human antibodies can be produced using mouse-human hybridomas. For example, human peripheral blood lymphocytes transformed with Epstein-Barr virus (EBV) can be fused with mouse myeloma cells to produce mouse-human hybridomas secreting human monoclonal antibodies, and these mouse-human hybridomas can be screened to determine ones which secrete human monoclonal antibodies that specifically bind to a target antigen (*e.g.*, LY6K (*e.g.*, human LY6K)). Such methods are known and are described in the art, *see, e.g.*, Shinmoto H *et al.*, (2004) Cytotechnology 46: 19-23; Naganawa Y *et al.*, (2005) Human Antibodies 14: 27-31, each of which is herein incorporated by reference in its entirety.

Kits

[00223] Also provided are kits comprising one or more antibodies described herein, or pharmaceutical compositions or conjugates thereof. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies provided herein. In certain embodiments, the kits contain a pharmaceutical composition described herein and any prophylactic or therapeutic agent, such as those described herein. In certain embodiments, the kits may contain a T cell mitogen, such as, *e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00224] Also provided are kits that can be used in the above methods. In certain embodiments, a kit comprises an antibody described herein, preferably purified antibody, in one or more containers. In a specific embodiment, kits described herein contain a substantially isolated LY6K (*e.g.*, human LY6K) antigen as a control. In another specific embodiment, the kits described herein further comprise a control antibody which does not react with LY6K (*e.g.*, human LY6K) antigen. In another specific embodiment, kits described herein contain one or more elements for detecting the binding of an antibody to a LY6K (*e.g.*, human LY6K) antigen

(e.g., the antibody can be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody can be conjugated to a detectable substrate). In specific embodiments, a kit provided herein can include a recombinantly produced or chemically synthesized LY6K (e.g., human LY6K) antigen. The LY6K (e.g., human LY6K) antigen provided in the kit can also be attached to a solid support. In a more specific embodiment, the detecting means of the above-described kit includes a solid support to which a LY6K (e.g., human LY6K) antigen is attached. Such a kit can also include a non-attached reporter-labeled anti-human antibody or anti-mouse/rat antibody. In this embodiment, binding of the antibody to the LY6K (e.g., human LY6K) antigen can be detected by binding of the said reporter-labeled antibody. In certain embodiments, the present disclosure relates to the use of a kit of the present disclosure for *in vitro* assaying and/or detecting LY6K (e.g., human LY6K) antigen in a biological sample.

EXAMPLES

[00225] The following examples are offered by way of illustration and not by way of limitation.

Example 1: Generation of anti-LY6K antibodies

[00226] Anti-LY6K antibodies were generated via immunization of mice in a standard RIMMS protocol using human LY6K as the immunogen at 10 ug/site. When test bleed titers of greater than 5000 by ELISA on LY6K were achieved, bone marrow and spleen were harvested. Both plasma B cells and antigen reactive B cells were sorted into single wells by FACS staining with dye labeled LY6K and standard B cell and plasma B markers and VH and VL sequences were amplified by PCR. Transient transfection of CHO cells and ELISA with unique VH and VL sequences was then used to select mAbs that were reactive with LY6K by ELISA but not an irrelevant Her2-His labeled protein.

Example 2: Selectivity of exemplary anti-LY6K antibodies for human LY6K

[00227] The selectivity of the anti-LY6K antibodies for human LY6K was measured using ELISA. Human LY6K ("hLY6K"), cynomolgus monkey LY6K ("cyLY6K"), rat LY6K ("rLY6K"), and human LY6E ("hLY6E") sourced from R&D Systems were coated on High Bind ELISA plates in PBS overnight. The plates were washed and blocked in PBS 1% BSA and probed with the anti-LY6K antibodies formatted as human IgG1 monoclonal antibodies at 10 ug/ml in PBS 1% BSA. After 1 hour, the plates were washed and probed with an anti-human

F(ab)₂ HRPO conjugate (for hLY6K, cyLY6K, and rLY6K) or an anti-human Ig Fc gamma HRPO conjugate (for hLY6E) for 1 hour, followed by washing, addition of TMB substrate, and plate reading. Binding data for hLY6K, cyLY6K, rLY6K, and hLY6E are shown in **Table 7** (expressed as a percentage of the maximum value for a commercial anti-LY6K mAb on human LY6K).

Table 7. Binding of anti-LY6K antibodies to indicated protein.

Ab	hLY6K	cyLY6K	rLY6K	LY6E
2659	ND	ND	ND	ND
2660	95.1	106.2	-0.1	3.1
3035	65.2	71.4	1	5.6
3047	6.2	3	1.5	1.7
3048	81.2	0.1	1.5	2.5
3055	22.6	40.3	0.4	26
3056	ND	ND	ND	ND
3063	71.6	2.6	-0.2	4.2
3074	89.2	-0.2	-1.2	3.4
3075	58.3	16.7	0.7	1.6
3082	87.2	95.2	-0.5	2.1
3090	ND	ND	ND	ND
3096	35	37.2	0	1
3101	94.9	3	0.6	2.4
3102	38.4	40.1	0.2	3.8
3481	99.4	0.2	0.9	2.7
3501	85.6	2	0.4	4.3
3503	66.6	76.4	0.7	2.9
3507	2.6	2.6	-1.2	1.7
3514	4	2.6	0	2.9
3518	67	2.7	2.1	2.1
3520	61.2	13.6	0.7	2.8
3522	2.1	2.6	0.7	4.3
3527	54.6	58	1.1	4.6
3529	3.6	1.5	0.4	2.8
3553	26	28.9	2.4	5
3704	2.2	2	0.6	3.2
3705	102.5	1.1	0	7.8
3719	48.8	0.8	-1.7	4.2
3724	6.2	3.2	3.3	3.9
3728	96.4	110.4	-1.3	1
3741	67.6	66.4	-1.6	3.1
3743	105.6	3.5	2.6	5

3746	76.9	78.7	3.1	1.2
3785	43.7	57.2	2.5	4.5
3815	20.2	29.1	2.2	3.5

ND: not determined

[00228] The selectivity of a subset of anti-LY6K antibodies for LY6K over various LY6 family members was measured using ELISA. LY6K, LY6E, LY6D, and LY6H sourced from R&D Systems, along with BSA as a negative control, were coated on High Bind ELISA plates in PBS overnight. The plates were washed and blocked in PBS 1% BSA and probed with the subset of anti-LY6K antibodies formatted as human IgG1 monoclonal antibodies at 10 ug/ml in PBS 1% BSA. After 1 hour, the plates were washed and probed with an anti-human F(ab)2 HRPO conjugate for 1 hour, followed by washing, addition of TMB substrate, and plate reading. As shown in **FIG. 1**, each of the anti-LY6K antibodies selectively binds LY6K.

Example 3: Affinity of exemplary anti-LY6K antibodies for human LY6K

[00229] The apparent affinity of a subset of the anti-LY6K antibodies for cell-surface anchored LY6K was measured using flow cytometry where primary anti-LY6K mAbs were incubated in 96-well U bottom plates with 10(5) target cells for 30 minutes at 4 degrees C, washed twice by spinning at 1500 RPM and 2nd stage goat F(ab)2 anti-human Fc gamma dye labeled polyclonal (Southern goat 1012-09) added at 1:200 dilution for 30 minutes. Cells were then washed and analyzed on a FACSCAN for Mean Fluorescence, and these values were used in Prism to calculate the apparent affinity for each of the subset of anti-LY6K antibodies for cell-surface anchored LY6K, represented as half maximal effective concentration (EC50), as shown in Table 8. The apparent affinity of an anti-LY6K antibody commercially available from R&D Systems (#MAB6648, referred to as “R&D” in Table 8) was also determined as a comparison.

Table 8. Apparent affinity (EC50) of exemplary anti-LY6K antibodies to cell-surface anchored LY6K.

Ab	EC50 (nM)
2660	0.3645
3035	1.04039E+13
3048	3.334
3063	90.53
3074	163.8
3075	0.8055
3082	3.901E+30

3481	2.839
3501	13098
3503	0.576
3520	3.61
3705	58.08
3741	1.97E+20
3743	1.181
3746	3.206
R&D	0.7235

[00230] The apparent affinity of a subset of the anti-LY6K antibodies for LY6K was also measured using an ELISA assay in which individual antibodies were HRP-labeled using an Abcam Kit (ab102890). High Bind ELISA plates were coated with 2 ug/mL of recombinant human LY6K (Wuxi) overnight, washed and blocked in PBS 1% BSA. HRPO linked anti-LY6K mAbs were then added as a titration for 1 hour, after which the plate was washed, and TMB was added before reading on a plate GloMax plate reader at 450 nM. The apparent affinity for each of the subset of anti-LY6K antibodies for LY6K, generated using Graphpad Prism and represented as half maximal effective concentration (EC₅₀), is shown in **Table 9**. The apparent affinity of an anti-LY6K antibody commercially available from R&D Systems (“R&D”) was also determined as a comparison.

Table 9. Apparent affinity (EC₅₀) of exemplary anti-LY6K antibodies to LY6K.

Ab	EC ₅₀ (nM)
2660	1.57
3035	2.862
3048	2.65
3063	4.674
3074	5.196
3075	1.557
3082	4.593
3481	2.08
3501	18.59
3503	2.675
3520	2.344
3705	16.2
3741	3.078
3743	2.317
3746	3.035
R&D	2.504

[00231] The affinity of each of a subset of the anti-LY6K antibodies for LY6K (“hLY6K”), cynomolgus monkey LY6K (“cyLY6K”), and rat LY6K (“rLY6K”) was measured using surface plasmon resonance. To measure binding kinetics, a capture and binding assay was performed on the Catterra LSA system. Briefly, an amine-coupled anti-human IgG lawn was generated using an HC30M chip with anti-human IgG-Fc specific antibody (Jackson Immuno-Research). All test antibodies were expressed at 1mL scale in CHO cells for 6 days, and supernatant was cleared of cells by centrifugation. CHO supernatants were diluted to approximately 1ug/mL antibody and injected over the capture chip, resulting in a captured antibody array. Non-regenerative kinetics were measured by injection of hLY6K-his, hLY6K-mFc, cyLY6K-mFc, or rLY6K-mFc starting at a concentration of 1.37E-9 M, with 3-fold increase in concentration up to 1.00E-6 M. Each analyte injection was flowed over the array for a 5-minute association phase, followed by a 10-minute buffer dissociation phase. Binding was detected and relative response units (RU) were collected for each antibody on the surface. KD values were determined using the Catterra software. The results are shown in **Table 10**.

Table 10. Affinity of exemplary anti-LY6K antibodies for hLY6K, cyLY6K, and rLY6K.

Ab	hLY6K-his KD (M)	hLY6K-mFc KD (M)	cyLY6K-mFc KD (M)	rLY6K-mFc KD (M)
2659	6.1329E-09	3.4039E-11	N/A	N/A
2660	3.5941E-09	7.017E-12	5.1847E-11	N/A
3035	weak	N/A	N/A	N/A
3047	N/A	2.7184E-06	2.1628E-05	1.2945E-07
3048	4.6953E-09	4.278E-11	N/A	N/A
3056	4.7249E-10	2.3252E-11	N/A	N/A
3074	3.2337E-09	1.6394E-10	N/A	N/A
3082	2.0628E-09	4.4412E-11	1.0264E-10	2.3992E-07
3096	6.3751E-08	1.3586E-09	9.4857E-09	N/A
3101	1.8261E-09	2.6441E-11	N/A	N/A
3481	1.1897E-09	1.5692E-11	N/A	N/A
3501	N/A	7.205E-10	N/A	N/A
3503	3.4906E-09	5.5255E-11	1.9694E-10	N/A
3518	2.747E-08	2.5442E-10	N/A	N/A
3520	3.191E-08	3.7316E-10	1.1709E-07	N/A
3522	N/A	N/A	N/A	weak
3705	6.3113E-09	1.8533E-10	N/A	N/A
3719	N/A	4.3025E-10	N/A	N/A
3728	4.96E-09	7.335E-12	7.8634E-11	N/A
3741	5.6589E-09	5.048E-11	3.7902E-10	N/A
3743	7.0032E-10	4.5046E-11	N/A	N/A
3746	2.5014E-09	3.615E-11	2.1571E-10	N/A

3785	7.4845E-09	2.6254E-10	1.3911E-09	N/A
3815	1.0957E-07	7.6286E-10	1.1734E-08	N/A

N/A: low/no binding, KD not measurable

Example 4: Sensitivity of exemplary anti-LY6K antibodies for detection of LY6K

[00232] Capture ELISA was used to determine the sensitivity of a subset of the anti-LY6K antibodies for detecting LY6K. Two commercially available anti-LY6K antibodies were used as a reference (R&D Systems MAB6648 and Abcam ab246486). The capture antibodies were diluted to 2 ug/mL and added to the plate (MSD L55XB-3). Human LY6K (2 ug/mL Wuxi LY^hKGLY138(1-38TR)₈His) was used. A commercial polyclonal anti-hLY6K antibody (R&D Systems, AF6648) was sulfo-tagged (R31AA-1) according to manufacturer protocol and used at 200 ng/mL for detection. The results are shown in **FIG. 2**. The EC₅₀ for LY6K was determined by Prism software by nonlinear regression. Sensitivity refers to lower limit of detection, which was determined using MSD Discover workbench software and calculated as the concentration 2.5 standard deviations above the lowest point on the calibration (no antigen).

Example 5. Internalization of anti-LY6K antibodies.

[00233] Temperature sensitive internalization of exemplary LY6K antibodies was tested in OVCAR-8 cells. The anti-LY6K antibodies were used at 1ug/mL to stain 2000,000 OVCAR-8 cells for 6 hr at either 4 degrees or 37 degrees Celsius. The IgG isotypes were used as a negative control (Jackson 015-000-003, 009-000-003) and trastuzumab (Absolute antibodies T1722A01) was used as a positive control. Cells were washed two times, and a fluorescent secondary was incubated on ice for 40 min (Jackson 109-116-190 1:200 dilution, Southern Biotech 1012-09 1:100 dilution). Cells were washed two times and fixed with fixation buffer (BD 554655). Cells were washed, and fluorescence was recorded using Attune Nxt (Invitrogen A24858). The percent internalization was calculated based on the geometric mean fluorescence fold increase of each antibody, with 4 degrees Celsius set to max fluorescence.

[00234] pH sensitive internalization of exemplary LY6K antibodies was tested in OVCAR-8 and HEKLY6K expressing cells. The cells were seeded into a tissue culture white plate at 30,000 cells/well (50 uL) and incubated overnight in phenol red free media supplemented with FBS (Gibco 11835-030). The Fabfluor-pH sensitive antibody (Satorius 4722) was incubated with individual anti-LY6K antibodies or control antibodies trastuzumab (Absolute antibodies T1722A01) and huIgG1 (Wuxi at a 1:3 molar ratio and incubated for 20mins). The Fabfluor antibody mix (50 uL) was added to the cell plate at a final concentration of 2 ug/mL (13.33 nM) and incubated for 18 hr on OVCAR-8 cells or 2 hr on HEKLY6K cells. After incubation,

cells were washed two times with PBS in the plate. Cells were removed from the plate by versene (ThermoFischer Scientific 15040066) and washed two times. Fluorescence was recorded on an Attune Nxt (Invitrogen A24858). The percent internalization on OVCAR-8 cells was calculated based on the geometric mean fluorescence of each antibody with trastuzumab set to max fluorescence. The percent internalization on HEKLY6K cells was calculated based on each antibody's geometric mean fluorescence with the highest mean fluorescence intensity (MFI) for the group, 3035, set to max fluorescence (100% internalization).

[00235] The temperature sensitive internalization and pH sensitive internalization results for the exemplary anti-LY6K antibodies are shown in **Table 11**, and a representative fluorescence plot for antibody 3082 labeled with pH-sensitive dye is shown in **FIG. 3**. The figure demonstrates that anti-LY6K antibody 3082 (clear solid line) internalized and endocytosed, releasing fluorescent signal, more than negative control huIgG1(shaded black) by an increase in MFI due to a decrease in pH in OVCAR-8 cells. Trastuzumab, a known commercially available internalizer (dashed line), was used as a positive control.

Table 11. Percent internalization of exemplary anti-LY6K antibodies.

Ab	Temperature sensitive internalization (OVCAR-8)	Fab-Fluor pH sensitive internalization (OVCAR-8)	Fab-Fluor pH sensitive internalization (HEKLY6K)
3082	47.5	247.44	96.8
3035	19.2	220.4	100
3481	26.2	218.86	56.2
3705	30.7	218.52	68.9
3074	48.6	127.73	45.6
3075	32.2	125.51	38.6
2660	60.5	118	98.8
3503	26.4	108	66
3048	50.7	85.34	55.6
3520	37	82.27	30.4
3743	48.3	63.52	72.3
3047	ND	19.15	ND
3101	ND	15.8	ND
3741	65.4	-5.06	27.6
3063	92.6	-10.97	ND
3527	ND	-26.19	ND
3785	ND	-32.33	14.8
3096	ND	-51.99	ND
3518	ND	-53.52	ND

3815	ND	-59.89	ND
3501	93.8	-62.5	2.1
3102	ND	-67.61	ND

Example 6. Epitope binning of exemplary anti-LY6K antibodies

[00236] Epitope binning for a subset of the anti-LY6K antibodies was performed using a competitive immunoassay. The exemplary anti-LY6K antibodies, along with a commercial anti-LY6K antibody (R&D MAB6648; “R&D” in **Table 12**), were HRP-labeled using a Lightning link HRP conjugation Kit (Abcam ab10289). The HRP conjugated antibodies were titrated and EC80 values were determined. Each individual purified anti-LY6K antibody had a corresponding HRP-conjugated antibody, which was used against itself to calculate percent competition. If the antigen of the non-HRP capture mAb prevented 60% of the binding of the competing HRP-labeled antibody to human LY6K (2ug/mL Wuxi LY^ΔKGLY138(1-38TR)₈His), then these mAbs were considered to bind similar or overlapping epitopes. Conversely, if the binding of the unlabeled antibody to the LY6K did not interfere with the binding of the other HRP-labeled antibody, then they were considered to bind to distinct, non-overlapping epitopes. The binning results are shown in **Table 12**.

Table 12. Epitope binning of exemplary anti-LY6K antibodies.

1	2	3	Not Determined
3075	2660/3728	3082	3501
3520	3035	3748/3503	3785
	3048	3741	
	3074		
	3481		
	3705		
	3743		
	3048		
	3063		
	R&D		

Example 7. Detection of LY6K via immunohistochemistry using exemplary anti-LY6K antibodies

[00237] Exemplary anti-LY6K antibodies were used to detect LY6K in 293 cells overexpressing LY6K, OVCAR-8 cells, and 293 cells (negative control) via immunohistochemistry (IHC). Briefly, sections were processed by removing paraffin and rehydrating, incubated 20 mins at 4 degrees Celsius, washed, put in Bloxall for 10 minutes, followed by normal serum for 30 minutes, and stained overnight with an anti-LY6K antibody

formatted as a human IgG1 monoclonal antibody or with Abcam (ab246486) anti-LY6K peptide (positive control) at 5 ug/ml in PBS 5% mouse serum followed by biotinylated anti-rabbit or anti-human IgG for 30 minutes, AB 30 minutes, and then hemtaxoylin stained. Exemplary IHC images for antibody 2660 are shown in **FIG. 4**, along with positive control (Abcam anti-LY6K) and negative control (IgG) images. IHC results for the remaining anti-LY6K antibodies are summarized in **Table 13**.

Table 13. IHC results for exemplary anti-LY6K antibodies.

Ab	IHC 293 LY6K	IHC OVCAR8	IHC 293
2659	ND	ND	ND
2660	++	++	-
3035	+	+	-
3047	-	NA	-
3048	+	+/-	-
3055	+/-	+/-	-
3056	ND	ND	ND
3063	+	-	-
3074	++	+/-	-
3075	-	NA	-
3082	-	+/-	-
3090	ND	ND	ND
3096	+/-	-	-
3101	++	++	-
3102	++	+/-	-
3481	+	+	-
3501	+	+	-
3503	-	+/-	-
3507	-	NA	-
3514	+	-	-
3518	-	NA	-
3520	-	NA	-
3522	-	NA	-
3527	-	NA	-
3529	-	NA	-
3553	++	+/-	-
3704	-	NA	-
3705	+	++	-
3719	-	NA	-
3724	-	-	-
3728	++	NA	-
3741	-	NA	-
3743	-	NA	-

3746	-	NA	-
3785	-	NA	-
3815	ND	ND	ND

(++) Best; (+) Positive; (+/-) Marginal or diffuse stain; (-) No stain or nonspecific;
(NA) Did not stain OVCAR-8 if 293 LY6K result was negative; (ND) not determined

Example 8. Tumor cell killing with anti-LY6K antibody-based T Cell Engagers

[00238] Exemplary anti-LY6K antibodies were used to make L2K formatted bispecific T cell engagers targeting CD3. Th1 lymphocytes were generated by activation for 4 days with Miltenyi Transact beads in media (RPMI 10% FBS+NEAA and P/S), followed by 9 days in culture with media + 5ng/ml IL2, were placed in RPMI 5% FBS +NEAA+P/S at 10(6) cells/ml with OVCAR-8 GFP luciferase lines at 10(5) cell/ml. Anti-LY6K T cell engagers were added at various concentrations using a 4D5-based 1+1 T cell engager against Her2 as a comparison. After 18 hours, luciferin was added to 200 ug/ml and luminescence readings were taken. The results are shown in **FIG. 5**.

Example 9. Epitope mapping of exemplary anti-LY6K antibodies

[00239] Epitopes were mapped for five exemplary anti-LY6K antibodies (2660, 3481, 3501, 3520, and 3741) using linear and conformational epitope mapping.

[00240] Peptide synthesis: to reconstruct epitopes of LY6K, a library of linear peptide-based mimics was synthesized using Fmoc-based solid-phase peptide synthesis. An amino functionalized polypropylene support was obtained by grafting with a proprietary hydrophilic polymer formulation, followed by reaction with t-butyloxycarbonyl-hexamethylenediamine (BocHMDA) using dicyclohexylcarbodiimide (DCC) with N-hydroxybenzotriazole (HOBt) and subsequent cleavage of the Boc-groups using trifluoroacetic acid (TFA). Standard Fmoc-peptide synthesis was used to synthesize peptides on the amino-functionalized solid support by custom modified JANUS liquid handling stations (Perkin Elmer). Three sets of linear peptides were synthesized. The first set included peptides of length 7 derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue. The second set included peptides of length 10 derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue. The third set included peptides of length 15 derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue.

[00241] Conformational epitope structural mimics were synthesized using the Chemically Linked Peptides on Scaffolds (CLIPS™) technology (Biosynth). *See, e.g., Timmerman et al., 2007, J. Mol. Recognit. 20:283-299 and Langedijk et al., 2011, Analytical Biochemistry 417:149-155.* CLIPS technology allows peptides to adopt thermodynamically favored

conformations, including single loops, double-loops, triple loops, sheet-like folds, helix-like folds, and combinations thereof. CLIPS scaffolds are coupled to cysteine residues. The side-chains of multiple cysteines in the peptides are coupled to a CLIPS scaffold with two or three reactive groups. For example, a 0.5 mM solution of the P2 CLIPS (2,6-bis(bromomethyl)pyridine) was dissolved in ammonium bicarbonate (20 mM, pH 7.8)/acetonitrile (1:3(v/v)), and this solution was added onto the peptide arrays where the CLIPS template bound to side-chains of two cysteines introduced in the solid-phase bound peptides of the peptide-arrays. The peptide arrays were gently shaken in the solution for 30 to 60 minutes while completely covered in solution. Finally, the peptide arrays were washed extensively with excess of H₂O and sonicated in disruption buffer (1 % SDS/0.1 % 2,2'-(Ethylenedioxy)diethanethiol in PBS (pH 7.2)) at 70 °C for 30 minutes, followed by sonication in H₂O for another 45 minutes. The T3 CLIPS carrying peptides were made in a similar way with three cysteines. Three sets of conformational structural mimic peptides were synthesized. The first set included constrained single loop peptides of length 15, where positions 2-14 were 13-mer peptides derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue. Cys residues were inserted on positions 1 and 15 and joined by mP2 CLIPS in order to create a loop mimic. Native Cys residues were replaced by Cys-acm. The second set included β -turn peptide mimics of length 22, where positions 2-21 were 20-mer peptides derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue. Residues on positions 11 and 12 were replaced by a "PG" motif in order to induce the β -turn formation. Cys residues were inserted on positions 1 and 22 and joined by mP2 CLIPS in order to stabilize the mimic. Native Cys residues were replaced by Cys-acm. The third set included α -helical peptide mimics of length 19 derived from the sequence of human LY6K (SEQ ID NO: 232) with an offset of one residue. Cys residues were inserted on positions 1 and 5 and joined by means of mP2 CLIPS to nucleate an α -helical structure. Native Cys residues were replaced by Cys- acm (denoted "2").

[00242] To verify the quality of the synthesized peptides, a separate set of positive and negative control peptides was synthesized in parallel. These were screened with commercial antibodies 3C9 and 57.9 (*see* Posthumus *et al.*, 1990, *J. Virol.* 64:3304–3309).

[00243] ELISA screening: antibody binding to each of the synthesized peptides was tested via ELISA. Peptide arrays were incubated with primary antibody solution overnight at 4 °C. After washing, the peptide arrays were incubated with a 1/1000 dilution of a goat anti-human HRP conjugate antibody (Southern Biotech, cat. # 2010-05) for one hour at 25 °C. After washing, the peroxidase substrate 2,2'-azino-di-3-ethylbenzthiazoline sulfonate (ABTS) and

20 µl/ml of 3 percent H₂O₂ were added. After one hour, the color development was measured. The color development was quantified with a charge coupled device (CCD) camera and an image processing system. The values obtained from the CCD camera ranged from 0 to 3000 mAU, similar to a standard 96-well plate ELISA-reader. Occasionally a well contains an air-bubble, resulting in a false-positive value. Such false-positives are scored as 0 by manual inspection.

[00244] The sample screens were optimized for sample concentration and blocking conditions for each sample until clear signals over background values were observed. Generally, peaks are defined as at least two times the background value (defined as the value for the isotype control screening for each peptide for the specific peptide mimic). In the absence of an isotype control, the individual antibody samples were used as internal controls, and distinctly different binding regions were observed. A binding event was only noted if multiple overlapping peaks were present within this binding region. Putative core epitopes were identified from adjacent peptides with similar or maximally 20% lower intensity than the top peak within a binding region. In addition, if peaks were well-defined, containing multiple overlapping peptides, lower intensity peaks were also included. For full evaluation of putative epitopes, information was taken from multiple mimic types where possible.

[00245] All five antibodies showed distinct binding peaks in different regions of the canonical human LY6K sequence. The putative core epitopes are listed in Table 14. The residue numbers refer to the position of the putative core epitope sequence in the canonical human LY6K sequence set forth in SEQ ID NO: 232. Underlined sequences represent the most likely core epitope sequence.

Table 14. Putative core epitopes of exemplary anti-LY6K antibodies.

Ab	Residues	Putative core epitope sequence	SEQ ID NO
2660	16-30	WTDANL <u>TARQRDPED</u>	233
3481	25-34	QRDPEDSQRT	235
3501	18-29	DANL <u>TARQRDPE</u>	236
3520	52-61	FECQNPRRCK	237
3741	97-106	PEEKRFLEE	238

[00246] As demonstrated in Examples 2 and 3, some of the exemplary anti-LY6K antibodies, including 2660, 3520, and 3741, are cross-reactive and bind both human LY6K and cynomolgus monkey LY6K ("cyLY6K"). Furthermore, antibodies 2660, 3520, and 3741 seem to bind different epitopes within LY6K, based on the putative epitopes shown in Table 14 and

on the binning data described in Example 6. The amino acid sequence of cyLY6K was compared (*i.e.*, via BLAST alignment) to that of human LY6K to evaluate whether the exemplary cross-reactive anti-LY6K antibodies may be binding similar epitopes. As shown in Table 15, the cyLY6K amino acid sequences corresponding to the putative epitope regions in Table 14 have a high degree of similarity to the human LY6K epitope sequences for the cross-reactive anti-LY6K antibodies. As in Table 14, underlined sequences in Table 15 represent the most likely core epitope sequence. The regions from rat LY6K (“rLY6K”) and mouse LY6K (“mLY6K”) corresponding to the putative epitope for the 2660 anti-LY6K antibody are also shown in Table 15. As demonstrated in Examples 2 and 3, the 2660 antibody did not react with rLY6K.

Table 15. Putative cross-reactive epitopes of exemplary anti-LY6K antibodies.

Ab	Species	Putative core epitope sequence	SEQ ID NO
2660*	Human LY6K (residues 16-30)	WTDAN <u>LTARQ</u> RDPE <u>D</u>	233
	cyLY6K	WTHLNLTARQQDPED	239
	rLY6K	KTRH <u>P</u> LEMVILLALL	241
	mLY6K	QSNAL <u>T</u> CHVCEA <u>Q</u> NS	243
3481	Human LY6K (residues 25-34)	QRDPEDSQRT	235
	cyLY6K	QQDPEDTPQT	245
3501	Human LY6K (residues 18-29)	DANLTARQRDPE	236
	cyLY6K	HLNLTARQQDPE	246
3520*	Human LY6K (residues 52-61)	FECQNPRRCK	237
	cyLY6K	FECENPRRCQ	247
3741*	Human LY6K (residues 97-106)	PEEKRFLL <u>EE</u>	238
	cyLY6K	PEEKRFLL <u>EE</u>	238

*: antibody displayed cross-reactivity with cyLY6K (see Examples 2 and 3)

* * *

[00247] The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[00248] All references (*e.g.*, publications or patents or patent applications) cited herein are incorporated herein by reference in their entireties and for all purposes to the same extent as if

each individual reference (*e.g.*, publication or patent or patent application) was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[00249] Other embodiments are within the following claims.

WHAT IS CLAIMED:

1. An antibody that specifically binds human LY6K, the antibody comprising: a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34; and a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68.
2. The antibody of claim 1, wherein the VH amino acid sequence and VL amino acid sequence are as set forth in: SEQ ID NOs: 1 and 35, 2 and 36, 3 and 37, 4 and 38, 5 and 39, 6 and 40, 7 and 41, 8 and 42, 9 and 43, 10 and 44, 11 and 45, 12 and 46, 13 and 47, 14 and 48, 15 and 49, 16 and 50, 17 and 51, 18 and 52, 19 and 53, 20 and 54, 21 and 55, 22 and 56, 23 and 57, 24 and 58, 25 and 59, 26 and 60, 27 and 61, 28 and 62, 29 and 63, 30 and 64, 31 and 65, 32 and 66, 33 and 67, or 34 and 68, respectively.
3. The antibody of any one of the preceding claims, wherein the antibody comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in: SEQ ID NOs: 69, 90, and 124; 70, 91, and 125; 71, 92, and 126; 72, 93, and 127; 69, 94, and 124; 73, 95, and 128; 74, 96, and 129; 75, 97, and 130; 74, 98, and 131; 76, 99, and 132; 77, 100, and 133; 78, 101, and 134; 79, 102, and 135; 74, 103, and 136; 80, 104, and 137; 74, 105, and 138; 74, 106, and 139; 81, 107, and 140; 81, 108, and 141; 82, 109, and 142; 83, 110, and 143; 84, 99, and 144; 85, 111, and 145; 81, 112, and 146; 86, 113, and 147; 87, 114, and 148; 74, 115, and 149; 74, 116, and 150; 74, 117, and 151; 88, 118, and 152; 89, 119, and 153; 81, 120, and 154; 74, 121, and 155; 85, 122, and 156; or 86, 123, and 157, respectively.
4. The antibody of any one of the preceding claims, wherein the antibody comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in: SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs:

174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198; SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs: 178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

5. The antibody of any one of the preceding claims, wherein the antibody comprises the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in: SEQ ID NOs: 69, 90, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 70, 91, 125, 159, WAS, and SEQ ID NO: 199; SEQ ID NOs: 71, 92, 126, 160, STT, and SEQ ID NO: 200; SEQ ID NOs: 72, 93, 127, 161, WAS, and SEQ ID NO: 201; SEQ ID NOs: 69, 94, 124, 158, KIS, and SEQ ID NO: 198; SEQ ID NOs: 73, 95, 128, 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 74, 96, 129, 163, 185, and 203; SEQ ID NOs: 75, 97, 130, 164, 185, and 204; SEQ ID NOs: 74, 98, 131, 165, 185, and 205; SEQ ID NOs: 76, 99, 132, 166, 186, and 206; SEQ ID NOs: 77, 100, 133, 167, 187, and 207; SEQ ID NOs: 78, 101, 134, 168, 188, and 208; SEQ ID NOs: 79, 102, 135, 169, 186, and 209; SEQ ID NOs: 74, 103, 136, 170, 185, and 198; SEQ ID NOs: 80, 104, 137, 169, 189, and 210; SEQ ID NOs: 74, 105, 138, 170, 185, and 211; SEQ ID NOs: 74, 106, 139, 171, 187, and 212; SEQ ID NOs: 81, 107, 140, 172, 187, and 213; SEQ ID NOs: 81, 108, 141, 173, 190, and 214; SEQ ID NOs: 82, 109, 142, 174, 191, and 215; SEQ ID NOs: 83, 110, 143, 175, 186, and 216; SEQ ID NOs: 84, 99, 144, 176, 186, and 217; SEQ ID NOs: 85, 111, 145, 170, 192, and 198; SEQ ID NOs: 81, 112, 146, 171, 193, and 218; SEQ ID NOs: 86, 113, 147, 177, 187, and 219; SEQ ID NOs: 87, 114, 148, 178, 189, and 220; SEQ ID NOs: 74, 115, 149, 179, 187, and 221; SEQ ID NOs: 74, 116, 150, 165, 185, and 222; SEQ ID NOs: 74, 117, 151, 180, 187, and 223; SEQ ID NOs: 88, 118, 152, 181, 194, and 224; SEQ ID NOs: 89, 119, 153, 182, 195, and 199; SEQ ID NOs: 81, 120, 154, 172, 187, and 225; SEQ ID NOs: 74, 121, 155, 165, 185, and 222; SEQ ID NOs: 85, 122, 156, 183, 196, and 226; or SEQ ID NOs: 86, 123, 157, 184, 197, and 227, respectively.

6. The antibody of any one of the preceding claims, wherein the antibody comprises the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34.

7. The antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain constant region, optionally selected from the group consisting of human IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂.
8. The antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain constant region that is a variant of a wild-type heavy chain constant region, wherein the variant heavy chain constant region binds to an FcγR with lower affinity than the wild-type heavy chain constant region binds to the FcγR.
9. The antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 228 or 229.
10. The antibody of any one of the preceding claims, wherein the antibody comprises the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68.
11. The antibody of any one of the preceding claims, wherein the antibody comprises a light chain constant region comprising the amino acid sequence of SEQ ID NO: 230 or 231.
12. The antibody of any one of the preceding claims, wherein the VH and VL comprise the amino acid sequences set forth in: SEQ ID NOs: 1 and 35, 2 and 36, 3 and 37, 4 and 38, 5 and 39, 6 and 40, 7 and 41, 8 and 42, 9 and 43, 10 and 44, 11 and 45, 12 and 46, 13 and 47, 14 and 48, 15 and 49, 16 and 50, 17 and 51, 18 and 52, 19 and 53, 20 and 54, 21 and 55, 22 and 56, 23 and 57, 24 and 58, 25 and 59, 26 and 60, 27 and 61, 28 and 62, 29 and 63, 30 and 64, 31 and 65, 32 and 66, 33 and 67, or 34 and 68, respectively, respectively.
13. An antibody that specifically binds to an amino acid sequence selected from the group consisting of SEQ ID NOs: 233-238.
14. An antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 233 and 239.
15. An antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 234 and 240.

16. An antibody that specifically binds to the amino acid sequence of SEQ ID NOs: 237 and 247.

17. The antibody of any one of the preceding claims, wherein the antibody is a multispecific antibody comprising a CD3-binding region, optionally wherein the CD3-binding region comprises a single-chain fragment variable (scFv) that specifically binds to CD3, optionally human CD3.

18. A polypeptide comprising a VH comprising the CDRH1, CDRH2, and CDRH3 amino acid sequences of the VH amino acid sequence set forth in any one of SEQ ID NOs: 1-34.

19. The polypeptide of claim 18, wherein the VH comprises the CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 69, 90, and 124; 70, 91, and 125; 71, 92, and 126; 72, 93, and 127; 69, 94, and 124; 73, 95, and 128; 74, 96, and 129; 75, 97, and 130; 74, 98, and 131; 76, 99, and 132; 77, 100, and 133; 78, 101, and 134; 79, 102, and 135; 74, 103, and 136; 80, 104, and 137; 74, 105, and 138; 74, 106, and 139; 81, 107, and 140; 81, 108, and 141; 82, 109, and 142; 83, 110, and 143; 84, 99, and 144; 85, 111, and 145; 81, 112, and 146; 86, 113, and 147; 87, 114, and 148; 74, 115, and 149; 74, 116, and 150; 74, 117, and 151; 88, 118, and 152; 89, 119, and 153; 81, 120, and 154; 74, 121, and 155; 85, 122, and 156; or 86, 123, and 157, respectively.

20. A polypeptide comprising a VL comprising the CDRL1, CDRL2, and CDRL3 amino acid sequences of the VL amino acid sequence set forth in any one of SEQ ID NOs: 35-68.

21. The polypeptide of claim 20, wherein the VL comprises the CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NO: 158, KIS, and SEQ ID NO: 198; SEQ ID NO: 159, WAS, and SEQ ID NO: 199; SEQ ID NO: 160, STT, and SEQ ID NO: 200; SEQ ID NO: 161, WAS, and SEQ ID NO: 201; SEQ ID NO: 162, AAS, and SEQ ID NO: 202; SEQ ID NOs: 163, 185, and 203; SEQ ID NOs: 164, 185, and 204; SEQ ID NOs: 165, 185, and 205; SEQ ID NOs: 166, 186, and 206; SEQ ID NOs: 167, 187, and 207; SEQ ID NOs: 168, 188, and 208; SEQ ID NOs: 169, 186, and 209; SEQ ID NOs: 170, 185, and 198; SEQ ID NOs: 169, 189, and 210; SEQ ID NOs: 170, 185, and 211; SEQ ID NOs: 171, 187, and 212; SEQ ID NOs: 172, 187, and 213; SEQ ID NOs: 173, 190, and 214; SEQ ID NOs: 174, 191, and 215; SEQ ID NOs: 175, 186, and 216; SEQ ID NOs: 176, 186, and 217; SEQ ID NOs: 170, 192, and 198;

SEQ ID NOs: 171, 193, and 218; SEQ ID NOs: 177, 187, and 219; SEQ ID NOs: 178, 189, and 220; SEQ ID NOs: 179, 187, and 221; SEQ ID NOs: 165, 185, and 222; SEQ ID NOs: 180, 187, and 223; SEQ ID NOs: 181, 194, and 224; SEQ ID NOs: 182, 195, and 199; SEQ ID NOs: 172, 187, and 225; SEQ ID NOs: 183, 196, and 226; or SEQ ID NOs: 184, 197, and 227, respectively.

22. A polypeptide comprising the amino acid sequence set forth in any one of SEQ ID NOs: 1-68.

23. The antibody or polypeptide of any one of the preceding claims, wherein the antibody or polypeptide is conjugated to a cytotoxic agent, cytostatic agent, toxin, radionuclide, or detectable label.

24. A polynucleotide encoding: a VH, a VL, a heavy chain, and/or a light chain of an antibody of any one of claims 1-17; or a polypeptide of any one of claims 18-22.

25. A vector comprising the polynucleotide of claim 24.

26. A recombinant host cell comprising:

- (a) the polynucleotide of claim 24;
- (b) the vector of claim 25;
- (c) a first polynucleotide encoding a heavy chain variable region or a heavy chain of the antibody of any one of claims 1-17 and a second polynucleotide encoding a light chain variable region or a light chain of the antibody of any one of claims 1-17; and/or
- (d) a first vector comprising a first polynucleotide encoding a heavy chain variable region or a heavy chain of the antibody of any one of claims 1-17 and a second vector comprising a second polynucleotide encoding a light chain variable region or a light chain of the antibody of any one of claims 1-17.

27. A composition comprising the antibody of any one of claims 1-17 or 23, the polypeptide of any one of claims 18-23, the polynucleotide of claim 24, the vector of claim 25, or the host cell of claim 26, and a pharmaceutically acceptable carrier or excipient.

28. A method of producing an antibody, the method comprising culturing the host cell of claim 26 under suitable conditions such that the polynucleotide is expressed, and the antibody is produced.

29. A method of treating cancer in a subject, the method comprising administering to the subject an effective amount of: the antibody of any one of claims 1-17 or 23; the polypeptide of any one of claims 18-23; the polynucleotide of claim 24; the vector of claim 25; the host cell of claim 26; or the composition of claim 27.

30. The method of claim 29, further comprising administering an additional therapeutic agent to the subject.

31. The method of claim 30, wherein the additional therapeutic agent is a chemotherapeutic, a radiotherapeutic, or a checkpoint targeting agent.

32. The method of claim 31, wherein the checkpoint targeting agent is selected from the group consisting of an antagonist anti-PD-1 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, an antagonist anti-CTLA-4 antibody, an antagonist anti-TIM-3 antibody, an antagonist anti-LAG-3 antibody, an antagonist anti-VISTA antibody, an antagonist anti-TIGIT antibody, an antagonist anti-CD96 antibody, an antagonist anti-CEACAM1 antibody, an agonist anti-CD137 antibody, an agonist anti-GITR antibody, and an agonist anti-OX40 antibody.

33. Use of the antibody of any one of claims 1-17 or 23; the polypeptide of any one of claims 18-23; the polynucleotide of claim 24; the vector of claim 25; the host cell of claim 26; or the composition of claim 27, for the manufacture of a medicament for treating cancer.

34. The antibody of any one of claims 1-17 or 23; the polypeptide of any one of claims 18-23; the polynucleotide of claim 24; the vector of claim 25; the host cell of claim 26; or the composition of claim 27, for use in medicine.

35. The antibody of any one of claims 1-17 or 23; the polypeptide of any one of claims 18-23; the polynucleotide of claim 24; the vector of claim 25; the host cell of claim 26; or the composition of claim 27, for use in treating cancer in a subject.