# ANTI-HK2 CHIMERIC ANTIGEN RECEPTOR (CAR)

## SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 30, 2020, is named JBI6124WOPCT1_SL.txt and is 562,160 bytes in size.

## TECHNICAL FIELD

The invention relates to hK2-targeting chimeric antigen receptors (CARs) comprising hK2-targeting single-chain variable fragments and engineered hK2-targeting immune cells expressing the CARs. Also provided are nucleic acids and expression vectors encoding the CARs, recombinant cells containing the vectors, and compositions comprising the engineered immune cells expressing the hK2-targeting CARs. Methods of making the CARs, and engineered immune cells, and methods of using the engineered immune cells to treat conditions including cancer are also provided.

## BACKGROUND

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males worldwide. The course of prostate cancer from diagnosis to death is best categorized as a series of clinical stages based on the extent of disease, hormonal status, and absence or presence of detectable metastases: localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate stage. Although surgery, radiation, or a combination of both can be curative for patients with localized disease, a significant proportion of these patients have recurrent disease as evidenced by a rising level of PSA, which can lead to the development of metastases, especially in the high-risk group—a transition to the lethal stage of the disease.

Androgen depletion therapy (ADT) is the standard treatment with a generally predictable outcome: decline in PSA, a period of stability in which the tumor does not proliferate, followed by rising PSA and regrowth as castration-resistant disease. Historically, ADT has been the standard of care for patients with metastatic prostate cancer.

Kallikrein related peptidase 2 (hK2, HK2) is a trypsin-like enzyme with androgen receptor (AR)-driven expression specific to prostate tissue and prostate cancer. hK2 is activated by Transmembrane Protease, Serine 2 (TMPRSS2) and secreted into the ducts of the prostate, where it initiates a cascade that cleaves semenogelin, the extracellular matrix in ejaculate, to enhance sperm motility. hK2 expression is restricted to the prostate and prostate cancer tissue, however it has recently been demonstrated that hK2 was detectable in breast cancer lines and primary patient samples after appropriate activation of the AR-pathway by steroid hormones (U.S. Pat. Publ. No. 2018/0326102). Similar to PSA, retrograde release of catalytically inactive hK2 into the blood occurs when the highly structured organization of the prostate is compromised upon hypertrophy or malignant transformation.

T cell therapy utilizes isolated T cells that have been genetically modified to enhance their specificity for a specific tumor associated antigen. Genetic modification may involve the expression of a chimeric antigen receptor (CAR) or an exogenous T cell receptor to provide new antigen specificity onto the T cell. T cells expressing chimeric antigen receptors (CAR-T cells) can induce tumor immunoreactivity. There is a need for better cancer therapies utilizing CAR-T cells.

## SUMMARY

Disclosed herein are chimeric antigen receptors (CARs), e.g., CARs that target a human Kallikrein-2 (hK2), cells comprising the CARs, vectors encoding the CARs, e.g., recombinant expression vectors, and nucleic acid molecules encoding the CARs, methods of making the CARs, compositions, polypeptides, proteins, nucleic acids, host cells, populations of cells and methods of treating disorders, e.g., cancer, using the disclosed CARs.

In one aspect is provided a chimeric antigen receptor (CAR) comprising:

(a) an extracellular domain comprising an scFv that specifically binds to the human Kallikrein-2 (hK2) antigen,

(b) a transmembrane domain, and

(c) an intracellular signaling domain optionally comprising at least one co-stimulatory domain.

In some embodiments, the CAR further comprises

(d) a CD8a-hinge region,

wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide; and

wherein the intracellular signaling domain comprises a co-stimulatory domain comprising a TNF receptor superfamily member 9 (CD137) component and a primary signaling domain comprising a T-cell surface glycoprotein CD3 zeta chain (CD3z) component.

In some embodiments, the CD8a-hinge region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25, 269, 270, 271, or 272;

the transmembrane domain comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 26; and/or

the intracellular signaling domain comprises a co-stimulatory domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 27, and a primary signaling domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 28.

In another aspect is provided a chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, where the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 92, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 93, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 94;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid

sequence of SEQ ID NO: 106, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122,

where the extracellular antigen-binding domain binds the hK2 antigen.

In another aspect is provided a chimeric antigen receptor (CAR) comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, where the extracellular antigen-binding domain comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139,

where the extracellular antigen-binding domain binds the hK2 antigen.

In some embodiments, the extracellular antigen-binding domain further comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

In another aspect is provided a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain variable domain (VL) comprising an amino acid sequence selected from SEQ ID NOS: 1, 2, 3, 74, 75, 147, 148, 149, 150, 151, 152 and 318; and/or

a heavy chain variable domain (VH) comprising an amino acid sequence selected from SEQ ID NOS: 4, 5, 6, 76, 77, 140, 141, 142, 143, 144, 145, 146 and 317;

wherein the extracellular antigen-binding domain binds the human Kallikrein-2 (hK2) antigen.

In some embodiments, the extracellular antigen-binding domain comprises:

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

In some embodiments, the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv). In some embodiments, the scFv comprises a linker polypeptide between the light chain variable region (VL) and the heavy chain variable region (VH). In some embodiments, the linker polypeptide comprises an amino acid sequence of SEQ ID NO: 7. In some embodiments, the scFv comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 8-23, 169-184 and 340-343. In some embodiments, the extracellular antigen-binding domain comprises a signal polypeptide. In some embodiments, the signal polypeptide comprises an amino acid sequence of SEQ ID NO: 24.

In some embodiments, the intracellular signaling domain comprises a polypeptide component selected from the group consisting of a TNF receptor superfamily member 9 (CD137) component, a T-cell surface glycoprotein CD3 zeta chain (CD3z) component, a cluster of differentiation (CD27) component, a cluster of differentiation superfamily member component, and a combination thereof. In some embodiments, the CD137 component comprises an amino acid sequence of SEQ ID NO: 27. In some embodiments, the CD3z component comprises an amino acid sequence of SEQ ID NO: 28. In some embodiments, the intracellular signaling domain comprises an amino acid sequence of SEQ ID NO: 45. In some embodiments, the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide. In some embodiments, the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 26.

In various embodiments, the CAR further comprises a hinge region linking the transmembrane domain to the extracellular antigen-binding domain. In some embodiments, the hinge region is a CD8a-hinge region. In some embodiments, the CD8a-hinge region comprises an amino acid sequence of SEQ ID NO: 25, 269, 270, 271, or 272. In some embodiments, the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and

273-308. In some embodiments, the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220.

In another aspect is provided an isolated lymphocyte expressing any of the above-described CARs. In some embodiments, the lymphocyte is a T lymphocyte. In some embodiments, the lymphocyte is a natural killer (NK) cell.

Also provided is an isolated nucleic acid molecule encoding any of the above-described CARs. Also provided is a vector comprising the nucleic acid molecule. In addition, a cell expressing the nucleic acid molecule is also provided.

Further provided is a pharmaceutical composition comprising an effective amount of any of the above lymphocytes, and a pharmaceutically acceptable excipient.

In one aspect, the present disclosure provides a CAR according to the present disclosure for use in a method of therapy.

In one aspect, the present disclosure provides a lymphocyte according to the present disclosure for use in a method of therapy.

In one aspect, the present disclosure provides a composition, e.g. a pharmaceutical composition, according to the present disclosure for use in a method of therapy.

In one aspect, the present disclosure provides a CAR according to the present disclosure for use in a method of treating cancer.

In one aspect, the present disclosure provides a lymphocyte according to the present disclosure for use in a method of treating cancer.

In one aspect, the present disclosure provides a composition, e.g. a pharmaceutical composition, according to the present disclosure for use in a method of treating cancer.

In one embodiment, the cancer is prostate cancer.

In one embodiment, the cancer is androgen receptor (AR) expressing breast cancer.

In another aspect is provided a method of treating a subject having cancer. The method comprises administering a therapeutically effective amount of any of the above lymphocytes to a subject in need thereof, whereby the lymphocyte induces killing of

cancer cells in the subject. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is androgen receptor (AR) expressing breast cancer.

In another aspect is provided a method of targeted killing of a cancer cell, the method comprising contacting the cancer cell with any of the above lymphocytes, whereby the lymphocyte induces killing of the cancer cell. In some embodiments, the cancer cell is a prostate cancer cell. In some embodiments, the cancer is androgen receptor (AR) expressing breast cancer.

In another aspect is provided a method of detecting the presence of cancer in a subject, comprising:

(a) contacting a cell sample obtained from the subject with any of the above CARs, thereby forming a CAR-cell complex, and

(b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.

## BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing will be apparent from the following more particular description of example embodiments, as illustrated in the accompanying drawings.

This patent application file contains at least one drawing executed in color. Copies of this patent application with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

**Figures 1A-1C** show the construction and expression of hK2 CAR on human T cells. **Figure 1A** shows a schematic illustration of the construct for the hK2 CARs; TM: transmembrane. **Figures 1B** and **1C** show hK2 CAR expression on T cells-surface. Primary human T cells were electroporated with no mRNA (MOCK) or 10µg of mRNA expressing either an hK2 scFv CAR or irrelevant control CAR. 24 hours post-electroporation CAR surface expression was measured by flow cytometry following staining with 2 µg/ml biotinylated L-protein and streptavidin-conjugated PE (**Figure 1B**) or biotinylated hK2 (1 µg/ml) and streptavidin-conjugated PE (**Figure 1C**).

**Figure 2** shows cytotoxicity of hK2-expressing tumor cells by CAR-T cells in 20-hour flow based assay at the indicated effector-to-target cell (E/T) ratio. 24 hours after transient transfection, target cells (Vcap and DU145) were labeled with Cell Trace Violet (CTV) fluorescent dye and then co-cultured with hK2 CAR-T cells. Mock T cells served as negative effector controls. Percent killing is the ratio of the absolute number of live (viability dye negative) target (CTV positive) cells remaining in the co-culture relative to the number of live targets cultured without CAR-T cells.

**Figures 3A-3B** show real-time hK2-specific CAR-T cell-mediated cytotoxicity. Normalized cell index (CI) plot for target cells (**Figure 3A**) VCap (5E4) and (**Figure 3B**) DU145 (5E3) incubated with Mock, 10μg mRNA electroporated (24 hours post transfection) hK2 11B6 CAR LH or control CAR-T cells at different E:T ratios for approximately 72 hours. When seeded alone, target cells adhere to the plate and proliferate, increasing the CI readout. When T cells were added to target cells, hK2 CAR- and control CAR-T cells caused hK2 (+) VCap cell cytolysis and subsequent progressive decrease in CI at an E/T ratio from 5:1 to 0.156:1. The reduction in CI value after addition of effector cells reflects the loss of viability of target cells. A parallel experiment using hK2(-) DU145 target cells was also performed, as shown in (**Figure 3B**); at the E:T ratios tested in this experiment, hK2 and control CAR T cells did not reduce CI after addition which displayed no cytolytic activity. The Y-axis is the normalized CI generated by the RTCA software and displayed in real time. X-axis is the time of cell culture and treatment time in hour. Mean values of the CI were plotted ± standard deviation.

**Figure 4** shows Th1 cytokine interferon-γ (IFN-γ) production of antigen-stimulated CAR-T cells. Supernatant was collected from xCELLigence based killing assay (see **Figures 3A-3B**) approximately 70 hours co-culture (VCap#5E4, DU145#5E3). hK2 CAR LH-and Control CAR modified T cells secrete IFN-γ during co-culture with hK2-expressing VCap cells, but not hK2-negative DU145 cells. Mean IFN-γ concentration ± standard deviation (pg/ml) from duplicate cultures is shown.

**Figures 5A-5B** show that 11B6 thermally stabilized scFvs CAR clones were evaluated in the JNL reporter assay for antigen-dependent activity. **Figure 5A** shows Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed

JNL cells), were transduced with the various hK2 CAR constructs. Expression was determined by biotinylated hK2 followed by streptavidin-conjugated PE. **Figure 5B** shows binding between the CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. JNL cells containing the indicated CAR clones and un-transduced JNL cells (UTD) were co-cultured with target cells lines (VCap or DU145 cells) and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells.

**Figure 6** shows hK2 CAR expression on T cells-surface. Primary human T cells were transduced with 11B6 thermally stabilized and parental scFvs based CAR lentivirus (multiplicity of infection (MOI): 3) and CAR expression was determined by biotinylated hK2 (1µg/ml) followed by streptavidin-conjugated PE 14 days post transduction.

**Figures 7A-7B** show that 11B6 thermally stabilized scFv CAR-T cells were evaluated in the real-time IncuCyte killing assay for antigen-dependent cytotoxicity. Thermally stabilized hK2 CAR-T cells and parental 11B6 CAR-Ts were co-incubated with VCaP cells (**Figure 7A**) and PC3 cells (**Figure 7B**) for 88 hours. Effector-to-target (E/T) ratio was calculated based on CAR expression data (see **Figure 6**). Target cells were stably expressing a red nuclear dye which was measured by IncuCyte imaging system in a real-time fashion. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Figure 7C** shows percent tumor cell growth inhibition of hK2 positive VCaP cells at effector:target ratio of 1:1 or 0.5:1 by T cells transduced with CAR1-10 or the parental 11B6_HL or 11B6_LH. in the real-time IncuCyte killing assay assessing antigen-dependent cytotoxicity. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Figure 7D** shows percent tumor cell growth inhibition of PC3 cells at effector:target ratio of 1:1 by T cells transduced with CAR1-10 or the parental 11B6_HL or 11B6_LH. in the real-time IncuCyte killing assay assessing antigen-dependent cytotoxicity. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Figure 7E** shows percent tumor cell growth inhibition of hK2 positive VCaP cells by CAR-T cells transduced with CAR17 (B413HL in the Figure), CAR18 (B413LH in the Figure), CAR19 (B359HL in the Figure) and CAR20 (B359LH in the Figure) in the real-time IncuCyte killing assay assessing antigen-dependent cytotoxicity. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Figure 7F** shows percent tumor cell growth inhibition of hK2 negative DU145 cells by CAR-T cells transduced with CAR17 (B413HL in the Figure), CAR18 (B413LH in the Figure), CAR19 (B359HL in the Figure) and CAR20 (B359LH in the Figure) in the real-time IncuCyte killing assay assessing antigen-dependent cytotoxicity. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Figure 8** shows cytokine release by hK2 lenti-CAR-T cells. Supernatant collected from overnight (approximately 20 hours) co-culture of hK2 CAR-T cells with VCap cells at 1:1 of E/T ratio was analyzed using 13-plex Milliplex Human High Sensitivity T cell kit (HSTCMAG28SPMX13). hK2 CAR modified T cells secrete cytokines during co-culture with hK2-expressing VCap cells, but minimal for un-transduced T cells (UTD). Mean cytokine concentration ± standard deviation (pg/ml) from duplicate cultures is shown.

**Figure 9** shows IFN-γ release by hK2 lenti-CAR-T cells. Supernatant collected from overnight (approximately 20 hours) co-culture of hK2 CAR-T cells with VCap, DU145 (5E4 cells) cells at 1:1 of E/T ratio. hK2 CAR modified T cells secrete IFN-γ during co-culture with hK2-expressing VCap cells, but not hK2-negative DU145 cells. Mean IFN-γ concentration ± standard deviation (pg/ml) from duplicate cultures is shown. CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively.

**Figures 10A-10E** show the results from an hK2 CAR-T cells proliferation assay. (**Figures 10A, 10C**) hK2 CAR and un-transduced (UTD) T cells were labelled with CellTrace Violet (CTV; 5μM) and co-cultured with hK2 (+) VCap and hK2 (-) DU145 cells. Five days post co-culture, cells were harvested and stained with CD3, CD25, NearIR live/dead

Dye and hK2 CAR. Flow cytometric analysis was performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes were identified by live CD3, and the frequencies of CAR+T cells with CTV dye dilution and activation marker CD25 were determined. (**Figures 10B, 10D**) CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. The data in **Figure 10E** shows that hK2 CAR+ T cells proliferate more robustly than CD3/28 beads positive control after 5 days of coculture with VCap cells. Different CAR constructs engineered T cells have different proliferation activity and displayed different CAR+ T cells counts. The CAR+ T cells counts based on mean absolute cell count +/- SEM from three technical replicates.

**Figures 11A-11B** show the results of assays to determine the level of expression of hK2 CARs on primary T cells using biotin-labeled hK2 protein. **Figure 11A** is a schematic illustration of the construct for the hK2 CARs; TM: transmembrane. In **Figure 11B**, primary human T cells were transduced with novel hK2 scFvs based KL2B413 HL&LH and rehumanized 11B6 KL2B359 HL&LH CARS lentivirus (MOI 3) and CAR expression was determined by biotinylated hK2(1ug/ml) followed by streptavidin-conjugated PE 14 day post transduction. **Figure 11B** provides a summary of the percentage of hK2 CAR + T cells (% positive) detected by novel KL2B413 HL&LH and rehumanized 11B6 KL2B359 HL&LH CARS analyzed. As shown, different clones have different CAR expression level, ranges from 45.1% to 59.9%. All CAR T cells were normalized to the equal CAR+ T cells for subsequent functional assays.

**Figures 12A-12B** show the results of evaluation of novel hK2 KL2B413 and rehumanized 11B6 CAR clones in the JNL reporter assay for antigen-dependent activity. In **Figure 12A**, Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed JNL cells), were transduced with the various hK2 CAR constructs. Expression was determined by biotinylated hK2 followed by streptavidin-conjugated PE. CAR expression in transduced JNL cells was confirmed for the selected clones with 46–50% of cells expression on rehumanized 11B6 KL2B359 CARs and 73.7-96% of cells on KL2B413 CARs. The data shown in **Figure 12B** indicates that binding between the hK2 CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. JNL cells containing the indicated CAR clones and JNL cells

(UTD) were co-cultured with target cells lines (VCap, LNCap/Hk2, LNCap, C4-2B, 22Rv1 or DU145 cells) and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells. No antigen-dependent activation was found for the novel KL2B413 and rehumanized 11B6 HL&LH CARs.

**Figures 13A-13B** show the results of an evaluation of HK2 CAR-T cells in the real-time IncuCyte killing assay for antigen-dependent cytotoxicity. HK2 CAR-T cells were co-incubated with HK2+ VCaP cells (**Fig. 13A**) and HK2- DU145 cells (**Fig. 13B**) for 96 hours. The Effector-to-Target (ET) ratio was calculated based on CAR expression data (**Fig. 11B**). Target cells were stably expressing a red nuclear dye which was measured by IncuCyte imaging system in a real-time fashion. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%)

**Figure 14** illustrates data showing Th1 cytokine IFN-gamma production of antigen-stimulated CAR-T Cells. IFN-γ produced by cytotoxic T cells is critical for exerting immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*. To determine whether hK2 CAR-modified human T cells were able to recognize and activated by hK2 (+) tumor cells, primary T cells containing the indicated CAR clones and control untransduced T cells (UTD) were co-cultured with target cells lines (LNCap/Hk2, LNCap, C4-2B, 22Rv1 or DU145 cells) and supernatant were collected for IFN-g concentration measurement. As shown, hK2 CAR modified T cells secrete IFN-gamma during co-culture with hK2-expressing LNCap/hK2 cells, even very low Hk2 expressing C4-2B and LNCap cells but not hK2-negative DU145 cells. Undisclosed control CAR secreted much higher amount of IFN- γ due to the much higher antigen expression level than hK2. Mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures is shown.

**Figure 15** shows the results of a CD107a degranulation assay to evaluate hK2 CAR T cells' antitumor activity. Target cells ($5 \times 10^4$) were cocultured with an equal number of effector cells in 0.1ml per well in a 96-well plate. Control wells contained T cells alone. Anti-CD107a (5µl per well) was added in addition to 1µl/sample of monensin (BD

Biosciences) and incubated for 4 hours at 37°C. Cells were washed two times with PBS, stained for expression of the hK2 CAR, CD3, and CD8 and analyzed on a flow cytometer BD Fortessa. As shown, the presence of hK2 antigen on Vcap cells leads to an increase in CD107A+ hK2 CAR(+) T cells, but not in hK2 CAR(-) and UTD T cells measured by flow cytometry, whereas only the background staining(<2%) was seen in the CAR T cells only without tumor cells stimulation. Phorbol 12-myristate 13-acetate (PMA) in combination with ionomycin(eBioscience™ Cell Stimulation Cocktail; 500X) was a consistent inducer of CD107a cell surface expression in this 4-hour cell culture model, which was used as a positive control. Results are shown for representative donor T cells and are reproducible in multiple donors .

**Figures 16A-16D** show the results of a hK2 CAR T cell proliferation assay. hK2 CAR and untransduced (UTD) T cells were labelled with CellTrace Violet(CTV; 5uM) and co-cultured with HK2 (+) VCap and HK2 (-) DU145 cells. Five days post co-culture, cells were harvested and stained with CD3, CD25, NearIR live/dead Dye and hK2 CAR. Flow cytometric analysis was performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes were identified by live CD3, and the frequencies of CAR+T cells with CTV dye dilution and activation marker CD25 were determined. By gating on CD3+ T cells, as shown in **Figures 16A-16B**, the hK2(+) Vcap cells but not hK2(-) DU145 cells promoted the all CAR constructs engineered T cells proliferation and upregulation of activation marker CD25, as shown in **Figures 16C-16D**. CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. T cells only without any stimulation do not proliferate, and CD3/28 beads stimulated T cells displayed equivalent proliferation pattern. As shown, hK2 CAR+ T cells proliferate more robustly than CD3/28 beads positive control after 5 days of coculture with VCap cells. Different CAR constructs engineered T cells have different proliferation activity and displayed different CAR+ T cells counts. The summary of percentage of proliferating T cells and CD25 expressing T cells based on mean absolute cell count +/- SEM from duplicate is shown in **Figures 16B** and **16D.**

**Figure 17A** shows the sequence alignment of the VH domains of mu11B6, hu11B6, KL2B357, KL2B358, KL2B359, KL2B360, HCF3 and HCG5. Figure 17A discloses SEQ

ID NOS 317, 5, 140, 141, 77, 140, 6, 4 and 345, respectively, in order of appearance. **Figure 17B** shows the protected segments mapped onto the sequence of hK2 antigen to visualize the binding epitopes of hK2 antibodies identified through HDX-MS. Figure 17B discloses SEQ ID NOS 351, 351, 351, 351, 351 and 351, respectively, in order of appearance.

## DETAILED DESCRIPTION

A description of example embodiments follows.

The present disclosure provides for chimeric antigen receptors (CARs) that target human Kallikrein-2 (hK2), cells comprising such CARs, and methods of treating cancer (e.g., prostate cancer or AR-expressing breast cancer) using the CARs described herein. The CARs of the invention have antigen specificity for hK2. The phrases "have antigen specificity" and "elicit antigen-specific response" as used herein mean that the CAR can specifically bind to and immunologically recognize an antigen, such that binding of the CAR to the hK2 antigen elicits an immune response. Methods of testing the CARs for antigen specificity and for the ability to recognize target cells are known in the art.

The disclosure also provides related nucleic acids, recombinant expression vectors, host cells, populations of cells, antibodies, or antigen binding portions thereof, and pharmaceutical compositions relating to the CARs of the invention.

Several aspects of the invention are described below, with reference to examples for illustrative purposes only. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the invention. One having ordinary skill in the relevant art, however, will readily recognize that the invention can be practiced without one or more of the specific details or practiced with other methods, protocols, reagents, cell lines and animals. The present invention is not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts, steps or events are required to implement a methodology in accordance with the present invention. Many of the techniques and procedures described, or referenced herein, are well

understood and commonly employed using conventional methodology by those skilled in the art.

Unless otherwise defined, all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. It will be further understood that terms, such as those defined in commonly-used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the relevant art and/or as otherwise defined herein.

When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

## Definitions

As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes a combination of two or more cells, and the like.

The transitional terms "comprising," "consisting essentially of," and "consisting of" are intended to connote their generally accepted meanings in the patent vernacular; that is, (i) "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim; and (iii) "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Embodiments described in terms of the phrase

"comprising" (or its equivalents) also provide as embodiments those independently described in terms of "consisting of" and "consisting essentially of."

"Activation" or "stimulation" or "activated" or "stimulated" refers to induction of a change in the biologic state of a cell resulting in expression of activation markers, cytokine production, proliferation or mediating cytotoxicity of target cells. Cells may be activated by primary stimulatory signals. Co-stimulatory signals can amplify the magnitude of the primary signals and suppress cell death following initial stimulation resulting in a more durable activation state and thus a higher cytotoxic capacity. A "co-stimulatory signal" refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to T cell and/or NK cell proliferation and/or upregulation or downregulation of key molecules.

"Antigen binding fragment" or "antigen binding domain" refers to a portion of the protein that binds an antigen. Antigen binding fragments may be synthetic, enzymatically obtainable or genetically engineered polypeptides and include portions of an immunoglobulin that bind an antigen, such as the VH, the VL, the VH and the VL, Fab, Fab', $F(ab')_2$, Fd and Fv fragments, domain antibodies (dAb) consisting of one VH domain or one VL domain, shark variable IgNAR domains, camelized VH domains, VHH domains, minimal recognition units consisting of the amino acid residues that mimic the CDRs of an antibody, such as FR3-CDR3-FR4 portions, the HCDR1, the HCDR2 and/or the HCDR3 and the LCDR1, the LCDR2 and/or the LCDR3, alternative scaffolds that bind an antigen, and multispecific proteins comprising the antigen binding fragments. Antigen binding fragments (such as VH and VL) may be linked together via a synthetic linker to form various types of single antibody designs where the VH/VL domains may pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chains, to form a monovalent antigen binding domain, such as single chain Fv (scFv) or diabody. Antigen binding fragments may also be conjugated to other antibodies, proteins, antigen binding fragments or alternative scaffolds which may be monospecific or multispecific to engineer bispecific and multispecific proteins.

"Cancer" refers to a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth results in the

formation of malignant tumors that invade neighboring tissues and may also metastasize to distant parts of the body through the lymphatic system or bloodstream. A "cancer" or "cancer tissue" can include a tumor.

"Full length antibody" is comprised of two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds as well as multimers thereof (e.g. IgM). Each heavy chain is comprised of a heavy chain variable domain (VH) and a heavy chain constant domain, the heavy chain constant domain comprised of subdomains CH1, hinge, CH2 and CH3. Each light chain is comprised of a light chain variable domain (VL) and a light chain constant domain (CL). The VH and the VL may be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with framework regions (FR). Each VH and VL is composed of three CDRs and four FR segments, arranged from amino-to-carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

"Human antibody" refers to an antibody that is optimized to have minimal immune response when administered to a human subject. Variable regions of human antibody are derived from human immunoglobulin sequences. If human antibody contains a constant region or a portion of the constant region, the constant region is also derived from human immunoglobulin sequences. Human antibody comprises heavy and light chain variable regions that are "derived from" sequences of human origin if the variable regions of the human antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice or rats carrying human immunoglobulin loci. "Human antibody" typically contains amino acid differences when compared to the immunoglobulins expressed in humans due to differences between the systems used to obtain the human antibody and human immunoglobulin loci, introduction of somatic mutations or intentional introduction of substitutions into the frameworks or CDRs, or both. Typically, "human antibody" is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical in amino acid sequence to an amino acid sequence encoded by human germline immunoglobulin or rearranged

immunoglobulin genes. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al., (2000) J Mol Biol 296:57-86, or a synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al., (2010) J Mol Biol 397:385-96, and in Int. Patent Publ. No. WO2009/085462. Antibodies in which at least one CDR is derived from a non-human species are not included in the definition of "human antibody".

"Humanized antibody" refers to an antibody in which at least one CDR is derived from non-human species and at least one framework is derived from human immunoglobulin sequences. Humanized antibody may include substitutions in the frameworks so that the frameworks may not be exact copies of expressed human immunoglobulin or human immunoglobulin germline gene sequences.

"Isolated" refers to a homogenous population of molecules (such as synthetic polynucleotides or polypeptides) which have been substantially separated and/or purified away from other components of the system the molecules are produced in, such as a recombinant cell, as well as a protein that has been subjected to at least one purification or isolation step. "Isolated" refers to a molecule that is substantially free of other cellular material and/or chemicals and encompasses molecules that are isolated to a higher purity, such as to 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% purity.

"Modulate" refers to either enhanced or decreased ability of a test molecule to mediate an enhanced or a reduced response (*i.e.,* downstream effect) when compared to the response mediated by a control or a vehicle.

"Natural killer cell" and "NK cell" are used interchangeably and synonymously herein. NK cell refers to a differentiated lymphocyte with a $CD16^+$ $CD56^+$ and/or $CD57^+$ $TCR^-$ phenotype. NK cells are characterized by their ability to bind to and kill cells that fail to express "self" MHC/HLA antigens by the activation of specific cytolytic enzymes, the ability to kill tumor cells or other diseased cells that express a ligand for NK activating

receptors, and the ability to release protein molecules called cytokines that stimulate or inhibit the immune response.

"Specifically binds," "specific binding," "specifically binding" or "binds" refer to a proteinaceous molecule binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the proteinaceous molecule binds to the antigen or the epitope within the antigen with an equilibrium dissociation constant ($K_D$) of about $1x10^{-7}$ M or less, for example about $5x10^{-8}$ M or less, about $1x10^{-8}$ M or less, about $1x10^{-9}$ M or less, about $1x10^{-10}$ M or less, about $1x10^{-11}$ M or less, or about $1x10^{-12}$ M or less, typically with the $K_D$ that is at least one hundred fold less than its $K_D$ for binding to a non-specific antigen (e.g., BSA, casein). In the context of the prostate neoantigens described here, "specific binding" refers to binding of the proteinaceous molecule to the prostate neoantigen without detectable binding to a wild-type protein the neoantigen is a variant of.

"Tumor cell" or a "cancer cell" refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, or in tissue culture, that has spontaneous or induced phenotypic changes. These changes do not necessarily involve the uptake of new genetic material. Although transformation may arise from infection with a transforming virus and incorporation of new genomic nucleic acid, uptake of exogenous nucleic acid or it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, modulation of tumor specific marker levels, invasiveness, tumor growth in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo*.

The term "chimeric antigen receptor" or "CAR" as used herein is defined as a cell-surface receptor comprising an extracellular target-binding domain, a transmembrane domain and an intracellular signaling domain, all in a combination that is not naturally found together on a single protein. This particularly includes receptors wherein the extracellular domain and the intracellular signaling domain are not naturally found together on a single receptor protein. The chimeric antigen receptors of the present invention are intended primarily for use with lymphocyte such as T cells and natural killer (NK) cells.

The terms "T cell" and "T lymphocyte" are interchangeable and used synonymously herein. As used herein, T cell includes thymocytes, naive T lymphocytes, immature T lymphocytes, mature T lymphocytes, resting T lymphocytes, or activated T lymphocytes. A T cell can be a T helper (Th) cell, for example a T helper 1 (Th1) or a T helper 2 (Th2) cell. The T cell can be a helper T cell (HTL; CD4+ T cell) CD4+ T cell, a cytotoxic T cell (CTL; CD8+ T cell), a tumor infiltrating cytotoxic T cell (TIL; CD8+ T cell), CD4+CD8+ T cell, or any other subset of T cells. Other illustrative populations of T cells suitable for use in particular embodiments include naive T cells and memory T cells. Also included are "NKT cells", which refer to a specialized population of T cells that express a semi-invariant αβ T-cell receptor, but also express a variety of molecular markers that are typically associated with NK cells, such as NK1.1. NKT cells include NK1.1+ and NK1.1-, as well as CD4+, CD4-, CD8+ and CD8- cells. The TCR on NKT cells is unique in that it recognizes glycolipid antigens presented by the MHC I-like molecule CD Id. NKT cells can have either protective or deleterious effects due to their abilities to produce cytokines that promote either inflammation or immune tolerance. Also included are "gamma-delta T cells (γδ T cells)," which refer to a specialized population that to a small subset of T cells possessing a distinct TCR on their surface, and unlike the majority of T cells in which the TCR is composed of two glycoprotein chains designated α- and β-TCR chains, the TCR in γδ T cells is made up of a γ-chain and a δ-chain. γδ T cells can play a role in immunosurveillance and immunoregulation, and were found to be an important source of IL-17 and to induce robust CD8+ cytotoxic T cell response. Also included are "regulatory T cells" or "Tregs", which refer to T cells that suppress an abnormal or excessive immune response and play a role in immune tolerance. Tregs are typically transcription factor Foxp3-positive CD4+T cells and can also include transcription factor Foxp3-negative regulatory T cells that are IL-10-producing CD4+T cells.

The terms "natural killer cell" and "NK cell" are interchangeable and used synonymously herein. As used herein, NK cell refers to a differentiated lymphocyte with a CD 16+ CD56+ and/or CD57+ TCR- phenotype. NK cells are characterized by their ability to bind to and kill cells that fail to express "self" MHC/HLA antigens by the activation of specific cytolytic enzymes, the ability to kill tumor cells or other diseased cells that express a

ligand for NK activating receptors, and the ability to release protein molecules called cytokines that stimulate or inhibit the immune response.

As used herein, the term "antigen" refers to any agent (e.g., protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, portions thereof, or combinations thereof) molecule capable of being bound by a T-cell receptor. An antigen is also able to provoke an immune response. An example of an immune response may involve, without limitation, antibody production, or the activation of specific immunologically competent cells, or both. A skilled artisan will understand that an antigen need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample, or might be macromolecule besides a polypeptide. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a fluid with other biological components, organisms, subunits of proteins/antigens, killed or inactivated whole cells or lysates.

The terms "antibody" and "antibodies" refer to monoclonal antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, single-chain Fvs (scFv), single chain antibodies, Fab fragments, F(ab′) fragments, disulfide-linked Fvs (sdFv), intrabodies, minibodies, diabodies and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antigen-specific TCR), and epitope-binding fragments of any of the above. The terms "antibody" and "antibodies" also refer to covalent diabodies such as those disclosed in U.S. Pat. Appl. Pub. 2007/0004909 and Ig-DARTS such as those disclosed in U.S. Pat. Appl. Pub. 2009/0060910. Antibodies useful as a TCR-binding molecule include immunoglobulin molecules and immunologically active fragments of immunoglobulin molecules, i.e., molecules that contain an antigen-binding site. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgM1, IgM2, IgA1 and IgA2) or subclass.

The term "host cell" means any cell that contains a heterologous nucleic acid. The heterologous nucleic acid can be a vector (*e.g.*, an expression vector). For example, a host cell can be a cell from any organism that is selected, modified, transformed, grown, used or manipulated in any way, for the production of a substance by the cell, for example the expression by the cell of a gene, a DNA or RNA sequence, a protein or an enzyme. An

appropriate host may be determined. For example, the host cell may be selected based on the vector backbone and the desired result. By way of example, a plasmid or cosmid can be introduced into a prokaryote host cell for replication of several types of vectors. Bacterial cells such as, but not limited to DH5α, JM109, and KCB, SURE® Competent Cells, and SOLOPACK Gold Cells, can be used as host cells for vector replication and/or expression. Additionally, bacterial cells such as E. coli LE392 could be used as host cells for phage viruses. Eukaryotic cells that can be used as host cells include, but are not limited to yeast (*e.g.*, YPH499, YPH500 and YPH501), insects and mammals. Examples of mammalian eukaryotic host cells for replication and/or expression of a vector include, but are not limited to, HeLa, NIH3T3, Jurkat, 293, COS, CHO, Saos, and PC12.

Host cells of the present disclosure include T cells and natural killer cells that contain DNA or RNA sequences encoding the CAR and that express the CAR on the cell surface. Host cells may be used for enhancing T cell activity, natural killer cell activity, treatment of cancer, and treatment of autoimmune disease.

"Activation" or "stimulation" means to induce a change in the cells' biologic state by which the cells (*e.g.*, T cells and NK cells) express activation markers, produce cytokines, proliferate and/or become cytotoxic to target cells. All these changes can be produced by primary stimulatory signals. Co-stimulatory signals can amplify the magnitude of the primary signals and suppress cell death following initial stimulation resulting in a more durable activation state and thus a higher cytotoxic capacity. A "co-stimulatory signal" refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to T cell and/or NK cell proliferation and/or upregulation or downregulation of key molecules.

The term "proliferation" refers to an increase in cell division, either symmetric or asymmetric division of cells. The term "expansion" refers to the outcome of cell division and cell death.

The term "differentiation" refers to a method of decreasing the potency or proliferation of a cell or moving the cell to a more developmentally restricted state.

The terms "express" and "expression" mean allowing or causing the information in a gene or DNA sequence to become produced, for example producing a protein by activating the cellular functions involved in transcription and translation of a corresponding gene or DNA sequence. A DNA sequence is expressed in or by a cell to form an "expression product" such as a protein. The expression product itself, e.g., the resulting protein, may also be said to be "expressed" by the cell. An expression product can be characterized as intracellular, extracellular or transmembrane.

The term "transfection" means the introduction of a "foreign" (*i.e.*, extrinsic or extracellular) nucleic acid into a cell using recombinant DNA technology. The term "genetic modification" means the introduction of a "foreign" (*i.e.*, extrinsic or extracellular) gene, DNA or RNA sequence to a host cell, so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein or enzyme coded by the introduced gene or sequence. The introduced gene or sequence may also be called a "cloned" or "foreign" gene or sequence, may include regulatory or control sequences operably linked to polynucleotide encoding the chimeric antigen receptor, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The gene or sequence may include nonfunctional sequences or sequences with no known function. A host cell that receives and expresses introduced DNA or RNA has been "genetically engineered." The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or from a different genus or species.

The term "transduction" means the introduction of a foreign nucleic acid into a cell using a viral vector.

The term "regulatory element" refers to any cis-acting genetic element that controls some aspect of the expression of nucleic acid sequences. In some embodiments, the term "promoter" comprises essentially the minimal sequences required to initiate transcription. In some embodiments, the term "promoter" includes the sequences to start transcription, and in addition, also include sequences that can upregulate or downregulate transcription, commonly termed "enhancer elements" and "repressor elements", respectively.

As used herein, the term "operatively linked," and similar phrases, when used in reference to nucleic acids or amino acids, refer to the operational linkage of nucleic acid sequences or amino acid sequence, respectively, placed in functional relationships with each other. For example, an operatively linked promoter, enhancer elements, open reading frame, 5' and 3' UTR, and terminator sequences result in the accurate production of a nucleic acid molecule (e.g., RNA). In some embodiments, operatively linked nucleic acid elements result in the transcription of an open reading frame and ultimately the production of a polypeptide (i.e., expression of the open reading frame). As another example, an operatively linked peptide is one in which the functional domains are placed with appropriate distance from each other to impart the intended function of each domain.

By "enhance" or "promote," or "increase" or "expand" or "improve" refers generally to the ability of a composition contemplated herein to produce, elicit, or cause a greater physiological response (i.e., downstream effects) compared to the response caused by either vehicle or a control molecule/composition. A measurable physiological response may include an increase in T cell expansion, activation, effector function, persistence, and/or an increase in cancer cell death killing ability, among others apparent from the understanding in the art and the description herein. In certain embodiments, an "increased" or "enhanced" amount can be a "statistically significant" amount, and may include an increase that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (e.g., 500, 1000 times) (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.) the response produced by vehicle or a control composition.

By "decrease" or "lower," or "lessen," or "reduce," or "abate" refers generally to the ability of composition contemplated herein to produce, elicit, or cause a lesser physiological response (i.e., downstream effects) compared to the response caused by either vehicle or a control molecule/composition. In certain embodiments, a "decrease" or "reduced" amount can be a "statistically significant" amount, and may include a decrease that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (e.g., 500, 1000 times) (including all integers and decimal points in between and above 1, e.g., 1.5, 1.6, 1.7. 1.8, etc.) the response (reference response) produced by vehicle, a control composition, or the response in a particular cell lineage.

The term "effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a subject in need thereof. Note that when a combination of active ingredients is administered, the effective amount of the combination may or may not include amounts of each ingredient that would have been effective if administered individually. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular drug or drugs employed, the mode of administration, and the like.

The phrase "pharmaceutically acceptable", as used in connection with compositions described herein, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (*e.g.*, a human). Preferably, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

The term "protein" is used herein encompasses all kinds of naturally occurring and synthetic proteins, including protein fragments of all lengths, fusion proteins and modified proteins, including without limitation, glycoproteins, as well as all other types of modified proteins (e.g., proteins resulting from phosphorylation, acetylation, myristoylation, palmitoylation, glycosylation, oxidation, formylation, amidation, polyglutamylation, ADP-ribosylation, pegylation, biotinylation, etc.).

The terms "nucleic acid", "nucleotide", and "polynucleotide" encompass both DNA and RNA unless specified otherwise. By a "nucleic acid sequence" or "nucleotide sequence" is meant the nucleic acid sequence encoding an amino acid; these terms may also refer to the nucleic acid sequence including the portion coding for any amino acids added as an artifact of cloning, including any amino acids coded for by linkers.

The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as

peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Alternatively, the carrier can be a solid dosage form carrier, including but not limited to one or more of a binder (for compressed pills), a glidant, an encapsulating agent, a flavorant, and a colorant. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

The term "about" or "approximately" includes being within a statistically meaningful range of a value. Such a range can be within an order of magnitude, preferably within 50%, more preferably within 20%, still more preferably within 10%, and even more preferably within 5% of a given value or range. The allowable variation encompassed by the term "about" or "approximately" depends on the particular system under study, and can be readily appreciated by one of ordinary skill in the art.

"Kallikrein related peptidase 2", "hK2", or "klk2" refers to a known protein which is also called kallikrein-2, glandular kallikrein 2, or HK2. hK2 is produced as a preproprotein and cleaved during proteolysis to generate active protease. All hK2 isoforms and variants are encompassed in "hK2". The amino acid sequences of the various isoforms are retrievable from GenBank accession numbers NP_005542.1, NP_001002231.1 and NP_001243009. The amino acid sequence of a full length hK2 is shown in SEQ ID NO: 62. The sequence includes the signal peptide (residues 1-18) and the pro-peptide region (residues 19-24).

The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. As used herein, the indefinite articles "a", "an" and "the" should be understood to include plural reference unless the context clearly indicates otherwise.

**Chimeric Antigen Receptors**

The present invention relates generally to the use of T cells genetically modified to stably express a desired chimeric antigen receptor. A chimeric antigen receptor (CAR) is an artificially constructed hybrid protein or polypeptide containing the antigen binding

domains of an antibody (scFv) linked to T-cell signaling domains. Characteristics of CARs can include their ability to redirect T-cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives T cells expressing CARs the ability to recognize antigens independent of antigen processing, thus bypassing a major mechanism of tumor evasion. Moreover, when expressed in T-cells, CARs advantageously do not dimerize with endogenous T cell receptor (TCR) alpha and beta chains.

The CARs described herein provide recombinant polypeptide constructs comprising at least an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain (also referred to herein as "a cytoplasmic signaling domain") comprising a functional signaling domain derived from a stimulatory molecule as defined below. T cells expressing a CAR are referred to herein as CAR T cells, CAR-T cells or CAR modified T cells, and these terms are used interchangeably herein. The cell can be genetically modified to stably express an antibody binding domain on its surface, conferring novel antigen specificity that is MHC independent.

In some instances, the T cell is genetically modified to stably express a CAR that combines an antigen recognition domain of a specific antibody with an intracellular domain of the CD3-zeta chain or FcγRI protein into a single chimeric protein. In one embodiment, the stimulatory molecule is the zeta chain associated with the T cell receptor complex.

An "intracellular signaling domain," or a "cytoplasmic signaling domain", as used herein, refers to an intracellular portion of a molecule. It is the functional portion of the protein which acts by transmitting information within the cell to regulate cellular activity via defined signaling pathways by generating second messengers or functioning as effectors by responding to such messengers. The intracellular signaling domain generates a signal that promotes an immune effector function of the CAR containing cell, e.g., a CAR-T cell. Examples of immune effector function, e.g., in a CAR-T cell, include cytolytic activity and helper activity, including the secretion of cytokines.

In an embodiment, the intracellular signaling domain can comprise a primary intracellular signaling domain. Example primary intracellular signaling domains include those derived

from the molecules responsible for primary stimulation, or antigen dependent simulation. In an embodiment, the intracellular signaling domain can comprise a co-stimulatory intracellular domain. Example co-stimulatory intracellular signaling domains include those derived from molecules responsible for co-stimulatory signals, or antigen independent stimulation. For example, in the case of a CAR-T, a primary intracellular signaling domain can comprise a cytoplasmic sequence of a T cell receptor, and a co-stimulatory intracellular signaling domain can comprise cytoplasmic sequence from co-receptor or co-stimulatory molecule.

A primary intracellular signaling domain can comprise a signaling motif which is known as an immunoreceptor tyrosine-based activation motif or ITAM. Examples of ITAM containing primary cytoplasmic signaling sequences include, but are not limited to, those derived from CD3-zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD5, CD22, CD79a, CD79b, and CD66d DAP10 and DAP12.

The term "zeta" or alternatively "zeta chain", "CD3-zeta" or "TCR-zeta" is defined as the protein provided as GenBank Acc. No. BAG36664.1, or the equivalent residues from a nonhuman species, e.g., murine, rabbit, primate, mouse, rodent, monkey, ape and the like, and a "zeta stimulatory domain" or alternatively a "CD3-zeta stimulatory domain" or a "TCR-zeta stimulatory domain" is defined as the amino acid residues from the cytoplasmic domain of the zeta chain that are sufficient to functionally transmit an initial signal necessary for T cell activation. At times, e.g. in or the aspects and/or embodiments of the disclosure, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is also referred to as "primary signaling domain". In one aspect, the cytoplasmic domain of CD3-zeta stimulatory domain comprises residues 52 through 164 of GenBank Acc. No. BAG36664.1 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, that are functional orthologs thereof. In a preferred embodiment, the intracellular signaling domain comprises a CD3-zeta stimulatory domain. In one aspect, the "zeta stimulatory domain" or a "CD3-zeta stimulatory domain" is the sequence provided as SEQ ID NO: 28, or a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at

least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 28.

The term "co-stimulatory molecule" refers to the cognate binding partner on a T cell that specifically binds with a co-stimulatory ligand, thereby mediating a co-stimulatory response by the T cell, such as, but not limited to, proliferation. Co-stimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Co-stimulatory molecules include, but are not limited to an MHC class 1 molecule, BTLA and a Toll ligand receptor, as well as OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) and 4-1BB (CD137).

A co-stimulatory intracellular signaling domain can be the intracellular portion of a co-stimulatory molecule. A co-stimulatory molecule can be represented in the following protein families: TNF receptor proteins, Immunoglobulin-like proteins, cytokine receptors, integrins, signaling lymphocytic activation molecules (SLAM proteins), and activating NK cell receptors. Examples of such molecules include CD27, CD28, 4-1BB (CD137), OX40, GITR, CD30, MyD88, CD40, ICOS, BAFFR, HVEM, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, and a ligand that specifically binds with CD83, and the like.

The intracellular signaling domain can comprise the entire intracellular portion, or the entire native intracellular signaling domain, of the molecule from which it is derived, or a functional fragment thereof.

The term "4-1BB" or alternatively "CD137" refers to a member of the TNFR superfamily with an amino acid sequence provided as GenBank Acc. No. AAA62478.2, or the equivalent residues from a nonhuman species, e.g., mouse, rodent, monkey, ape and the like; and a "4-1BB co-stimulatory domain" is defined as amino acid residues 214-255 of GenBank accession no. AAA62478.2, or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like. At times, e.g. in aspects and/or embodiments of the disclosure, the "4-1BB co-stimulatory domain" is also referred to as "co-stimulatory domain".

In a preferred embodiment, the intracellular signaling domain comprises a costimulatory intracellular signaling domain, wherein the costimulatory intracellular signaling domain is a 4-1BB costimulatory domain or "CD137 co-stimulatory domain". In one aspect, the "4-1BB co-stimulatory domain" or "CD137 co-stimulatory domain" is the sequence provided as SEQ ID NO: 27 or the equivalent residues from a non-human species, e.g., mouse, rodent, monkey, ape and the like, or a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 27. In a preferred embodiment the 4-1BB costimulatory domain is the sequence provided as SEQ ID No:27.

In one embodiment, a transmembrane domain that naturally is associated with one of the domains in the CAR is used. In another embodiment, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. In one example embodiment, the transmembrane domain comprises the CD8α hinge domain. In one embodiment, the CAR comprises a CD8α hinge domain and a CD8α transmembrane domain.

In some embodiments, the cytoplasmic signaling domain further comprises one or more functional signaling domains derived from at least one co-stimulatory molecule as defined herein. In one embodiment, the co-stimulatory molecule is chosen from 4-1BB (i.e., CD137), CD27, CD3-zeta and/or CD28. CD28 is a T cell marker important in T cell co-stimulation. CD27 is a member of the tumor necrosis factor receptor superfamily and acts as a co-stimulatory immune checkpoint molecule. 4-1BB transmits a potent co-stimulatory signal to T cells, promoting differentiation and enhancing long-term survival of T lymphocytes. CD3-zeta associates with TCRs to produce a signal and contains immunoreceptor tyrosine-based activation motifs (ITAMs). In another embodiment, the co-stimulatory molecule is MyD88 or CD40.

In one embodiment, the CAR comprises an intracellular hinge domain comprising CD8 and an intracellular T cell receptor signaling domain comprising CD28, 4-1BB, and CD3-

zeta. In another embodiment, the CAR comprises an intracellular hinge domain and an intracellular T cell receptor signaling domain comprising CD28, 4-1BB, and CD3-zeta, wherein the hinge domain comprises all or part of the extracellular region of CD8, CD4 or CD28; all or part of an antibody constant region; all or part of the FcγRIIIa receptor, an IgG hinge, an IgM hinge, an IgA hinge, an IgD hinge, an IgE hinge, or an Ig hinge. The IgG hinge may be from IgG1, IgG2, IgG3, IgG4, IgM1, IgM2, IgA1, IgA2, IgD, IgE, or a chimera thereof.

CARs described herein provide recombinant polypeptide constructs comprising at least an extracellular antigen binding domain, a transmembrane domain and an intracellular signaling domain (also referred to herein as "a cytoplasmic signaling domain") comprising, e.g., a functional signaling domain derived from a stimulatory molecule as defined below In one embodiment, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a stimulatory molecule. In one embodiment, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising a functional signaling domain derived from a co-stimulatory molecule and a functional signaling domain derived from a stimulatory molecule. In one embodiment, the CAR comprises a chimeric fusion protein comprising an extracellular antigen recognition domain, a transmembrane domain and an intracellular signaling domain comprising at least two functional signaling domains derived from one or more co-stimulatory molecule(s) and a functional signaling domain derived from a stimulatory molecule.

The CARs of the invention can be designed to comprise the CD28 and/or 4-1BB signaling domain by itself or be combined with any other desired cytoplasmic domain(s) useful in the context of the CARs of the invention. In one embodiment, the cytoplasmic domain of the CAR can further comprise the signaling domain of CD3-zeta. For example, the cytoplasmic domain of the CAR can include but is not limited to CD3-zeta, 4-1BB and CD28 signaling modules and combinations thereof.

In one embodiment, the CAR comprises a hinge domain comprising a CD8α hinge domain, a CD8α transmembrane domain. and an intracellular signaling domain comprising 4-1BB, and CD3-zeta. In one embodiment, the CAR comprises a hinge domain comprising a CD8α hinge domain, a CD8α transmembrane domain. and an intracellular signaling domain comprising CD28, 4-1BB, and CD3-zeta.

In another embodiment, the CAR comprises a CD8α hinge domain, a CD8α transmembrane domain, and an intracellular signaling domain comprising the signaling domain of CD3-zeta and a 4-1BB costimulatory domain.

In another embodiment, the CAR comprises a CD8a-hinge region comprising the amino acid sequence of SEQ ID NO: 25; a transmembrane domain comprising the amino acid sequence of SEQ ID NO: 26; and an intracellular signaling domain comprising a co-stimulatory domain comprising an amino acid sequence of SEQ ID NO: 27, and a primary signaling domain comprising an amino acid sequence of SEQ ID NO: 28.

Accordingly, the invention provides CAR T cells and methods of their use for adoptive therapy.

The disclosure further provides variants, e.g., functional variants, of the CARs, nucleic acids, polypeptides, and proteins described herein. "Variant" refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions or deletions. The term "functional variant" as used herein refers to a CAR, polypeptide, or protein having substantial or significant sequence identity or similarity to a parent CAR, polypeptide, or protein, which functional variant retains the biological activity of the CAR, polypeptide, or protein for which it is a variant. Functional variants encompass, e.g., those variants of the CAR, polypeptide, or protein described herein (the parent CAR, polypeptide, or protein) that retain the ability to recognize target cells to a similar extent, the same extent, or to a higher extent, as the parent CAR, polypeptide, or protein. In reference to the parent CAR, polypeptide, or protein, the functional variant can, for example, be at least about 30%, about 40%, about 50%, about 60%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%,

about 99% or more identical in amino acid sequence to the parent CAR, polypeptide, or protein.

Herein, the structure of polypeptides is in places defined on the basis of % sequence identity with a recited reference sequence (with a given SEQ ID NO). In this context, % sequence identity between two amino acid sequences may be determined by comparing these two sequences aligned in an optimum manner and in which the amino acid sequence to be compared can comprise additions or deletions with respect to the reference sequence for an optimum alignment between these two sequences. The percentage of identity is calculated by determining the number of identical positions for which the amino acid residue is identical between the two sequences, by dividing this number of identical positions by the total number of positions in the comparison window and by multiplying the result obtained by 100 in order to obtain the percentage of identity between these two sequences. Typically, the comparison window with correspond to the full length of the sequence being compared. For example, it is possible to use the BLAST program, "BLAST 2 sequences" (Tatusova et al, "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 174:247-250) available on the site http://www.ncbi.nlm.nih.gov/ gorf/bl2.html, the parameters used being those given by default (in particular for the parameters "open gap penalty": 5, and "extension gap penalty": 2; the matrix chosen being, for example, the matrix "BLOSUM 62" proposed by the program), the percentage of identity between the two sequences to be compared being calculated directly by the program. Determining sequence identity of a query sequence to a reference sequence is within the ability of the skilled person and can be performed using commercially available analysis software such as BLAST™.

A functional variant can, for example, comprise the amino acid sequence of the parent CAR, polypeptide, or protein with at least one conservative amino acid substitution. In another embodiment, the functional variants can comprise the amino acid sequence of the parent CAR, polypeptide, or protein with at least one non-conservative amino acid substitution. In this case, the non-conservative amino acid substitution may not interfere with or inhibit the biological activity of the functional variant. The non-conservative amino acid substitution may enhance the biological activity of the functional variant such that the

biological activity of the functional variant is increased as compared to the parent CAR, polypeptide, or protein.

Amino acid substitutions of the inventive CARs may be conservative amino acid substitutions. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same or similar chemical or physical properties. For example, the conservative amino acid substitution can be an acidic amino acid substituted for another acidic amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Trp, Val, etc.), a basic amino acid substituted for another basic amino acid (Lys, Arg, etc.), an amino acid with a polar side chain substituted for another amino acid with a polar side chain (Asn, Cys, Gln, Ser, Thr, Tyr, etc.), etc.

The CAR, polypeptide, or protein can consist essentially of the specified amino acid sequence or sequences described herein, such that other components e.g., other amino acids, do not materially change the biological activity of the functional variant.

The CARs, polypeptides, and proteins of embodiments of the disclosure (including functional portions and functional variants) can be of any length, i.e., can comprise any number of amino acids, provided that the CARs, polypeptides, or proteins (or functional portions or functional variants thereof) retain their biological activity, e.g., the ability to specifically bind to an antigen, detect diseased cells (e.g., cancer cells) in a host, or treat or prevent disease in a host, etc. For example, the polypeptide can be about 50 to about 5000 amino acids long, such as about 50, about 70, about 75, about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, about 650, about 675, about 700, about 725, about 750, about 775, about 800, about 825, about 850, about 875, about 900, about 925, about 950, about 975, about 1000 or more amino acids in length. The polypeptides of the invention also include oligopeptides.

The CARs, polypeptides, and proteins of embodiments of the invention (including functional portions and functional variants of the invention) can comprise synthetic amino acids in place of one or more naturally-occurring amino acids. Such synthetic amino acids are known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, α-amino n-decanoic acid, homoserine, S-acetylaminomethyl-cysteine, trans-3- and trans-4-hydroxyproline, 4-aminophenylalanine, 4-nitrophenylalanine, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid, α,β-diaminopropionic acid, homophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, N′-benzyl-N′-methyl-lysine, N′,N′-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aminomalonic acid, aminomalonic acid monoamide, and α-tert-butylglycine.

The CARs, polypeptides, and proteins of embodiments of the invention (including functional portions and functional variants) can be subject to post-translational modifications. They can be glycosylated, esterified, N-acylated, amidated, carboxylated, phosphorylated, esterified, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt. In some embodiments, they are dimerized or polymerized, or conjugated.

The CARs, polypeptides, and/or proteins of embodiments of the invention (including functional portions and functional variants thereof) can be obtained by methods known in the art. Suitable methods of *de novo* synthesizing polypeptides and proteins are described in references, such as Chan et al., *Fmoc Solid Phase Peptide Synthesis*, Oxford University Press, Oxford, United Kingdom, 2000; *Peptide and Protein Drug Analysis*, ed. Reid, R., Marcel Dekker, Inc.,2000; and *Epitope Mapping*, ed. Westwood et al., Oxford University Press, Oxford, United Kingdom, 2001. Also, polypeptides and proteins can be recombinantly produced using the nucleic acids described herein using standard recombinant methods. See, for instance, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 3rd ed., Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 2001; and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates

and John Wiley & Sons, NY, 1994. Further, some of the CARs, polypeptides, and proteins of the invention (including functional portions and functional variants thereof) can be isolated and/or purified from a source, such as a plant, a bacterium, an insect, a mammal, etc. Methods of isolation and purification are known in the art. Alternatively, the CARs, polypeptides, and/or proteins described herein (including functional portions and functional variants thereof) can be commercially synthesized. In this respect, the CARs, polypeptides, and proteins can be synthetic, recombinant, isolated, and/or purified.

Examples of modified nucleotides that can be used to generate the recombinant nucleic acids utilized to produce the polypeptides described herein include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, $N^6$-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5″-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-$N^6$-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queuosine, beta-D-galactosylqueosine, inosine, $N^6$-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine.

The nucleic acid can comprise any isolated or purified nucleotide sequence which encodes any of the CARs, polypeptides, or proteins, or functional portions or functional variants thereof. Alternatively, the nucleotide sequence can comprise a nucleotide sequence which is degenerate to any of the sequences or a combination of degenerate sequences.

Some embodiments of the invention also provide an isolated or purified nucleic acid comprising a nucleotide sequence which is complementary to the nucleotide sequence of any of the nucleic acids described herein or a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of any of the nucleic acids described herein.

The nucleotide sequence which hybridizes under stringent conditions may hybridize under high stringency conditions. By "high stringency conditions" is meant that the nucleotide sequence specifically hybridizes to a target sequence (the nucleotide sequence of any of the nucleic acids described herein) in an amount that is detectably stronger than non-specific hybridization. High stringency conditions include conditions which would distinguish a polynucleotide with an exact complementary sequence, or one containing only a few scattered mismatches from a random sequence that happened to have a few small regions (e.g., 3-12 bases) that matched the nucleotide sequence. Such small regions of complementarity are more easily melted than a full-length complement of 14-17 or more bases, and high stringency hybridization makes them easily distinguishable. Relatively high stringency conditions would include, for example, low salt and/or high temperature conditions, such as provided by about 0.02-0.1 M NaCl or the equivalent, at temperatures of about 50-70° C. Such high stringency conditions tolerate little, if any, mismatch between the nucleotide sequence and the template or target strand, and are particularly suitable for detecting expression of any of the CARs described herein. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

In an embodiment, the nucleic acids of the invention can be incorporated into a recombinant expression vector. The present disclosure provides recombinant expression vectors comprising any of the nucleic acids of the invention. As used herein, the term "recombinant expression vector" means a genetically-modified oligonucleotide or polynucleotide construct that permits the expression of an mRNA, protein, polypeptide, or peptide by a host cell, when the construct comprises a nucleotide sequence encoding the mRNA, protein, polypeptide, or peptide, and the vector is contacted with the cell under conditions sufficient to have the mRNA, protein, polypeptide, or peptide expressed within the cell. The vectors described herein are not naturally-occurring as a whole; however, parts of the vectors can be naturally-occurring. The described recombinant expression vectors can comprise any type of nucleotides, including, but not limited to DNA and RNA, which can be single-stranded or double-stranded, synthesized or obtained in part from natural sources, and which can contain natural, non-natural or altered nucleotides. The recombinant expression vectors can

comprise naturally-occurring or non-naturally-occurring internucleotide linkages, or both types of linkages. The non-naturally occurring or altered nucleotides or internucleotide linkages do not hinder the transcription or replication of the vector.

In an embodiment, the recombinant expression vector of the invention can be any suitable recombinant expression vector, and can be used to transform or transfect any suitable host. Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the group consisting of the pUC series (Fermentas Life Sciences, Glen Burnie, Md.), the pBluescript series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as λGT10, λGT11, λEMBL4, and λNM1149, λZapII (Stratagene) can be used. Examples of plant expression vectors include pBI01, pBI01.2, pBI121, pBI101.3, and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-Cl, pMAM, and pMAMneo (Clontech). The recombinant expression vector may be a viral vector, e.g., a retroviral vector, e.g., a gamma retroviral vector.

In an embodiment, the recombinant expression vectors of the invention are prepared using standard recombinant DNA techniques described in, for example, Sambrook et al., supra, and Ausubel et al., supra. Constructs of expression vectors, which are circular or linear, can be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, e.g., from ColE1, SV40, 2μ plasmid, λ, bovine papilloma virus, and the like.

The recombinant expression vector may comprise regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host (e.g., bacterium, plant, fungus, or animal) into which the vector is to be introduced, as appropriate, and taking into consideration whether the vector is DNA- or RNA-based.

The recombinant expression vector can include one or more marker genes, which allow for selection of transformed or transfected hosts. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host to

provide prototrophy, and the like. Suitable marker genes for the described expression vectors include, for instance, neomycin/G418 resistance genes, histidinol x resistance genes, histidinol resistance genes, tetracycline resistance genes, and ampicillin resistance genes.

The recombinant expression vector can comprise a native or normative promoter operably linked to the nucleotide sequence encoding the CAR, polypeptide, or protein (including functional portions and functional variants thereof), or to the nucleotide sequence which is complementary to or which hybridizes to the nucleotide sequence encoding the CAR, polypeptide, or protein. The selection of promoters, e.g., strong, weak, tissue-specific , inducible and developmental-specific, is within the ordinary skill of the artisan. Similarly, the combining of a nucleotide sequence with a promoter is also within the skill of the artisan. The promoter can be a non-viral promoter or a viral promoter, e.g., a cytomegalovirus (CMV) promoter, an RSV promoter, an SV40 promoter, or a promoter found in the long-terminal repeat of the murine stem cell virus.

The recombinant expression vectors can be designed for either transient expression, for stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression.

Further, the recombinant expression vectors can be made to include a suicide gene. As used herein, the term “suicide gene” refers to a gene that causes the cell expressing the suicide gene to die. The suicide gene can be a gene that confers sensitivity to an agent, e.g., a drug, upon the cell in which the gene is expressed, and causes the cell to die when the cell is contacted with or exposed to the agent. Suicide genes are known in the art and include, for example, the Herpes Simplex Virus (HSV) thymidine kinase (TK) gene, cytosine deaminase, purine nucleoside phosphorylase, and nitroreductase.

Included in the scope of the invention are conjugates, e.g., bioconjugates, comprising any of the CARs, polypeptides, or proteins (including any of the functional portions or variants thereof), host cells, nucleic acids, recombinant expression vectors, populations of host cells, or antibodies, or antigen binding portions thereof. Conjugates, as well as methods of synthesizing conjugates in general, are known in the art (See, for instance, Hudecz, F.,

*Methods Mol. Biol.* 298: 209-223 (2005) and Kirin et al., *Inorg Chem.* 44(15): 5405-5415 (2005)).

An embodiment of the invention further provides an antibody, or antigen binding portion thereof, which binds, e.g., specifically binds, to an epitope of the CARs of the invention. The antibody can be any type of immunoglobulin that is known in the art. Immunoglobulins may be assigned to five major classes, IgA, IgD, IgE, IgG and IgM. IgA and IgG are further classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Antibody light chains of vertebrate species can be assigned to one of two types, kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains. The antibody can be of any class or isotype.

The antibodies include immunoglobulin molecules including monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, polyclonal, antigen-binding fragments, bispecific or multispecific antibodies, monomeric, dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen binding site of the required specificity. The antibody can be a naturally-occurring antibody, e.g., an antibody isolated and/or purified from a mammal, e.g., a murine, primate, mouse, rabbit, goat, horse, chicken, hamster, human, etc. Alternatively, the antibody can be an engineered (e.g., genetically-engineered) antibody.

Humanized antibodies have antigen binding sites derived from non-human species and the variable region frameworks are derived from human immunoglobulin sequences. Human antibodies have heavy and light chain variable regions in which both the framework and the antigen binding site are derived from sequences of human origin.

Also, the antibody can have any level of affinity or avidity for the functional portion of the CAR. In some embodiments, the antibody may bind the hK2 antigen with a range of affinities ($K_D$). In one embodiment according to the invention, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody binds to the hK2 antigen with high affinity, for example, with a $K_D$ equal to or less than about $10^{-7}$ M, such as but not limited to, 1-9.9 (or any range or value therein, such as 1, 2, 3, 4, 5, 6, 7,

8, or 9)$\times 10^{-8}$M, $10^{-9}$ M, $10^{-10}$ M, $10^{-11}$ M, $10^{-12}$ M, $10^{-13}$ M, $10^{-14}$ M, $10^{-15}$ M or any range or value therein, as determined by surface plasmon resonance or the Kinexa method, as practiced by those of skill in the art. One example affinity is equal to or less than $1\times 10^{-8}$ M. Another example affinity is equal to or less than $1\times 10^{-9}$ M.

Methods of testing antibodies for the ability to bind to any functional portion of the CARs are known in the art and include any antibody-antigen binding assay, such as, for example, radioimmunoassay (RIA), Western blot, enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, and competitive inhibition assays.

Suitable methods of making antibodies are known in the art. For instance, standard hybridoma methods are described in, e.g., Köhler and Milstein, *Eur. J. Immunol.*, 5, 511-519 (1976), Harlow and Lane (eds.), *Antibodies: A Laboratory Manual*, CSH Press (1988), and C. A. Janeway et al. (eds.), *Immunobiology*, 5th Ed., Garland Publishing, New York, N.Y. (2001)). Alternatively, other methods, such as EBV-hybridoma methods (Haskard and Archer, J. *Immunol. Methods*, 74(2), 361-67 (1984), and Roder et al., *Methods Enzymol.*, 121, 140-67 (1986)), and bacteriophage vector expression systems (see, e.g., Huse et al., *Science*, 246, 127581 (1989)) are known in the art. Further, methods of producing antibodies in non-human animals are described in, e.g., U.S. Patent Nos. 5,545,806, 5,569,825, and 5,714,352, and U.S. Patent Application Publication No. 2002/0197266 A1).

Phage display can also be used to generate an antibody. In this regard, phage libraries encoding antigen-binding variable (V) domains of antibodies can be generated using standard molecular biology and recombinant DNA techniques (see, e.g., Sambrook et al., supra, and Ausubel et al., supra). Phage encoding a variable region with the desired specificity are selected for specific binding to the desired antigen (i.e., hK2), and a complete or partial antibody is reconstituted comprising the selected variable domain. Nucleic acid sequences encoding the reconstituted antibody are introduced into a suitable cell line, such as a myeloma cell used for hybridoma production, such that antibodies having the characteristics of monoclonal antibodies are secreted by the cell (see, e.g., Janeway et al., supra, Huse et al., supra, and U.S. Pat. No. 6,265,150).

Antibodies can be produced by transgenic mice that are transgenic for specific heavy and light chain immunoglobulin genes. Such methods are known in the art and described in, for example U.S. Patent Nos. 5,545,806 and 5,569,825, and Janeway et al., supra.

Methods for generating humanized antibodies are known in the art and are described in, for example, Janeway et al., supra, U.S. Patent Nos. 5,225,539, 5,585,089 and 5,693,761, European Patent No. 0239400 B1, and United Kingdom Patent No. 2188638. Humanized antibodies can also be generated using the antibody resurfacing technology described in U.S. Patent No. 5,639,641 and Pedersen et al., J. Mol. Biol., 235, 959-973 (1994). Antibodies, as utilized herein, can be multiple or single chain, or intact immunoglobulins, and may be derived from natural sources or from recombinant sources. Antibodies can be tetramers of immunoglobulin molecules.

The term "antibody fragment" refers to at least one portion of an intact antibody, or recombinant variants thereof, that retains the antigen binding properties of the parental full length antibody. It refers to, for example, the antigen binding domain, e.g., an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and binding, e.g., specific binding of the antibody fragment to a target, such as an antigen. "Antigen- binding fragment" refers to a portion of an immunoglobulin molecule. Examples of antibody fragments include, but are not limited to, Fab, Fab′, $F(ab')_2$, and Fv fragments, single chain antibodies (scFv), linear antibodies, single domain antibodies such as sdAb (either VL or VH), camelid VHH domains, and multi-specific antibodies formed from antibody fragments.

The term "scFv" refers to a protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain. In some embodiments, the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, e.g., with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

An embodiment of the invention also provides antigen binding portions of any of the antibodies described herein. The antigen binding portion can be any portion that has at least one antigen binding site, such as Fab, F(ab′)2, dsFv, sFv, diabodies, and triabodies. In some embodiments, antigen-binding fragments are heavy chain complementarity determining regions (HCDR) 1, 2 and/or 3, light chain complementarity determining regions (LCDR) 1, 2 and/or 3, a heavy chain variable region (VH), or a light chain variable region (VL), Fab, F(ab′)2, Fd and Fv fragments and domain antibodies (dAb) comprising (e.g., consisting of) either one VH domain or one VL domain. VH and VL domains may be linked together via a linker, e.g., a synthetic linker.

"Complementarity determining regions (CDR)" are antigen binding sites in an antibody. CDRs may be defined using various terms: (i) Complementarity Determining Regions (CDRs), three in the VH (HCDR1, HCDR2, HCDR3) and three in the VL (LCDR1, LCDR2, LCDR3) are based on sequence variability (Wu and Kabat, J Exp Med 132:211-50, 1970; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991). (ii) "Hypervariable regions", "HVR", or "HV", three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3) refer to the regions of an antibody variable domains which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk, Mol Biol 196:901-17, 1987). The International ImMunoGeneTics (IMGT) database (http://www_imgt_org) provides a standardized numbering and definition of antigen-binding sites. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc et al., Dev Comparat Immunol 27:55-77, 2003. The term "CDR", "HCDR1", "HCDR2", "HCDR3", "LCDR1", "LCDR2" and "LCDR3" as used herein includes CDRs defined by any of the methods described supra, Kabat, Chothia or IMGT, unless otherwise explicitly stated in the specification.

Also, the antibody, or antigen binding portion thereof, can be modified to comprise a detectable label, such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

Also provided by the present disclosure is a nucleic acid comprising a nucleotide sequence encoding any of the CARs, polypeptides, or proteins described herein (including functional portions and functional variants thereof).

The portion of the CAR comprising an antibody or antibody fragment thereof may exist in a variety of forms where the antigen binding domain is expressed as part of a contiguous polypeptide chain including, for example, a single domain antibody fragment (sdAb), a scFv and a human chimeric or humanized antibody (Harlow et al., 1999, *In: Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, N.Y.; Harlow et al., 1989, *In: Antibodies: A Laboratory Manual*, Cold Spring Harbor, N.Y.; Houston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-5883; Bird et al., 1988, *Science* 242:423-426). In one aspect, the antigen binding domain of a CAR composition of the invention comprises an antibody fragment. In one aspect, the CAR comprises an antibody fragment that comprises a scFv.

The term "recombinant antibody" refers to an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage or yeast expression system. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using recombinant DNA or amino acid sequence technology which is available and known in the art.

The term "antigen" refers to a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full-length nucleotide sequence of a gene.

It is apparent that the present disclosure includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences are arranged in various combinations to encode polypeptides that elicit the desired immune response.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 74, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 76;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 77;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 147, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 140;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 141;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 140;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 148, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 142;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 149, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 143;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 150, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 144;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 151, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 145;

light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 152, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 317;

wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 3, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 1, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 2, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 74, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 76.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 77.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 147, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 140.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 141.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 75, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 140.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 148, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 142

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 149, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 143.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 150, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 144.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 151, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 145.

In one embodiment the extracellular antigen-binding domain comprises light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of

SEQ ID NO: 152, and heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 146.

In one embodiment the extracellular antigen-binding domain comprises a light chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain CDR1, CDR2, and CDR3 from a variable region comprising an amino acid sequence of SEQ ID NO: 317.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID NO: 86, SEQ ID NO: 92, SEQ ID NO: 102, SEQ ID NO: 105, SEQ ID NO: 107, SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 123, SEQ ID NO: 309, and SEQ ID NO: 314, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 73, SEQ ID NO: 87, SEQ ID NO: 93, SEQ ID NO: 103, SEQ ID NO: 106, SEQ ID NO: 108, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 116, SEQ ID NO: 119, SEQ ID NO: 121, SEQ ID NO: 124, SEQ ID NO: 310, and SEQ ID NO: 315, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO: 66, SEQ ID NO: 88, SEQ ID NO: 94, SEQ ID NO: 104, SEQ ID NO: 109, SEQ ID NO: 113, SEQ ID NO: 117, SEQ ID NO: 122, and SEQ ID NO: 311, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence

of SEQ ID NO: 87, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 92, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 93, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 94;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122,

wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ

ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 92, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 93, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 94.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122.

In one embodiment the extracellular antigen-binding domain comprises a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 89, SEQ ID NO: 95, SEQ ID NO: 97, SEQ ID NO: 125, SEQ ID NO: 128, SEQ ID NO: 133, SEQ ID NO: 136, and

SEQ ID NO: 312, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 90, SEQ ID NO: 96, SEQ ID NO: 126, SEQ ID NO: 137, SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 134, SEQ ID NO: 137, and SEQ ID NO: 313, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO: 71, SEQ ID NO: 91, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 135, SEQ ID NO: 138, and SEQ ID NO: 139, and conservative modifications thereof, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139,

wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

In one embodiment the extracellular antigen-binding domain comprises a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138;

wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises: a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises: a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises: a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130.

In one embodiment, the extracellular antigen-binding domain comprises:
a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132.

In one embodiment, the extracellular antigen-binding domain comprises:
a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135.

In one embodiment, the extracellular antigen-binding domain comprises:
a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino

acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of

SEQ ID NO: 124, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the extracellular antigen-binding domain comprises:
a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the extracellular antigen-binding domain comprises:
a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:
a light chain variable region (LCVR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-3, or a heavy chain variable region (HCVR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 4-6, or a combination of a LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-3, and a HCVR comprising an amino acid sequence

selected from the group consisting of SEQ ID NOS: 4-6, wherein the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment, the extracellular antigen-binding domain comprises:

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76; a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

In one embodiment, the extracellular antigen-binding domain comprises:

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93,

at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65,

at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 76;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 75 and a heavy chain variable region

comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98

or at least 99%, sequence identity with SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 317.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at

least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least

60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 4.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 6.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at

least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 5.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 76.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94,at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 77.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 140.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 141.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%,

sequence identity with SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 140.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 142.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 143.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at

least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 144.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 145.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 146.

In one embodiment, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 317.

In one embodiment, the extracellular antigen-binding domain comprises a scFv. In some embodiments, the scFv comprises a linker polypeptide between the light chain variable

region and the heavy chain variable region. In certain embodiments, the extracellular antigen-binding domain is a scFv which comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 8-23, 169-184 and 340-343, and specifically binds to a hK2 polypeptide (e.g., a human hK2 polypeptide having the amino acid sequence of SEQ ID NO: 62, or fragments thereof).

In recombinant expression systems, the linker is a peptide linker and may include any naturally occurring amino acid. Exemplary amino acids that may be included into the linker are Gly, Ser Pro, Thr, Glu, Lys, Arg, Ile, Leu, His and The. The linker should have a length that is adequate to link the VH and the VL in such a way that they form the correct conformation relative to one another so that they retain the desired activity, such as binding to hK2.

The linker may be about 5-50 amino acids long. In some embodiments, the linker is about 10-40 amino acids long. In some embodiments, the linker is about 10-35 amino acids long. In some embodiments, the linker is about 10-30 amino acids long. In some embodiments, the linker is about 10-25 amino acids long. In some embodiments, the linker is about 10-20 amino acids long. In some embodiments, the linker is about 15-20 amino acids long. In some embodiments, the linker is 6 amino acids long. In some embodiments, the linker is 7 amino acids long. In some embodiments, the linker is 8 amino acids long. In some embodiments, the linker is 9 amino acids long. In some embodiments, the linker is 10 amino acids long. In some embodiments, the linker is 11 amino acids long. In some embodiments, the linker is 12 amino acids long. In some embodiments, the linker is 13 amino acids long. In some embodiments, the linker is 14 amino acids long. In some embodiments, the linker is 15 amino acids long. In some embodiments, the linker is 16 amino acids long. In some embodiments, the linker is 17 amino acids long. In some embodiments, the linker is 18 amino acids long. In some embodiments, the linker is 19 amino acids long. In some embodiments, the linker is 20 amino acids long. In some embodiments, the linker is 21 amino acids long. In some embodiments, the linker is 22 amino acids long. In some embodiments, the linker is 23 amino acids long. In some embodiments, the linker is 24 amino acids long. In some embodiments, the linker is 25 amino acids long. In some embodiments, the linker is 26

amino acids long. In some embodiments, the linker is 27 amino acids long. In some embodiments, the linker is 28 amino acids long. In some embodiments, the linker is 29 amino acids long . In some embodiments, the linker is 30 amino acids long. In some embodiments, the linker is 31 amino acids long. In some embodiments, the linker is 32 amino acids long. In some embodiments, the linker is 33 amino acids long. In some embodiments, the linker is 34 amino acids long. In some embodiments, the linker is 35 amino acids long. In some embodiments, the linker is 36 amino acids long. In some embodiments, the linker is 37 amino acids long. In some embodiments, the linker is 38 amino acids long. In some embodiments, the linker is 39 amino acids long. In some embodiments, the linker is 40 amino acids long. Exemplary linkers that may be used are Gly rich linkers, Gly and Ser containing linkers, Gly and Ala containing linkers, Ala and Ser containing linkers, and other flexible linkers.

In one embodiment, the linker polypeptide comprises an amino acid sequence of SEQ ID NO: 7. In one embodiment, the linker polypeptide comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 7. In one embodiment, the linker polypeptide comprises an amino acid sequence of any one of SEQ ID NOS: 237-268. In one embodiment, the linker polypeptide comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 237-268.

In one embodiment, the scFv comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 8-23, 169-184 and 340-343. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 8, or the sequence of SEQ ID NO:8. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at

least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 9, or the sequence of SEQ ID NO:9. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 10, or the sequence of SEQ ID NO:10. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 11, or the sequence of SEQ ID NO:11. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 12, or the sequence of SEQ ID NO:12. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 13, or the sequence of SEQ ID NO:13. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 14, or the sequence of SEQ ID NO:14. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 15, or the sequence of SEQ ID NO:15. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 16, or the sequence of SEQ ID NO:16. In one embodiment, the scFv

comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 17, or the sequence of SEQ ID NO:17. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 18, or the sequence of SEQ ID NO:18. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 19, or the sequence of SEQ ID NO:19. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 20, or the sequence of SEQ ID NO:20. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 21, or the sequence of SEQ ID NO:21. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 22, or the sequence of SEQ ID NO:22. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 23, or the sequence of SEQ ID NO:23. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity

with SEQ ID NO: 169, or the sequence of SEQ ID NO:169. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 170, or the sequence of SEQ ID NO:170. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 171, or the sequence of SEQ ID NO:171. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 172, or the sequence of SEQ ID NO:172. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 173, or the sequence of SEQ ID NO:173. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 174, or the sequence of SEQ ID NO:174. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 175, or the sequence of SEQ ID NO:175. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 176, or the sequence of SEQ ID NO:176. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at

least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 177, or the sequence of SEQ ID NO:177. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 178, or the sequence of SEQ ID NO:178. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 179, or the sequence of SEQ ID NO:179. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 180, or the sequence of SEQ ID NO:180. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 181, or the sequence of SEQ ID NO:181. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 182, or the sequence of SEQ ID NO:182. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 183, or the sequence of SEQ ID NO:183. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 184, or the sequence of SEQ ID NO:184. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at

least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 340, or the sequence of SEQ ID NO:340. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 341, or the sequence of SEQ ID NO:341. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 342, or the sequence of SEQ ID NO:342. In one embodiment, the scFv comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 343, or the sequence of SEQ ID NO:343.

In one embodiment, the extracellular antigen-binding domain comprises a signal polypeptide. The signal polypeptide may be positioned at the N-terminus of the extracellular antigen binding domain that binds hK2. The signal polypeptide may be optionally cleaved from the extracellular antigen binding domain during cellular processing and localization of the CAR to the cellular membrane. Any of various signal polypeptides known to one of skill in the art may be used as the signal polypeptide. Non-limiting examples of peptides from which the signal polypeptides may be derived include FcεR, human immunoglobulin (IgG) heavy chain (HC) variable region, CD8α, or any of various other proteins secreted by T cells. In various embodiments, the signal polypeptide is compatible with the secretory pathway of a T cell. In some embodiments, the signal polypeptide comprises an amino acid sequence of SEQ ID NO: 24. In one embodiment, the signal polypeptide comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97,at least 98 or at least 99%, sequence identity with SEQ ID NO: 24.

In one aspect, the disclosure provides a CAR, comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and 273-308. Another feature of the CAR having an extracellular antigen-binding domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and 273-308 is that the extracellular antigen-binding domain binds the hK2 antigen.

In one embodiment, the intracellular signaling domain comprises a polypeptide component selected from the group consisting of a TNF receptor superfamily member 9 (CD137) component, a T-cell surface glycoprotein CD3 zeta chain (CD3z) component, a cluster of differentiation (CD27) component, a cluster of differentiation superfamily member (such as, e.g., CD28 or inducible T-cell co-stimulator (ICOS)) component, and a combination thereof.

In one embodiment, the CD137 component comprises an amino acid sequence of SEQ ID NO: 27. In one embodiment, the CD137 component comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 27.

In one embodiment, the CD3z component comprises an amino acid sequence of SEQ ID NO: 28. In one embodiment, the CD3z component comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 28.

In one embodiment, the intracellular signaling domain comprises an amino acid sequence of SEQ ID NO: 45. In one embodiment, the intracellular signaling domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 45.

In one embodiment, the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide. In some embodiments, the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 26. In some embodiments, the CD8a-TM polypeptide comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 26.

In one embodiment, the transmembrane domain comprises at least the transmembrane region(s) of) the α, β or ζ chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD8α, CD9, CD16, CD22, CD33, CD37, CD40, CD64, CD80, CD86, CD134, CD137, CD154. In another embodiment, the transmembrane domain comprises at least the transmembrane domain of ζ, ŋ or FcεR1γ and -β, MB1 (Igα.), B29 or CD3- γ, ζ, or η. In another embodiment, the transmembrane domain is synthetic, e.g., comprising predominantly hydrophobic residues such as leucine and valine, a triplet of phenylalanine, or tryptophan.

In one embodiment, the CAR further comprises a hinge region linking the transmembrane domain to the extracellular antigen-binding domain. In some embodiments, the hinge region is a CD8a-hinge region. In some embodiments, CD8a-hinge region comprises an amino acid sequence of SEQ ID NO: 25. In some embodiments, the CD8a-hinge region comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 25. In some embodiments, the hinge region comprises the sequence EPKSCDKTHTCPPCP (SEQ ID NO: 269), or comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with EPKSCDKTHTCPPCP (SEQ ID NO: 269). In some embodiments, the hinge region comprises the sequence ERKCCVECPPCP (SEQ ID NO: 270), or comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at

least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with ERKCCVECPPCP (SEQ ID NO: 270). In some embodiments, the hinge region comprises the sequence ELKTPLGDTTHTCPRCP(EPKSCDTPPPCPRCP)$_3$ (SEQ ID NO: 271), or comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with ELKTPLGDTTHTCPRCP(EPKSCDTPPPCPRCP)$_3$ (SEQ ID NO: 271),. In some embodiments, the hinge region comprises the sequence ESKYGPPCPSCP (SEQ ID NO: 272), or comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with ESKYGPPCPSCP (SEQ ID NO: 272).

In one embodiment, the CAR comprises an extracellular antigen-binding domain, a hinge region, a transmembrane domain and an intracellular signaling domain. In one such embodiment, the hinge region is a CD8α hinge region, the transmembrane domain is a CD8α-TM domain, and the intracellular signaling domain comprises a CD3-zeta domain and a 4-1BB/CD137 domain.

In one such embodiment, the hinge region is a CD8α hinge region comprising the amino acid sequence of SEQ ID No: 25, the transmembrane domain is a CD8α-TM domain comprising the amino acid sequence of SEQ ID NO: 26, and the intracellular signaling domain comprises a CD3-zeta domain and a 4-1BB/CD137 domain comprising an amino acid sequence of SEQ ID NO: 45.

In another embodiment, the hinge region is a CD8α hinge region comprising the amino acid sequence of SEQ ID No: 25, the transmembrane domain is a CD8α-TM domain comprising the amino acid sequence of SEQ ID NO: 26, and the intracellular signaling domain comprises a 4-1BB/CD137 domain comprising the amino acid sequence of SEQ ID NO 27, and a CD3-zeta domain comprising the amino acid sequence of SEQ ID NO: 28.

In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and

273-308. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 29, or the sequence of SEQ ID NO:29. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 30, or the sequence of SEQ ID NO:30. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 31, or the sequence of SEQ ID NO:31. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 32, or the sequence of SEQ ID NO:32. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 33, or the sequence of SEQ ID NO:33. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 34, or the sequence of SEQ ID NO:34. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 35, or the sequence of SEQ ID NO:35. In one embodiment, the

extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 36, or the sequence of SEQ ID NO:36. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 37, or the sequence of SEQ ID NO:37. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 38, or the sequence of SEQ ID NO:38. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 39, or the sequence of SEQ ID NO:39. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 40, or the sequence of SEQ ID NO:40. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 41, or the sequence of SEQ ID NO:41. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 42, or the sequence of SEQ ID NO:42. In one embodiment, the extracellular antigen-binding domain comprises an amino

acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 43, or the sequence of SEQ ID NO:43. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 44, or the sequence of SEQ ID NO:44. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 78, or the sequence of SEQ ID NO:78. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 79, or the sequence of SEQ ID NO:79. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 80, or the sequence of SEQ ID NO:80. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 81, or the sequence of SEQ ID NO:81. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 221, or the sequence of SEQ ID NO:221. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at

least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 222, or the sequence of SEQ ID NO:222. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 223, or the sequence of SEQ ID NO:223. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 224, or the sequence of SEQ ID NO:224. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 225, or the sequence of SEQ ID NO:225. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 226, or the sequence of SEQ ID NO:226. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 227, or the sequence of SEQ ID NO:227. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 228, or the sequence of SEQ ID NO:228. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at

least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 229, or the sequence of SEQ ID NO:229. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 230, or the sequence of SEQ ID NO:230. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 231, or the sequence of SEQ ID NO:231. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 232, or the sequence of SEQ ID NO:232. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 233, or the sequence of SEQ ID NO:233. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 234, or the sequence of SEQ ID NO:234. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 235, or the sequence of SEQ ID NO:235. In one embodiment, the extracellular antigen-binding domain comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at

least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 236, or the sequence of SEQ ID NO:236.

**CAR constructs and immunoresponsive cells expressing CARs**

The term "encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene, cDNA, or RNA, encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or a RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron(s).

The term "expression vector" refers to a vector comprising a recombinant polynucleotide comprising expression control sequences operatively linked to a nucleotide sequence to be expressed. An expression vector comprises sufficient cis-acting elements for expression; other elements for expression can be supplied by the host cell or in an *in vitro* expression system. Expression vectors include all those known in the art, including cosmids, plasmids (e.g., naked or contained in liposomes) and viruses (e.g., lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses) that incorporate the recombinant polynucleotide.

In one embodiment, the present disclosure provides a cell expressing the nucleic acid molecule encoding for a CAR. In one embodiment, the CAR of the present disclosure comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 46, or the sequence of SEQ ID NO: 46. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 47, or the sequence of SEQ ID NO: 47. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 48, or the sequence of SEQ ID NO: 48. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 49, or the sequence of SEQ ID NO: 49. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 50, or the sequence of SEQ ID NO: 50. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 51, or the sequence of SEQ ID NO: 51. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at

least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 52, or the sequence of SEQ ID NO: 52. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 53, or the sequence of SEQ ID NO: 53. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 54, or the sequence of SEQ ID NO: 54. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 55, or the sequence of SEQ ID NO: 55. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 56, or the sequence of SEQ ID NO: 56. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 57, or the sequence of SEQ ID NO: 57. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 58, or the sequence of SEQ ID NO: 58. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at

least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 59, or the sequence of SEQ ID NO: 59. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 60, or the sequence of SEQ ID NO: 60. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 61, or the sequence of SEQ ID NO: 61. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 82, or the sequence of SEQ ID NO: 82. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 83, or the sequence of SEQ ID NO: 83. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 84, or the sequence of SEQ ID NO: 84. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 85, or the sequence of SEQ ID NO: 85. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 205, or

the sequence of SEQ ID NO: 205. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 206, or the sequence of SEQ ID NO: 206. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 207, or the sequence of SEQ ID NO: 207. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 208, or the sequence of SEQ ID NO: 208. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 209, or the sequence of SEQ ID NO: 209. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 210, or the sequence of SEQ ID NO: 210. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 211, or the sequence of SEQ ID NO: 211. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 212, or the sequence of SEQ ID NO: 212. In some

embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 213, or the sequence of SEQ ID NO: 213. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 214, or the sequence of SEQ ID NO: 214. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 215, or the sequence of SEQ ID NO: 215. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 216, or the sequence of SEQ ID NO: 216. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 217, or the sequence of SEQ ID NO: 217. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 218, or the sequence of SEQ ID NO: 218. In some embodiments, the CAR of the present disclosure comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 219, or the sequence of SEQ ID NO: 219. In some embodiments, the CAR of the present disclosure comprises an

amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 220, or the sequence of SEQ ID NO: 220.

In certain embodiments, the CAR may comprise a signal polypeptide. In certain embodiments the signal peptide is at the N-terminus of the CAR sequence. In certain embodiments the signal peptide is at the C-terminus of the CAR sequence. In certain embodiments, the signal peptide comprises or consists of the amino acid sequence of SEQ ID No: 24.

Herein, the structure of nucleic acid molecules is in places defined in the basis of % sequence identity with a recited reference sequence (with a given SEQ ID NO). In this context, % sequence identity regarding nucleic acid molecules refers to the similarity between at least two different nucleic acid sequences. When a position in both of the two compared sequences is occupied by the same base e.g., if a position in each of two DNA molecules is occupied by adenine, then the molecules are identical at that position, The percent of identity between two sequences is a function of the number of matching or homologous positions shared by the two sequences divided by the number of positions compared and multiplied by 100. For example, if 6 of 10 of the positions in two sequences are matched or homologous then the two sequences are 60% identical (or homologous). By way of example, the DNA sequences ATTGCC and TATGGC share 50% identity (or homology). Generally, a comparison is made when two sequences are aligned to give maximum homology. The respective percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Search Tool (BLAST) described by Altshul et al. ((1990) J. MoI. Biol. 215:403-10); the algorithm of Needleman et al. ((1970) J. MoI. Biol. 48:444-53); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci. 4:11-17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two nucleotide sequences can also be determined using the algorithm of Meyers and Miller ((1989) CABIOS 4:11-17), which has been incorporated into the

ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4. The percent identity is usually calculated by comparing sequences of similar length.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 153-160. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 153-160.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 161-168. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprises a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 161-168.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 195-204. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprises a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 195-204.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 320-325. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprises a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at

least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 320-325.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 326-331. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprises a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 326-331.

In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence of any one of SEQ ID NOS: 336-339. In various embodiments, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprises a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with any one of SEQ ID NOS: 336-339.

In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 153, or the sequence of SEQ ID No:153. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 154, or the sequence of SEQ ID No:154. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or

at least 99%, sequence identity with SEQ ID NOS: 155, or the sequence of SEQ ID No:155. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 156, or the sequence of SEQ ID No:156. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 157, or the sequence of SEQ ID No:157. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 158, or the sequence of SEQ ID No:158. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 159, or the sequence of SEQ ID No:159. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 160, or the sequence of SEQ ID No:160. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 161, or the sequence of SEQ ID No:161. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at

least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 162, or the sequence of SEQ ID No:162. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 163, or the sequence of SEQ ID No:163. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 164, or the sequence of SEQ ID No:164. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 165, or the sequence of SEQ ID No:165. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 166, or the sequence of SEQ ID No:166. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 167, or the sequence of SEQ ID No:167. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 168,

or the sequence of SEQ ID No:168. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 195, or the sequence of SEQ ID No:195. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 196, or the sequence of SEQ ID No:196. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 197, or the sequence of SEQ ID No:197. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 198, or the sequence of SEQ ID No:198. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 199, or the sequence of SEQ ID No:199. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 200, or the sequence of SEQ ID No:200. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at

least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 201, or the sequence of SEQ ID No:201. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 202, or the sequence of SEQ ID No:202. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 203, or the sequence of SEQ ID No:203. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 204, or the sequence of SEQ ID No:204. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 320, or the sequence of SEQ ID No:320. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 321, or the sequence of SEQ ID No:321. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 322, or the sequence of SEQ ID No:322. In an embodiment, the

nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 323, or the sequence of SEQ ID No:323. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 324, or the sequence of SEQ ID No:324. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 325, or the sequence of SEQ ID No:325. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 326, or the sequence of SEQ ID No:326. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 327, or the sequence of SEQ ID No:327. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 328, or the sequence of SEQ ID No:328. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at

least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 329, or the sequence of SEQ ID No:329. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 330, or the sequence of SEQ ID No:330. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 331, or the sequence of SEQ ID No:331. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 336, or the sequence of SEQ ID No:336. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 337, or the sequence of SEQ ID No:337. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 338, or the sequence of SEQ ID No:338. In an embodiment, the nucleic acid molecule encoding for a CAR comprises a nucleic acid sequence comprising a sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NOS: 339, or the sequence of SEQ ID No:339.

In one aspect, the present disclosure provides isolated immunoresponsive cells comprising the CARs described herein. In some embodiments, the isolated immunoresponsive cell is transduced with the CAR, for example, the CAR is constitutively expressed on the surface of the immunoresponsive cell. In certain embodiments, the isolated immunoresponsive cell is further transduced with at least one co-stimulatory ligand such that the immunoresponsive cell expresses the at least one co-stimulatory ligand. In certain embodiments, the at least one co-stimulatory ligand is selected from the group consisting of 4-1BBL, CD48, CD70, CD80, CD86, OX40L, TNFRSF14, and combinations thereof. In certain embodiments, the isolated immunoresponsive cell is further transduced with at least one cytokine such that the immunoresponsive cell secretes the at least one cytokine. In certain embodiments, the at least cytokine is selected from the group consisting of IL-2, IL-3, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, IL-21, and combinations thereof. In some embodiments, the isolated immunoresponsive cell is selected from the group consisting of a T lymphocyte (T cell), a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a lymphoid progenitor cell, a T cell-precursor cell, and a pluripotent stem cell from which lymphoid cells may be differentiated.

In one embodiment, the CAR T cells of the disclosure can be generated by introducing a lentiviral vector comprising a desired CAR, for example, a CAR comprising anti-hK2, CD8α hinge and transmembrane domain, and human 4-1BB and CD3-zeta signaling domains, into the cells. The CAR T cells of the invention are able to replicate *in vivo* resulting in long-term persistence that can lead to sustained tumor control.

Embodiments of the invention further provide host cells comprising any of the recombinant expression vectors described herein. As used herein, the term "host cell" refers to any type of cell that can contain the recombinant expression vector. The host cell can be a eukaryotic cell, e.g., plant, animal, or algae, fungi, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5α *E.coli* cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells,

HEK293 cells, and the like. For purposes of amplifying or replicating the recombinant expression vector, the host cell may be a prokaryotic cell, e.g., a DH5α cell. For purposes of producing a recombinant CAR, polypeptide, or protein, the host cell may be a mammalian cell. The host cell may be a human cell. While the host cell can be of any cell type, can originate from any type of tissue, and can be of any developmental stage, the host cell may be a peripheral blood lymphocyte (PBL). The host cell may be a T cell.

For purposes herein, the T cell can be any T cell, such as a cultured T cell, e.g., a primary T cell, or a T cell from a cultured T cell line, e.g., Jurkat, SupT1, etc., or a T cell obtained from a mammal. If obtained from a mammal, the T cell can be obtained from numerous sources, including but not limited to bone marrow, blood, lymph node, the thymus, or other tissues or fluids. T cells can also be enriched for or purified. The T cell may be a human T cell. The T cell may be a T cell isolated from a human. The T cell can be any type of T cell and can be of any developmental stage, including but not limited to, $CD4^+/CD8^+$ double positive T cells, $CD8^+$ T cells (e.g., cytotoxic T cells), $CD4^+$ helper T cells, e.g., $Th_1$ and $Th_2$ cells, peripheral blood mononuclear cells (PBMCs), peripheral blood leukocytes (PBLs), tumor infiltrating cells, memory T cells, naïve T cells, and the like. The T cell may be a $CD8^+$ T cell or a $CD4^+$ T cell.

Also provided are a population of cells comprising at least one host cell described herein. The population of cells can be a heterogeneous population comprising the host cell comprising any of the recombinant expression vectors described, in addition to at least one other cell, e.g., a host cell (e.g., a T cell), which does not comprise any of the recombinant expression vectors, or a cell other than a T cell, e.g., a B cell, a macrophage, an erythrocyte, a neutrophil, a hepatocyte, an endothelial cell, an epithelial cell, a muscle cell, a brain cell, etc. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly host cells (e.g., consisting essentially of) comprising the recombinant expression vector. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising a recombinant expression vector, such that all cells of the population comprise the recombinant expression vector. In one embodiment, the population of cells is

a clonal population comprising host cells comprising a recombinant expression vector as described herein.

**Pharmaceutical Compositions/Administration**

In embodiments of the present disclosure, the CAR-expressing cells may be provided in compositions, e.g., suitable pharmaceutical composition(s) comprising the CAR-expressing cells and a pharmaceutically acceptable carrier. In one aspect, the present disclosure provides pharmaceutical compositions comprising an effective amount of a lymphocyte expressing one or more of the CARs described and a pharmaceutically acceptable excipient. Pharmaceutical compositions of the present disclosure may comprise a CAR-expressing cell, e.g., a plurality of CAR-expressing cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, excipients or diluents. As used herein, the term "**in combination with**" means that two or more therapeutic agents are be administered to a subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

A pharmaceutically acceptable carrier can be an ingredient in a pharmaceutical composition, other than an active ingredient, which is nontoxic to the subject.

A pharmaceutically acceptable carrier can include, but is not limited to, a buffer, excipient, stabilizer, or preservative. Examples of pharmaceutically acceptable carriers are solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible, such as salts, buffers, antioxidants, saccharides, aqueous or non-aqueous carriers, preservatives, wetting agents, surfactants or emulsifying agents, or combinations thereof. The amounts of pharmaceutically acceptable carrier(s) in the pharmaceutical compositions may be determined experimentally based on the activities of the carrier(s) and the desired characteristics of the formulation, such as stability and/or minimal oxidation.

Such compositions may comprise buffers such as acetic acid, citric acid, formic acid, succinic acid, phosphoric acid, carbonic acid, malic acid, aspartic acid, histidine, boric acid, Tris buffers, HEPPSO, HEPES, neutral buffered saline, phosphate buffered saline

and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); antibacterial and antifungal agents; and preservatives.

Compositions of the present disclosure can be formulated for a variety of means of parenteral or non-parenteral administration. In one embodiment, the compositions can be formulated for infusion or intravenous administration. Compositions disclosed herein can be provided, for example, as sterile liquid preparations, e.g., isotonic aqueous solutions, emulsions, suspensions, dispersions, or viscous compositions, which may be buffered to a desirable pH. Formulations suitable for oral administration can include liquid solutions, capsules, sachets, tablets, lozenges, and troches, powders liquid suspensions in an appropriate liquid and emulsions.

The term "pharmaceutically acceptable," as used herein with regard to pharmaceutical compositions, means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals and/or in humans.

In one aspect, the disclosure relates to administering a genetically modified T cell expressing a CAR for the treatment of a subject having cancer or at risk of having cancer using lymphocyte infusion. In at least one embodiment, autologous lymphocyte infusion is used in the treatment. Autologous PBMCs are collected from a subject in need of treatment and T cells are activated and expanded using the methods described herein and known in the art and then infused back into the subject.

In one aspect, the disclosure relates generally to the treatment of a subject at risk of developing cancer. The invention also includes treating a malignancy or an autoimmune disease in which chemotherapy and/or immunotherapy in a subject results in significant immunosuppression, thereby increasing the risk of the subject developing cancer. In one aspect, the present disclosure provides methods of preventing cancer, the methods comprising administering an amount of a lymphocyte expressing one or more of the CARs described to a subject in need thereof.

In one aspect, the present disclosure provides methods of treating a subject having cancer, the methods comprising administering a therapeutically effective amount of a lymphocyte expressing one or more of the CARs described to a subject in need thereof, whereby the lymphocyte induces or modulates killing of cancer cells in the subject.

In another aspect, the present disclosure provides methods of reducing tumor burden in a subject having cancer, the methods comprising administering a therapeutically effective amount of a lymphocyte expressing one or more of the CARs described herein to a subject in need thereof, whereby the lymphocyte induces killing of cancer cells in the subject. In another aspect, the present disclosure provides methods of increasing survival of a subject having cancer, the methods comprising administering a therapeutically effective amount of a lymphocyte expressing one or more of the CARs described to a subject in need thereof, whereby the survival of the subject is lengthened. Generally, the lymphocytes expressing the CAR(s) induce killing of cancer cells in the subject and result in reduction or eradication of the tumors/cancer cells in the subject. A non-limiting list of cancers, inclusive of metastatic lesions, that can be targeted, includes prostate cancer and prostate-derived cancer. In one embodiment, the cancer being treated in a subject is prostate cancer. In some embodiments, the cancer is an androgen receptor (AR) expressing breast cancer.

In one aspect, the methods described herein are applicable to treatment of noncancerous conditions that are at risk of developing into a cancerous condition, such as, e.g., enlarged prostate, benign prostate hyperplasia (BPH), and high PSA levels in absence of diagnosed prostate cancer.

In one aspect, methods of treating a subject having cancer are provided that comprise administering a therapeutically effective amount of a lymphocyte expressing a CAR, the CAR having an extracellular antigen-binding domain that binds the hK2 antigen, to a subject in need thereof, whereby the lymphocyte induces killing of cancer cells in the subject. In some embodiments, the at least one of the CARs comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at

least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 46, or the sequence of SEQ ID NO: 46. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 47, or the sequence of SEQ ID NO: 47. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 48, or the sequence of SEQ ID NO: 48. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 49, or the sequence of SEQ ID NO: 49. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 50, or the sequence of SEQ ID NO: 50. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 51, or the sequence of SEQ ID NO: 51. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 52, or the sequence of SEQ ID NO: 52. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 53, or the sequence of SEQ ID NO: 53. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at

least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 54, or the sequence of SEQ ID NO: 54. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 55, or the sequence of SEQ ID NO: 55. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 56, or the sequence of SEQ ID NO: 56. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 57, or the sequence of SEQ ID NO: 57. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 58, or the sequence of SEQ ID NO: 58. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 59, or the sequence of SEQ ID NO: 59. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 60, or the sequence of SEQ ID NO: 60. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 61, or the sequence of SEQ ID NO: 61.

In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 82, or the sequence of SEQ ID NO: 82. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 83, or the sequence of SEQ ID NO: 83. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 84, or the sequence of SEQ ID NO: 84. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 85, or the sequence of SEQ ID NO: 85. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 205, or the sequence of SEQ ID NO: 205. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 206, or the sequence of SEQ ID NO: 206. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 207, or the sequence of SEQ ID NO: 207. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at

least 98 or at least 99%, sequence identity with SEQ ID NO: 208, or the sequence of SEQ ID NO: 208. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 209, or the sequence of SEQ ID NO: 209. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 210, or the sequence of SEQ ID NO: 210. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 211, or the sequence of SEQ ID NO: 211. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 212, or the sequence of SEQ ID NO: 212. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 213, or the sequence of SEQ ID NO: 213. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 214, or the sequence of SEQ ID NO: 214. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 215, or the sequence of SEQ ID NO: 215. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at

least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 216, or the sequence of SEQ ID NO: 216. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 217, or the sequence of SEQ ID NO: 217. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 218, or the sequence of SEQ ID NO: 218. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 219, or the sequence of SEQ ID NO: 219. In some embodiments, the CAR comprises an amino acid sequence having at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98 or at least 99%, sequence identity with SEQ ID NO: 220, or the sequence of SEQ ID NO: 220.

In one aspect, a method of targeted killing of a cancer cell is disclosed, the method comprising contacting the cancer cell with a lymphocyte expressing one or more of the CARs described, whereby the lymphocyte induces killing of the cancer cell. A non-limiting list of cancer cells, inclusive of metastatic cancer cells, that can be targeted include prostate cancer, and combinations thereof. In one embodiment, the cancer cell is a prostate cancer cell.

Pharmaceutical compositions of the present disclosure may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the subject, and the type and severity of the subject's disease, although appropriate dosages may be determined by clinical trials.

The terms "treat" or "treatment" refer to therapeutic treatment wherein the object is to slow down (lessen) an undesired physiological change or disease, or provide a beneficial or desired clinical outcome during treatment. Beneficial or desired clinical outcomes include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and/or remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if a subject was not receiving treatment. Those in need of treatment include those subjects already with the undesired physiological change or disease as well as those subjects prone to have the physiological change or disease.

"Prevent," "preventing," "prevention," or "prophylaxis" of a disease or disorder means preventing that a disorder occurs in a subject.A "therapeutically effective amount" or "effective amount", used interchangeably herein, refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Example indicators of an effective therapeutic or combination of therapeutics that include, for example, improved wellbeing of the patient, reduction of a tumor burden, arrested or slowed growth of a tumor, and/or absence of metastasis of cancer cells to other locations in the body.

As used herein, the term "subject" refers to an animal. The terms "subject" and "patient" may be used interchangeably herein in reference to a subject. As such, a "subject" includes a human that is being treated for a disease, or prevention of a disease, as a patient. The methods described herein may be used to treat an animal subject belonging to any classification. Examples of such animals include mammals. Mammals, include, but are not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. The mammals may be from the order Carnivora, including Felines (cats) and Canines (dogs). The mammals may be from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). The mammals may be of the order Primates, Ceboids, or

Simoids (monkeys) or of the order Anthropoids (humans and apes). In one embodiment, the mammal is a human.

When a therapeutically effective amount is indicated, the precise amount of the compositions of the present disclosure to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the subject. It can generally be stated that a pharmaceutical composition comprising the T cells described herein may be administered at a dosage of about $10^4$ to about $10^{10}$ cells/kg body weight, in some instances about $10^5$ to about $10^6$ cells/kg body weight, including all integer values within those ranges. In some embodiments, a pharmaceutical composition comprising the T cells described herein may be administered at a dosage of about $10^6$ cells/kg body weight. T cell compositions may also be administered multiple times at these dosages. The cells can be administered by using infusion techniques that are commonly known in immunotherapy (see, e.g., Rosenberg et al., *New Eng. J. of Med.* 319:1676, 1988).

Delivery systems useful in the context of embodiments of the invention may include time-released, delayed release, and sustained release delivery systems such that the delivery of the T cell compositions occurs prior to, and with sufficient time to cause, sensitization of the site to be treated. The composition can be used in conjunction with other therapeutic agents or therapies. Such systems can avoid repeated administrations of the composition, thereby increasing convenience to the subject and the physician, and may be particularly suitable for certain composition embodiments of the invention.

Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polyesteramides, polyorthoesters, polycaprolactones, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are lipids including sterols such as cholesterol, cholesterol esters, and fatty acids or neutral fats such as mono-di- and tri-glycerides; sylastic systems; peptide based systems; hydrogel release systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not

limited to: (a) erosional systems in which the active composition is contained in a form within a matrix such as those described in U.S. Patent Nos. 4,452,775; 4,667,014; 4,748,034; and 5,239,660 and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Patent Nos. 3,854,480 and 3,832,253. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

In certain aspects, it may be desirable to administer activated T cells to a subject and then subsequently redraw blood (or have an apheresis performed), activate the T cells according to the present disclosure, and reinfuse the subject with these activated and expanded T cells. This process can be carried out multiple times every few weeks. In certain aspects, T cells can be activated from blood draws of from 10 cc to 400 cc. In certain aspects, T cells are activated from blood draws of 20 cc, 30 cc, 40 cc, 50 cc, 60 cc, 70 cc, 80 cc, 90 cc, or 100 cc.

The administration of the CAR-T cells and compositions may be carried out in any manner, e.g., by parenteral or nonparenteral administration, including by aerosol inhalation, injection, infusions, ingestion, transfusion, implantation or transplantation. For example, the CAR-T cells and compositions described herein may be administered to a patient trans-arterially, intradermally, subcutaneously, intratumorally, intramedullary, intranodally, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In one aspect, the compositions of the present disclosure are administered by i.v. injection. In one aspect, the compositions of the present disclosure are administered to a subject by intradermal or subcutaneous injection. The compositions of T cells may be injected, for instance, directly into a tumor, lymph node, tissue, organ, or site of infection.

Administration can be autologous or non-autologous. For example, immunoresponsive cells expressing a human Kallikrein-2 (e.g., hK2)-specific CAR can be obtained from one subject, and administered to the same subject or a different, compatible subject. Peripheral blood derived T cells of the present disclosure, or expanded T cells (e.g., *in vivo, ex vivo* or *in vitro* derived) can be administered via, e.g., intravenous injection, localized injection, systemic injection, catheter administration, or parenteral administration.

In particular embodiments, subjects may undergo leukapheresis, wherein leukocytes are collected, enriched, or depleted *ex vivo* to select and/or isolate the cells of interest, e.g., T cells. These T cell isolates may be expanded by methods known in the art and treated such that one or more CAR constructs of the present disclosure may be introduced, thereby creating a CAR-T cell. Subjects in need thereof may subsequently undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain aspects, following or concurrent with the transplant, subjects receive an infusion of the expanded CAR-T cells. In one aspect, expanded cells are administered before or following surgery.

The dosage administered to a patient having a malignancy is sufficient to alleviate or at least partially arrest the disease being treated ("therapeutically effective amount"). The dosage of the above treatments to be administered to a subject will vary with the precise nature of the condition being treated and the recipient of the treatment. The scaling of dosages for human administration can be performed according to practices generally accepted in the art.

The CAR T cells of the invention can undergo *in vivo* T cell expansion and can establish hK2-specific memory cells that persist at high levels for an extended amount of time in blood and bone marrow. In some instances, the CAR T cells of the invention infused into a subject can eliminate cancer cells, e.g., prostate cancer cells or AR-expressing breast cancer, *in vivo* in subjects with advanced chemotherapy-resistant cancer.

In one embodiment, a CAR of the present disclosure is introduced into T cells, e.g., using *in vitro* transcription, and the subject (e.g., human) receives an initial administration of CAR-T cells of the disclosure, and one or more subsequent administrations of the CAR-T cells, wherein the one or more subsequent administrations are administered less than 15 days, e.g., 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 days after the previous administration. In one embodiment, more than one administration of the CAR-T cells are administered to the subject (e.g., human) per week, e.g., 2, 3, or 4 administrations of the CAR-T cells are administered per week. In one embodiment, the subject receives more than one administration of the CAR-T cells per week (e.g., 2, 3 or 4 administrations per week) (also referred to herein as a cycle), followed by a week of no CAR-T cell administrations,

and then one or more additional administration of the CAR-T cells (e.g., more than one administration of the CAR-T cells per week) is administered to the subject. In another embodiment, the subject receives more than one cycle of CAR-T cells, and the time between each cycle is less than 10, 9, 8, 7, 6, 5, 4, or 3 days. In one embodiment, the CAR-T cells are administered every other day for 3 administrations per week. In one embodiment, the CAR-T cells are administered for at least two, three, four, five, six, seven, eight or more weeks.

In one embodiment, administration may be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration may be at the same dose or at a different dose.

The CAR-T cells may be administered in the methods of the invention by maintenance therapy, such as, e.g., once a week for a period of 6 months or more.

In one embodiment, CAR-T cells are generated using lentiviral viral vectors, such as lentivirus. CAR-T cells generated with such viral vectors will generally have stable CAR expression.

In one embodiment, CAR-T cells transiently express CAR vectors for 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 days after transduction. Transient expression of CARs can be affected by RNA CAR vector delivery. In one embodiment, the CAR RNA is transduced into the T cell by electroporation.

If a patient is at high risk of generating an anti-CAR antibody response during the course of transient CAR therapy (such as those generated by RNA transductions), CAR-T infusion breaks should not last more than ten to fourteen days.

A CAR-expressing cell described herein may be used in combination with other known agents and therapies. Administered “in combination”, as used herein, means that two (or more) different treatments are delivered to the subject during the course of the subject's treatment e.g., the two or more treatments are delivered after the subject has been diagnosed with the cancer and before the cancer has been cured or eliminated or treatment

has ceased for other reasons. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second begins, so that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery". In other embodiments, the delivery of one treatment ends before the delivery of the other treatment begins. In some embodiments of either case, the treatment is more effective because of combined administration. For example, the second treatment is more effective, e.g., an equivalent effect is seen with less of the second treatment, or the second treatment reduces symptoms to a greater extent, than would be seen if the second treatment were administered in the absence of the first treatment, or the analogous situation is seen with the first treatment. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one treatment delivered in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive. The delivery can be such that an effect of the first treatment delivered is still detectable when the second is delivered.

In one embodiment, other therapeutic agents such as factors may be administered before, after, or at the same time (simultaneous with) as the CAR-T cells, including, but not limited to, interleukins, as well as colony stimulating factors, such as G-, M- and GM-CSF, and interferons.

The CAR-expressing cell described herein and the at least one additional therapeutic agent can be administered simultaneously, in the same or in separate compositions, or sequentially. For sequential administration, the CAR-expressing cell described herein can be administered first, and the additional agent can be administered second, or the order of administration can be reversed.

In further embodiments, the CAR-expressing cells described herein may be used in a treatment regimen in combination with surgery, radiation, chemotherapy, immunosuppressive agents, antibodies, or other immunoablative agents. In another embodiment, the CAR-expressing cell described herein can be used in combination with an anti-androgen treatment. In one embodiment, the subject can be administered an agent

which enhances the activity of a CAR-expressing cell. For example, in one embodiment, the agent can be an agent which inhibits an inhibitory molecule.

A description of example embodiments follows.

1. A chimeric antigen receptor (CAR) comprising:

(a) an extracellular domain comprising an scFv that specifically binds to the human Kallikrein-2 (hK2) antigen,

(b) a transmembrane domain, and

(c) an intracellular signaling domain optionally comprising at least one co-stimulatory domain.

2. The CAR of embodiment 1, further comprising

(d) a CD8a-hinge region,

wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide; and

wherein the intracellular signaling domain comprises a co-stimulatory domain comprising a TNF receptor superfamily member 9 (CD137) component and a primary signaling domain comprising a T-cell surface glycoprotein CD3 zeta chain (CD3z) component.

3. The CAR of embodiment 2, wherein

(b) the CD8a-hinge region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25, 269, 270, 271, or 272;

(c) the transmembrane domain comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 26; and/or

(d) the intracellular signaling domain comprises a co-stimulatory domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 27, and a primary signaling domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 28.

4. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 92, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 93, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 94

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid

sequence of SEQ ID NO: 103, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 119, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122;

wherein the extracellular antigen-binding domain binds the hK2 antigen.

5. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139,

wherein the extracellular antigen-binding domain binds the hK2 antigen.

6. The CAR according to embodiment 4, wherein the extracellular antigen-binding domain further comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

7. The CAR according to embodiment 6, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

8. The CAR according to embodiment 6, wherein the extracellular antigen-binding domain comprises: a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

9. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain variable domain (VL) comprising an amino acid sequence selected from SEQ ID NOS: 1, 2, 3, 74, 75, 147, 148, 149, 150, 151, 152 and 318; and/or

a heavy chain variable domain (VH) comprising an amino acid sequence selected from SEQ ID NOS: 4, 5, 6, 76, 77, 140, 141, 142, 143, 144, 145, 146 and 317;

wherein the extracellular antigen-binding domain binds the human Kallikrein-2 (hK2) antigen.

10. The CAR of embodiment 9, wherein the extracellular antigen-binding domain comprises:

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5; or

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

11. The CAR of any of embodiments 1-10, wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv).

12. The CAR of embodiment 11, wherein the scFv comprises a linker polypeptide between the light chain variable region (VL) and the heavy chain variable region (VH).

13. The CAR of embodiment 12, wherein the linker polypeptide comprises an amino acid sequence of SEQ ID NO: 7.

14. The CAR of any of embodiments 11-12, wherein the scFv comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 8-23, 169-184 and 340-343.

15. The CAR of any of embodiments 1-14, wherein the extracellular antigen-binding domain comprises a signal polypeptide.

16. The CAR of embodiment 15, wherein the signal polypeptide comprises an amino acid sequence of SEQ ID NO: 24.

17. The CAR of any of embodiments 4-16, wherein the intracellular signaling domain comprises a polypeptide component selected from the group consisting of a TNF receptor superfamily member 9 (CD137) component, a T-cell surface glycoprotein CD3 zeta chain (CD3z) component, a cluster of differentiation (CD27) component, a cluster of differentiation superfamily member component, and a combination thereof.

18. The CAR of embodiment 17, wherein the CD137 component comprises an amino acid sequence of SEQ ID NO: 27.

19. The CAR of embodiment 17 or embodiment 18, wherein the CD3z component comprises an amino acid sequence of SEQ ID NO: 28.

20. The CAR of any one of embodiments 17-19, wherein the intracellular signaling domain comprises an amino acid sequence of SEQ ID NO: 45.

21. The CAR of any of embodiments 2-20, wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide.

22. The CAR of embodiment 21, wherein the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 26.

23. The CAR of any of embodiments 4-22, further comprising a hinge region linking the transmembrane domain to the extracellular antigen-binding domain.

24. The CAR of embodiment 23, wherein the hinge region is a CD8a-hinge region.

25. The CAR of embodiment 24, wherein the CD8a-hinge region comprises an amino acid sequence of SEQ ID NO: 25, 279, 280, 281, or 282.

26. The CAR of any of embodiments 1-25, wherein the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and 273-308.

27. The CAR of any of embodiments 1-26, wherein the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220.

28. An isolated lymphocyte expressing the CAR of any of claims 1-27.

29. The isolated lymphocyte of embodiment 28, wherein the lymphocyte is a T lymphocyte.

30. The isolated lymphocyte of embodiment 28, wherein the lymphocyte is a natural killer (NK) cell.

31. An isolated nucleic acid molecule encoding the CAR of any of embodiments 1-30.

32. A vector comprising the nucleic acid molecule of embodiment 31.

33. A cell expressing the nucleic acid molecule of embodiment 31.

34. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of embodiments 28-30.

35. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of embodiments 28-30 and a pharmaceutically acceptable excipient.

36. The CAR of any of embodiments 1-27 or the pharmaceutical composition of embodiments 34 or 35 for use in therapy.

37. The CAR of any of embodiments 1-27 or the pharmaceutical composition of embodiments 34 or 35 for use in a method of treating a subject having cancer.

38. A method of treating a subject having cancer, the method comprising: administering a therapeutically effective amount of the lymphocyte of any of embodiments 28-30 to a subject in need thereof, whereby the lymphocyte induces killing of cancer cells in the subject.

39. The method of embodiment 38, or the CAR or the pharmaceutical composition for use in a method of embodiment 37, wherein the cancer is prostate cancer or androgen receptor-expressing breast cancer.

40. The method of embodiment 38, or the CAR or the pharmaceutical composition for use in a method of embodiment 37, wherein the cancer is prostate cancer.

41. The method of embodiment 38, or the CAR or the pharmaceutical composition for use in a method of embodiment 37, wherein the cancer is androgen receptor-expressing breast cancer.

42. A method of targeted killing of a cancer cell, the method comprising:
contacting the cancer cell with the lymphocyte of any of embodiments 28-30,whereby the lymphocyte induces killing of the cancer cell.

43. The method of embodiment 42, wherein the cancer cell is a prostate cancer cell or androgen receptor-expressing breast cancer cell.

44. A method of detecting the presence of cancer in a subject, comprising:
(c) contacting a cell sample obtained from the subject with the CAR of any one of embodiments 1-27, thereby forming a CAR-cell complex, and
(d) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.
Preferably the embodiment is performed *in vitro*.

45. The CAR of embodiment 1, wherein the transmembrane domain comprises a CD8a-TM polypeptide comprising an amino acid sequence of SEQ ID NO: 26.

46. The CAR of embodiment 2, wherein the transmembrane domain comprises a CD8a-TM polypeptide comprising an amino acid sequence of SEQ ID NO: 26.

47. The CAR of embodiment 2 or 46, wherein the wherein the CD8a hinge region comprises an amino acid sequence of SEQ ID NO: 25.

48. The CAR of embodiment 2 or 47, wherein the CD137 component comprises an amino acid sequence of SEQ ID NO: 27.

49. The CAR of embodiment 2, 47 or 48, wherein the CD3z component comprises an amino acid sequence of SEQ ID NO: 28.

50. The CAR of embodiment 3, wherein

(b) the CD8a-hinge region comprises an amino acid sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 % identical to SEQ ID NO: 25, 269, 270, 271, or 272, preferably wherein the CD8a-hinge region comprises an amino acid sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 % identical to SEQ ID NO: 25;

(c) the transmembrane domain comprises an amino acid sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 26; and/or

(d) the intracellular signaling domain comprises a co-stimulatory domain having an amino acid sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 27, and a primary signaling domain having an amino acid sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 28.

51. The CAR of embodiment 3, wherein the CD8a hinge region comprises an amino acid sequence of SEQ ID NO: 25.

52. The CAR of embodiment 3, wherein the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 26.

53. The CAR of embodiment 3, wherein the CD137 component comprises an amino acid sequence of SEQ ID NO: 27.

54. The CAR of embodiment 3,, wherein the CD3z component comprises an amino acid sequence of SEQ ID NO: 28.

55. The CAR of embodiment 3, wherein

(b) the CD8a-hinge region comprises the amino acid sequence of SEQ ID NO: 25;

(c) the transmembrane domain comprises the amino acid sequence of SEQ ID NO: 26; and

(d) the intracellular signaling domain comprises a co-stimulatory domain comprising an amino acid sequence of SEQ ID NO: 27, and a primary signaling domain comprising an amino acid sequence of SEQ ID NO: 28.

56. The CAR of embodiments 45-55, wherein the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and 273-308.

57. The CAR of any of embodiments 45-55, wherein the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220.

58. An isolated lymphocyte expressing the CAR of any of claims 45-55.

59. The isolated lymphocyte of embodiment 58, wherein the lymphocyte is a T lymphocyte.

60. The isolated lymphocyte of embodiment 58, wherein the lymphocyte is a natural killer (NK) cell.

61. An isolated nucleic acid molecule encoding the CAR of any of embodiments 45-55.

62. A vector comprising the nucleic acid molecule of embodiment 61.

63. A cell expressing the nucleic acid molecule of embodiment 61.

64. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of embodiments 58-60.

65. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of embodiments 58-60 and a pharmaceutically acceptable excipient.

66. The CAR of any of embodiments 45-55 or the pharmaceutical composition of embodiments 64 or 65 for use in therapy.

67. The CAR of any of embodiments 45-55 or the pharmaceutical composition of embodiments 64 or 65 for use in a method of treating a subject having cancer.

68. A method of treating a subject having cancer, the method comprising: administering a therapeutically effective amount of the lymphocyte of any of embodiments 58-60 to a subject in need thereof, whereby the lymphocyte induces killing of cancer cells in the subject.

69. The method of embodiment 68, or the CAR or the pharmaceutical composition for use in a method of embodiment 67, wherein the cancer is prostate cancer or androgen receptor-expressing breast cancer.

70. The method of embodiment 68, or the CAR or the pharmaceutical composition for use in a method of embodiment 67, wherein the cancer is prostate cancer.

71. The method of embodiment 68, or the CAR or the pharmaceutical composition for use in a method of embodiment 67, wherein the cancer is androgen receptor-expressing breast cancer.

72. A method of targeted killing of a cancer cell, the method comprising:
contacting the cancer cell with the lymphocyte of any of embodiments 58-60, whereby the lymphocyte induces killing of the cancer cell.

73. The method of embodiment 72, wherein the cancer cell is a prostate cancer cell or androgen receptor-expressing breast cancer cell.

74. A method of detecting the presence of cancer in a subject, comprising:
(a) contacting a cell sample obtained from the subject with the CAR of any one of embodiments 45-55, thereby forming a CAR-cell complex, and
(b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.
Preferably the embodiment is performed *in vitro*.

EXAMPLES

The following examples are provided to further describe some of the embodiments disclosed herein. The examples are intended to illustrate, not to limit, the disclosed embodiments.

**Example 1: Construction and expression of hK2 scFv CARs with 11B6 scFv**

hK2 CAR constructs comprising an scFv derived from the hK2-targeting antibody 11B6 were constructed as illustrated in **Figure 1A**. Dynabeads Human T-Expander CD3/CD28 stimulated T cells were subjected to electroporation, then washed three times with OPTI-MEM (Invitrogen), and resuspended in OPTI-MEM at the final concentration of 50E6/ml. Subsequently, 0.1 ml of the cells (5E6) was mixed with 10ug of IVT CAR encoding RNA and electroporated in a 2-mm Gap cuvette (Harvard Apparatus BTX, Holliston, MA, USA)

using BTX ECM830 (Harvard Apparatus BTX, Holliston, MA, USA) by pressing the "pulse" button one time. (Settings: 500 Volts, 750 μsec Pulse Length and single(1) pulse, 100mSec interval.) Post electroporation, the T cells were transferred to a 6-well plate and immediately put back into a 37°C incubator. Primary human T cells were electroporated with no mRNA (MOCK) or 10μg of mRNA expressing either an hK2 scFv CAR or irrelevant control CAR. 24 hours post-electroporation CAR surface expression was measured by flow cytometry following staining with 2 μg/ml biotinylated L-protein and streptavidin-conjugated PE (**Figure 1B**) or biotinylated hK2 (1 μg/ml) and streptavidin-conjugated PE (**Figure 1C**).

Twenty-four hours post electroporation, the T cells were counted. 1E5 T cells were collected for each. The cells were washed with FACS buffer twice using 200 μL/well of FACS buffer for microtiter plates, with the supernatant discarded. All wells were stained with 100μl staining buffer containing Protein L (Genscript, Cat. No. M000971:500;2ug/ml), incubated for at least 30 minutes at 4°C while being protected from light. The cells were washed by adding FACS Buffer twice, using 150 μL/well for microtiter plates with FACS buffer. Centrifugation at 400x g was performed for 4 minutes at room temperature. The supernatant was then discarded. All wells were stained with 100μl Streptavidin-R-Phycoerythrin (SA-PE;1:250) and Live/dead Fixable Near-IR Dead Cell Stain dye (1:1000), incubated for at least 30 minutes at 4°C while being protected from light. The cells were then ready for flow cytometry analysis.

As shown in **Figure 1B**, protein L staining was observed on both HK2 HL & LH CARs (41.4% and 66.3%, respectively), whereas only the background staining (~5.5%) was seen in the control T cells that were T cells without mRNA electroporation. As shown in **Figure 1C**, CAR expression on primary human T cells also could be detected via J&J internal biotin-labeled recombinant HK2 protein (Biotin-Hk2 protein,Lot:20180810, CBIS ID:KL2W12.CB.003, 2.4mg/ml, 1mM Benzamidine) followed by SA-PE. As shown, T cells can efficiently express HK2 LH CAR (82.7%) as measured by flow cytometry, whereas only the background staining(~1.73% or 1.19%) was seen in the control T cells that were T cells without mRNA electroporation or undisclosed control CAR (non-HK2 specific). Results are shown for representative donor T cells and were reproducible in

multiple donors (at least n = 3). +Biotin label (EZ-Link™ Sulfo-NHS-LC-Biotin, Thermo Fisher Scientific cat#:21327)

**Example 2: Tumor cell killing by hK2 CAR-T cells**

Co-culture for CellTrace Violet (CTV, Thermo Fisher Scientific Catalog number: C34557) based cytotoxicity assay using flow cytometer was performed as follows.

T cells were prepared as follows. Twenty-four hours post EP, T cells were counted and resuspended at the concentration needed for the most concentrated/desired E:T. The T cells were added at 100 µl/well of assay ($2x10^6$ cells/ml; plated 100 µl in a 10:1 E:T ratio, i.e., 2E5 T cells per 2E4 target cells). A stock of the 10:1 E:T concentration was made, with two-fold serial dilutions made with complete T cell media (Optimizer w/CTS, 5% Human Serum, 1% GlutaMax) to 0.3125:1. The T cells were plated (100µl/well) in triplicate using a 96 well round bottom tissue culture treated plate.

CTV labeled target cells were prepared as follows. 20 µL DMSO was added to a vial of CTV staining solution. This stock solution was diluted into 20 mL of PBS (warmed to 37°C) for a 5 µM staining solution. 10E6 tumor cells were collected, washed with PBS twice and resuspended in 4E6/ml (2.5ml). An equal volume (2.5ml) of CTV staining solution was added. The cells were incubated for 20 minutes in a 37°C incubator. 40 ml PRMI+20% FBS was added to the cells to absorb any unbound dye. The cells were incubated for 5 minutes. The cells were centrifuged for 5 minutes at 400 x g. The cell pellet was resuspended in pre-warmed RPMI+10%FBS medium. In the meantime, T cells were seeded at the desired E/T ratio described above. The tumor cell lines Vcap (HK2+) and DU145(HK2-) were recounted, and then the cells were resuspended in 2E5/ml and 100µl in duplicate. The cells were co-incubated with labelled tumor cell lines in a flat-bottom 96-well plate.

A cytotoxicity assay was performed as follows using a flow cytometer. After 20 hours of co-culture, all of the cells were transferred to a U-bottom 96-well plate and washed. After 20 hours of co-culture all of the cells were collected from a flat-bottom 96-well plate and

transferred to a U-bottom 96-well plate, and then washed. 30 µl of 0.25% trypsin was added to all the wells and incubated for 5 minutes in a 37°C incubator. After 5 minutes, all of the tumor cells were collected to a U-bottom 96-well plate. The cells were centrifuged and washed for 5 minutes at 400 x g twice. The cell pellet was then resuspended in diluted (1:1000) LIVE/DEAD™ Fixable Near-IR staining dye (100 µl). The cells were incubated for 30 mins at 4 °C, and washed with FACS buffer twice by centrifuging the cells for 5 minutes at 400 x g. After washing, all of the cells were fixed for 10 minutes using 100 µl of BD Cytofix™ Fixation Buffer (50µl FACS buffer +50µlFixation Buffer). The cells were centrifuged and washed for 5 minutes at 400 x g once. The cell pellet was resuspended in FACS buffer. Stained samples were analyzed by multicolor flow cytometry after the end of the incubation period.

The percentage of cytotoxic activity was calculated using the following equation:

% specific death = % Near IR+CTV+(dead) cells - % spontaneous Near IR +CTV+ / (100% - % spontaneous Near IR +CTV+ (dead) cells) x 100%.

Twenty-four hours after transient transfection, target cells (Vcap and DU145) were labeled with Cell Trace Violet (CTV) fluorescent dye and then co-cultured with hK2 CAR-T cells. Mock T cells served as negative effector controls. Cells were co-cultured for 20 hours at the indicated effector-to-target cell (E/T) ratio shown in **Figure 2**. Percent killing is the ratio of the absolute number of live (viability dye negative) target (CTV positive) cells remaining in the co-culture relative to the number of live targets cultured without CAR-T cells. As shown, hK2 CAR LH T cells specifically and efficiently lysed the hK2(+) human prostate cancer cell lines VCap cells, but not K2 (-) DU145 cells E/T ratios of 10:1 to 0.3125:1, whereas only the background cytotoxicity was seen in the T cells that were Mock or hK2 HL CAR.

hK2-specific CAR-T cells were also tested for real-time cytotoxicity using xCELLigence as a real-time cell analysis system as a potency assay for immune cell-mediated cytolysis of target cells.

50 µL of target cancer cell culturing media was added to each well of the 96-well E-Plates (ACEA Biosciences), and the background impedance was measured and displayed as a

Cell Index. Then, adherent target cells VCap and DU145 were dissociated and seeded at a density of 5E4 (VCap), 5E3 (DU145) cells/well of the E-Plate in a volume of 100 µL, and allowed to passively adhere on the electrode surface. Post seeding, the E-Plate was kept at ambient temperature inside a laminar flow hood for 30 minutes and then transferred to the RTCA MP instrument inside a cell culture incubator. Data recording was initiated immediately at 15-minute intervals for the entire duration (96 hours) of the experiment.

At the time treatment was applied (24 hours post cancer cells seeding), data acquisition was paused, 50 µL of media was removed from each well, and effector CART cells were added at different effector to target (E:T) ratios in a volume of 50 µL. HK2 CAR+ and undisclosed control CAR (non-HK2 specific) T cells were resuspended. Two-fold dilutions were then performed in duplicate in a 96-well plate (from 5:1 to 0.156:1 E/T ratio). Target plus Mock effector controls (no RNA electroporation T cells) were also added to the target cells.

Target cells VCap (5E4) and DU145 (5E3) incubated with Mock, 10µg mRNA electroporated (24 hours post transfection) hK2 11B6 CAR LH or control CAR-T cells at different E/T ratios for approximately 72 hours. Normalized cell index (CI) plots for VCap and DU145 are shown in **Figure 3A** and **Figure 3B**, respectively. When seeded alone, target cells adhere to the plate and proliferate, increasing the CI readout. When T cells were added to target cells, hK2 CAR- and control CAR-T cells cause cell cytolysis and subsequent progressive decrease in CI.

**Example 3: Cytokine production of hK2 CAR-T cells**

Without wishing to be bound by theory, IFN-γ produced by cytotoxic T cells could allow for exertion of immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*. To determine whether hK2 CAR-modified human T cells were able to recognize and be activated by hK2 (+) tumor cells, the supernatant was collected from xCELLigence-based killing assay, as described in Example 2 and **Figures 3A-3B**. After about 70 hours co-culture, the supernatant was

collected and assayed by ELISA according to the directions provided with the ELISA kit (Human IFN-γ ELISA MAX™ Deluxe, BioLegend, Cat#:430106).

Th1 cytokine interferon-γ (IFN-γ) production of antigen-stimulated CAR-T cells is shown in **Figure 4**. hK2 CAR LH- and control CAR modified T cells secrete IFN-γ during co-culture with hK2-expressing VCap cells in a E:T ratio-dependent manner, but not hK2-negative DU145 cells. Undisclosed control CAR secreted much higher amount of IFN- γ due to the much higher antigen expression level than hK2. Mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures is shown.

## Example 4: Generation and characterization of thermally stabilized scFvs CAR constructs

The anti-HK2 antibody clone 11B6 was identified by immunization of BALB/c mice with recombinant HK2 by Väisänen et al (Clinical Chemistry 50:9, 1607–1617 (2004). Humanization of the murine-derived clone 11B6 was performed by the method described in Singh et al., MAbs. 2015;7(4):778-91. Because the exodomain of wild-type 11B6 as scFv did not retain binding at elevated temperature (55 °C), humanization was performed as scFv and the *E. coli*- expressed supernatants from the humanized variants were incubated at 60 °C for 15 minutes, followed by screening for binding to recombinant HK2 using ELISA. Ten hK2-targeting CARs containing a thermally stabilized scFv derived from the antibody 11B6 were generated.

Description and SEQ ID NOS of the ten CAR constructs containing thermally stabilized scFvs are provided in Table 1.

**Table 1. CAR constructs with 11B6 thermally stabilized scFvs**

| # of construct | Description | SEQ ID NO |
|---|---|---|
| **1** | HL_HCG5_LCD6_20AA | 46 |
| **2** | HL_HCG5_LCHumanized_20AA | 47 |
| **3** | HL_HCF3_LCB7_20AA | 48 |
| **4** | HL_HCG5_LCB7_20AA | 49 |

| | | |
|---|---|---|
| **5** | LH_LCD6_HCG5_20AA | 50 |
| **6** | LH_LCHumanized_HCF3_20AA | 51 |
| **7** | LH_LCHumanized_HCG5_20AA | 52 |
| **8** | LH_LCB7_HCF3_20AA | 53 |
| **9** | LH_LCB7_HCG5_20AA | 54 |
| **10** | LH_LCD6_HCF3_20AA | 55 |

To identify different scFv based CAR with antigen independent activation via Jurkat-Lucia™ NFAT Cells (JNLs). Nuclear factor of activated T-cells (NFAT) is a family of transcription factors first identified as a regulator of immune cells. T cell activation leads to calcium influx, activating calcineurin that dephosphorylates serine rich nuclear localization signal at the N-terminus of NFAT, leading to nuclear import of NFAT. Without wishing to be bound by theory, tonic signaling due to scFv clustering could be subsequently detected by Firefly luciferase driven by NFAT promoter in JNL reporter cell line.

JNL cells, i.e., Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter, were transduced with the various CAR constructs. Binding between the CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells.

Lentiviral transduction was performed as follows. JNL cells were harvested and re-suspended to 1E6/ml. 500 µl of JNL cells and lentiviral virus were added at a MOI of 3, and mixed by pipetting up and down. The mixture was incubate in a 37°C incubator for 24 hours. 500 µl JNL media was added to each well, with culturing continued in a 37°C incubator. The cells were transferred to a T25 flask on day 4. At days 5-6, transduction validation was performed. 150 µl of cells was harvested to examine CAR expression via appropriate detection reagent for the specific CAR you are using (e.g. biotin-hk2 Protein is used to detect hk2 CAR). The JNL cells were maintained at $5x10^5$/ml until enough cells were obtained to either freeze down or use in the assay.

The thermally stabilized scFvs CARs were evaluated in a JNL reporter assay for antigen-dependent activity. Jurkat cells containing the luciferase gene driven by the signaling-

responsive NFAT promoter (termed JNL cells) were transduced with the various hK2 CAR constructs. The assay was performed as follows. Coculturing with target cell lines was performed at an effector to target ratio of 2:1. The JNL cells were spun down to remove any secreted luciferase in the medium; the JNL cells were then resuspend in fresh media at $4x10^5$/ml. The cells were harvested. Then, both antigen-positive and antigen-negative target cell lines were prepared at 2E5/ml. 100 µl JNL was added to 100 µl target cells. For the JNL-only control, 100 µl media was added instead of target cells. For positive control, JNL cells only or CAR JNL cells were added to 1x Cell Stimulation Cocktail and incubate in a 37°C incubator for 24 hours. 150 µl of the supernatant was harvested into a 96-well plate and centrifuged to remove cells. 100 µl of supernatant was transferred from the plate to a solid bottom black plate. Then, 100 µl QUANTI-luc lucia detection reagent was added. The mixture was incubated at room temperature for 5 minutes before reading with Envision multiplate reader.

CAR expression was determined by biotinylated hK2 followed by streptavidin-conjugated PE, with the results shown in **Figure 5A**. CAR expression in transduced JNL cells was confirmed for all of the selected clones with 60–75% of cells showing detectable expression across the different clones and parental 11B6 CARs. JNL cells containing the indicated CAR clones and un-transduced JNL cells (UTD) were co-cultured with target cells lines (VCap or DU145 cells) and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells.

The binding between the CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells (**Figure 5B**). JNL cells containing the indicated CAR clones and JNL cells (untransduced, hereinafter "UTD") were co-cultured with target cells lines (VCap or DU145 cells) and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells. No antigen-dependent activation was found for all the 10 clones and parental 11B6 CAR HL and LH.

**Example 5: Expression of thermally stabilized scFvs CARs on T cells**

To evaluate the function of thermally stabilized 11B6 CARs T cells and pick top candidate construct, 11B6 thermally stabilized and parental scFvs based CAR T cells were generated using lentiviral transduction. Primary human T cells were transduced with 11B6 thermally stabilized and parental scFvs based CAR lentivirus with a multiplicity of infection (MOI) of 3. CAR expression was determined by biotinylated hK2 (1µg/ml) followed by streptavidin-conjugated PE 14 days post transduction.

The experimental protocol is as follows.

Lentiviral packaging was undertaken. 14E6 Lenti-X™ 293T cells were seeded per 150 $mm^2$ round-bottomed Corning™ BioCoat™ Collagen I coated culture dish, and incubated at 37°C overnight using DMEM+10% FBS medium.

With Lenti-X™ 293T cells at the ideal confluency of 80-85%, the following was prepared. Culture media was replaced with 21ml 293T growth media. Lipofectamine 2000 was diluted at room temperature and equilibrated OptiMEM. Diluted Lipofectamine 2000 was added to mixed plasmids drop-wise, and mixed well. The mixture was incubated at room temperature for 25 minutes. The transfection mixture was added to Lenti-X 293T cells dropwise, with the plate gently swirled to mix. The mixture was incubated in a 37°C incubator. Lentivirus was harvested 24 and 48 hours post transfection. The above reagents are summarized in the Table 2.

**Table 2**

| **Reagent** | **Amount per 15cm dish** |
|---|---|
| pMDLg/p | 18 µg |
| pRSV.Rev | 18 µg |
| pMD2.G | 7 µg |
| Transfer (CAR) plasmid | 15 µg |

| | |
|---|---|
| OptiMEM | 1500µl |

Lentiviral concentration was performed as follows. Lentivirus-containing supernatants were harvested and centrifuged at 500 x g for 10 min if excessive 293T cells are floating around before filtering through 0.45 µm cellulose acetate filters. Supernatant was transferred to a sterile container, combined with 1/3 volume of Lenti-X Concentrator (Clontech, Cat. # 631232), and mixed by gentle inversion. The mixture was incubated at 4°C overnight. The sample was centrifuged at 1,500 x g for 45 minutes at 4°C, with a white pellet visible after centrifugation. The supernatant was carefully removed without disturbing the pellet. Residual supernatants were removed with a pipette after a brief centrifugation at 1,500 x g. The pellet was gently resuspended in 1/10 of the original volume using cold T cell growth. The virus was aliquoted in 200 µl and immediately stored at –80°C.

Viral titering was performed as follows. Log-phase SupT1 was grown in complete RPMI. 100 µl 20,000 SupT1 cells/ml were seeded per well in a flat 96-well plate. Virus titration was then performed in 96-well round bottom plates). 100 µl media was added to all the wells in the plate. A virus aliquot was thawed from -80°C freezer with one's hands. The aliquot was pipetted up and down to mix well, with 50 µl virus added to the first well, followed by thorough mixing. A serial 1:3 dilution was performed by pipetting 50 µl virus to the next well. Then, 50 µl media was added to primary Ab only, secondary Ab only, and un-transduced controls. 50 µl of each was transferred from the titration plate to 100 µl SupT1 cells in the assay plate with a multi-channel pipette, and incubated at 37°C overnight. 100 µl of pre-warmed media was added to each sample, and incubated another two days. The transduction efficiency was determined by flow cytometry. Samples were transferred to a round bottom 96 well plate and spun at 1400 RPM for 3 minutes. The supernatant was discarded quickly, followed by blotting to remove excessive media in the hood. The wash was repeated with 150 µl FACS buffer. A staining protocol appropriate for CAR constructs was then undertaken. Samples were resuspended in 150 µl FACS buffer before flow cytometry analysis.

Viral titer calculation: Titer = (% CAR positive/100) x $2x10^4$ x 20 x dilution factor

To exclude multiple copy integrations, titers with the closest transduction to 20% is used. T-cell activation, transduction and expansion was performed as follows. A vial of naïve T cells was thawed in a water bath and added drop-wise to a 15 ml conical tube containing 9 ml of pre-warmed T-cell media (TCM CTS OpTmizer T Cell Expansion SFM+5% human serum +IL-2 100IU/ml). The cryovial was washed with 1 ml of media to recover maximum number, and spun at 300 x g for 8 minutes at room temperature. The pellet was resuspended in fresh 10 ml TCM, counted, and resuspended to 1E6 cells per milliner. 5E5 cells were added per well in 24-well plate. $1.5x10^6$ CD3/CD28 beads were added per well in 500 µl volume such that the total volume was 1 ml per well. Twenty-four hours post activation, virus was thawed at room temperature. Virus was added at a multiplicity of infection (MOI) of 3, gently swirled to mix, and returned to the plate at the incubator. (The lentiviral functional titer was previously determined with SupT1 titer assay.) One well was reserved for Untransduced (UTD) in which is no virus added.

Twenty four hours post-transduction, 1 ml TCM was added to each well. Penicillin-Streptomycin was added from this point onward (Day 2). On days 3-5, 4 ml TCM was added for each 2 ml of cells and transferred to a T25 tissue culture treated flask. The flasks were placed horizontally in the incubator (Day 3). Equal volume of TCM was added for T-cell culture (Day 4). On days 5-14, the cells were checked every other day, with the viability, size and total cell count recorded. The cell density was adjusted to one million cells per mL. The ideal time of harvest is donor dependent and determined by the cell size and the fold of expansion. Cells were generally frozen when the cell size was less than 8 µm based on the MOXI flow cell counter with the 100 to 200-fold of expansion.

Lentiviral transduction efficiency was checked on harvest day as follows. Cultures were mixed well. 100 µl of T-cells was harvested to a corresponding well in 96-well plate with 100 µl FACS Buffer, mixed, and spun at 1300 RPM for 3 minutes at room temperature. The cells were resuspended in 200 µl FACS buffer and centrifugation repeated at 4°C.

The cells were resuspended in 100 µl of Biotin labeled hK2 (1 µg/ml diluted in FACS buffer) and incubated on ice for 30 minutes. 100 µl of FACS buffer was added, and spun washed at 4°C. The spin wash was repeated after adding another 200 µl FACS buffer. Staining with 100 µl of master solution containing secondary antibody SA-PE (1:250), live dead fixable stain (1:500), αCD3, αCD4 and αCD8 antibodies was performed on ice for 30 minutes. 100 µl FACS buffer was added and spun wash at 4°C, discarded and re-suspended in 200 µl FACS buffer before spin washing at 4°C. The samples were resuspended in 100 µl FACS Buffer before analyzing by flow cytometry.

Cell harvest and freezing was performed as follows. The final cell count was determined. The culture was harvested and centrifuged at 300 x g for 10 minutes at room temperature. The culture was resuspended in a smaller volume of media to fit in a 50 ml conical tube. The tubes were placed in magnets at 4°C for 10 minutes to "de-bead". The cells were gently transferred from the tube to minimize disturbing the beads / magnet, and the exact volume recorded. Counting was repeated. Centrifugation was performed at 300 x g for 10 minutes, with the supernatant discarded. Cells were frozen in CS-10 CryoStor® cell cryopreservation media in a cooling container. The containers were immediately transferred to -80°C for 24-48 hours before permanent storage in liquid Nitrogen. The results are shown in **Figure 6**, and confirm hK2 CAR expression on the surface of the transduced T cells. Summary of the percentage of hK2 CAR + T cells (% positive) detected by each of the 10 thermally stabilized clones and parental 11B6 HL & LH analyzed is provided. As shown, different clones have different CAR expression level, ranges from 17.9% to 42.7%. All CAR T cells were normalized to the equal CAR+ T cells for subsequent functional assays.

## Example 6: Tumor cell killing by 11B6 thermally stabilized scFv CAR-T cells

11B6 thermally stabilized scFv CAR-T cells were evaluated in the real-time IncuCyte killing assay for antigen-dependent cytotoxicity. Thermally stabilized hK2 CAR-T cells and parental 11B6 CAR-T cells were co-incubated with VCaP cells (**Figure 7A**) and PC3 cells (**Figure 7B**) for 88 hours. Effector-to-target (E/T) ratio was calculated based on CAR

expression data (**Figure 6**). Target cells were stably expressing a red nuclear dye which was measured by IncuCyte imaging system in a real-time fashion. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

scFv CAR-T cells also were evaluated in the real-time IncuCyte tumor killing assay for antigen-dependent cytotoxicity. Thermally stabilized hK2 CAR-T cells and parental 11B6 CAR-T cells were co-incubated with VCaP cells (**Figure 7C**) or PC3 cells (**Figure 7D**) for 88 hours at effector:target ratio of 1:1 or 0.5:1 which was calculated based on CAR expression data. CAR-T cells transduced with CAR17, CAR18, CAR19 and CAR20 were co-incubated with hK2 positive VCaP cells and hK2 negative DU145 cells for 96 hours at effector-to-target (ET) ratio of 1:1 or 0.5:1 which was calculated based on CAR expression on T cells. The percent tumor cell growth inhibition over time of CAR-T cells transduced with CAR17, CAR18, CAR19 and CAR20 is shown in **Figure 7E** for VCap cells and in **Figure 7F** for DU145 cells. Target cells were stably expressing a red nuclear dye which was measured by IncuCyte imaging system in a real-time fashion. Tumor cell growth inhibition (%) =(Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%). Tested CAR-T cells achieved approximately 100% TGI whereas the untransduced control did not demonstrate any TGI. No TGI was observed with the tested CAR-T cells in hK2 negative DU145 cells.

**Example 7: Cytokine production of 11B6 thermally stabilized scFv CAR-T cells**

Supernatant was collected from overnight (approximately 20 hours) co-culture of hK2 CAR-T cells with VCap cells at 1:1 of E/T ratio and was analyzed using 13-plex Milliplex Human High Sensitivity T cell kit (HSTCMAG28SPMX13). hK2 CAR modified T cells secrete cytokines during co-culture with hK2-expressing VCap cells, but minimal for un-transduced T cells (UTD). The results of cytokine release by hK2 lenti-CAR-T cells are shown in **Figure 8.**

Supernatant was collected from overnight (approximately 20 hours) co-culture of hK2 CAR-T cells with VCap, DU145 (5E4 cells) cells at 1:1 of E/T ratio. hK2 CAR modified T

cells secrete IFN-γ during co-culture with hK2-expressing VCap cells, but not hK2-negative DU145 cells. CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. IFN-γ release by hK2 lenti-CAR-T cells is shown in **Figure 9.** (The protocol of Example 3 was used.) Mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures is shown. CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. As shown, different thermally stabilized CAR T cells produce different amount of IFN-gamma when co-culture with hK2 (+) VCap cells, which is associated with cytotoxic activity during cell-mediated immune response.

**Example 8: Proliferation of hK2 CAR-T cells**

hK2 CAR-T cells were evaluated in a proliferation assay. T-cell proliferation is an important *in vitro* parameter of *in vivo* immune function. To further evaluate the function of thermally stabilized 11B6 CARs T cells and pick top candidate construct, 11B6 thermally stabilized and parental scFvs based CAR T cells were labeled with CTV to assess T cell proliferation.

hK2 CAR and un-transduced (UTD) T cells were labelled with CellTrace Violet (CTV; 5μM) and co-cultured with hK2 (+) VCap and hK2 (-) DU145 cells. Five days post co-culture, cells were harvested and stained with CD3, CD25, NearIR live/dead Dye and hK2 CAR. Flow cytometric analysis was performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes were identified by live CD3, and the frequencies of CAR-T cells with CTV dye dilution and activation marker CD25 were determined. By gating on hK2 CAR+ T cells, as shown, the hK2(+) Vcap cells but not hK2(-) DU145 cells promoted the all CAR constructs engineered T cells proliferation and upregulation of activation marker CD25 (**Figures 10A, 10C**). CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. T cells only without any stimulation do not proliferate and CD3/28 beads stimulated T cells displayed equivalent proliferation pattern (**Figures 10B, 10D**). As shown in **Figure 10E**, hK2 CAR+ T cells proliferate more robustly than CD3/28 beads positive control after 5 days of coculture with VCap cells.

Different CAR constructs engineered T cells have different proliferation activity and displayed different CAR+ T cells counts. The CAR+ T cells counts based on mean absolute cell count +/- SEM from three technical replicates.

The protocol is as follows. The tumor cells Vcap and DU145 were collected, washed twice with PBS, and resuspended in 10E6/ml in PBS containing 100ug/ml Mitomycin C (MMC) for 1.5 hours in a 37°C incubator so as to block tumor cells proliferation. 20 µL of DMSO was added to a vial of CTV staining solution. 5 µl of the solution was diluted into 5mL (1:1000) PBS (warmed to 37°C) to provide a 5 µM staining solution. The 2E6 T cells were counted, collected, washed with PBS twice, and resuspended in 4E6/ml (0.5ml). An equal volume (0.5 ml) of CTV staining solution was added. The cells were incubated for 20 minutes at 37°C. Then, 4 ml PRMI+20% FBS was added to the cells to absorb any unbound dye. The cells were incubated for 5 minutes, and centrifuged for 5 minutes at 400 x g. The cell pellet was resuspended in pre-warmed RPMI+10%FBS medium. The T cells were counted, and 1E5 cells(100µl) were seeded in 96-wells flat bottom-plate.

In the meantime, MMC-treated tumor cells hK2(+) VCap and HK2(-) DU145 were collected and counted after 1.5 hours, and then resuspended at 1E6/ml. 1E5 of the cells (100 µl) were cocultured with T cells in a 96-well plate. T cells alone, and T cells added 3:1 CD3/28 beads to cells ratio, were used as negative and positive controls, respectively.

After 5 days of co-culture, all of the cells were collected from each well. The cells were centrifuged and washed for 5 minutes at 400 x g twice, then stained hK2CAR, CD3, CD8 and CD25, live/dead (Near-IR) in 96-well U bottom plate. After washing, all cells were fixed for 10 minutes using 100 µl BD Cytofix™ Fixation Buffer (50µl FACS buffer +50µlFixation Buffer). The stained samples were analyzed by multicolor flow cytometry after the end of the incubation period.

Data analysis was performed as follows. A CTV histogram was prepared. The CTV undiluted gate was set to encompass the far-right peak (CTV bright) of T cells cultured alone, and the CTV diluted gate to capture the rest of the population. This was applied to all samples.

**Example 9: Construction and expression of hK2 scFv CARs with anti-HK2 scFv**

hK2 CAR constructs comprising an scFv derived from the novel anti-HK2 scFv were constructed as illustrated in **Figure 11A**.

To evaluate the function of these novel anti-HK2 scFv CARs T cells and to pick a top candidate construct, hK2 HL and \ LH CAR-T cells were generated using lentiviral transduction. Primary human T cells were transduced with hK2 CAR HL and LH, novel scFvs based CAR lentivirus with a multiplicity of infection (MOI) of 3. CAR expression was determined by biotinylated hK2 (1μg/ml) followed by streptavidin-conjugated PE 14 days post transduction.

The experimental protocol is as follows.

Lentiviral packaging was undertaken. 14E6 Lenti-X™ 293T cells were seeded per 150 $mm^2$ round-bottomed Corning™ BioCoat™ Collagen I coated culture dish, and incubated at 37°C overnight using DMEM+10% FBS medium.

With Lenti-X™ 293T cells at the ideal confluency of 80-85%, the following was prepared. Culture media was replaced with 21ml 293T growth media. Lipofectamine 2000 was diluted at room temperature and equilibrated OptiMEM. Diluted Lipofectamine 2000 was added to mixed plasmids drop-wise, and mixed well. The mixture was incubated at room temperature for 25 minutes. The transfection mixture was added to Lenti-X 293T cells dropwise, with the plate gently swirled to mix. The mixture was incubated in a 37°C incubator. Lentivirus was harvested 24 and 48 hours post transfection. The above reagents are summarized in the Table 3.

**Table 3**

| **Reagent** | **Amount per 15cm dish** |
|---|---|
| pMDLg/p | 18 μg |
| pRSV.Rev | 18 μg |

| | |
|---|---|
| pMD2.G | 7 μg |
| Transfer (CAR) plasmid | 15 μg |
| OptiMEM | 1500μl |

Lentiviral concentration was performed as follows. Lentivirus-containing supernatants were harvested and centrifuged at 500 x g for 10 min if excessive 293T cells are floating around before filtering through 0.45 μm cellulose acetate filters. Supernatant was transferred to a sterile container, combined with 1/3 volume of Lenti-X Concentrator (Clontech, Cat. # 631232), and mixed by gentle inversion. The mixture was incubated at 4°C overnight. The sample was centrifuged at 1,500 x g for 45 minutes at 4°C, with a white pellet visible after centrifugation. The supernatant was carefully removed without disturbing the pellet. Residual supernatants were removed with a pipette after a brief centrifugation at 1,500 x g. The pellet was gently resuspended in 1/10 of the original volume using cold T cell growth. The virus was aliquoted in 200 μl and immediately stored at –80°C.

Viral titering was performed as follows. Log-phase SupT1 was grown in complete RPMI. 100 μl 20,000 SupT1 cells/ml were seeded per well in a flat 96-well plate. Virus titration was then performed in 96-well round bottom plates). 100 μl media was added to all the wells in the plate. A virus aliquot was thawed from -80°C freezer with one's hands. The aliquot was pipetted up and down to mix well, with 50 μl virus added to the first well, followed by thorough mixing. A serial 1:3 dilution was performed by pipetting 50 μl virus to the next well. Then, 50 μl media was added to primary Ab only, secondary Ab only, and un-transduced controls. 50 μl of each was transferred from the titration plate to 100 μl SupT1 cells in the assay plate with a multi-channel pipette, and incubated at 37°C overnight. 100 μl of pre-warmed media was added to each sample, and incubated another two days. The transduction efficiency was determined by flow cytometry. Samples were transferred to a round bottom 96 well plate and spun at 1400 RPM for 3 minutes. The supernatant was discarded quickly, followed by blotting to remove excessive media in the hood. The wash was repeated with 150 μl FACS buffer. A staining protocol appropriate

for CAR constructs was then undertaken. Samples were resuspended in 150 µl FACS buffer before flow cytometry analysis.

Viral titer calculation: Titer = (% CAR positive/100) x $2x10^4$ x 20 x dilution factor

To exclude multiple copy integrations, titers with the closest transduction to 20% is used.

T-cell activation, transduction and expansion was performed as follows. A vial of naïve T cells was thawed in a water bath and added drop-wise to a 15 ml conical tube containing 9 ml of pre-warmed T-cell media (TCM CTS OpTmizer T Cell Expansion SFM+5% human serum +IL-2 100IU/ml). The cryovial was washed with 1 ml of media to recover maximum number, and spun at 300 x g for 8 minutes at room temperature. The pellet was resuspended in fresh 10 ml TCM, counted, and resuspended to 1E6 cells per milliner. 5E5 cells were added per well in 24-well plate. $1.5x10^6$ CD3/CD28 beads were added per well in 500 µl volume such that the total volume was 1 ml per well. Twenty-four hours post activation, virus was thawed at room temperature. Virus was added at a multiplicity of infection (MOI) of 3, gently swirled to mix, and returned to the plate at the incubator. (The lentiviral functional titer was previously determined with SupT1 titer assay.) One well was reserved for Untransduced (UTD) in which is no virus added.

Twenty four hours post-transduction, 1 ml TCM was added to each well. Penicillin-Streptomycin was added from this point onward (Day 2). On days 3-5, 4 ml TCM was added for each 2 ml of cells and transferred to a T25 tissue culture treated flask. The flasks were placed horizontally in the incubator (Day 3). Equal volume of TCM was added for T-cell culture (Day 4). On days 5-14, the cells were checked every other day, with the viability, size and total cell count recorded. The cell density was adjusted to one million cells per mL. The ideal time of harvest is donor dependent and determined by the cell size and the fold of expansion. Cells were generally frozen when the cell size was less than 8 µm based on the MOXI flow cell counter with the 100 to 200-fold of expansion.

Lentiviral transduction efficiency was checked on harvest day as follows. Cultures were mixed well. 100 µl of T-cells was harvested to a corresponding well in 96-well plate with 100 µl FACS Buffer, mixed, and spun at 1300 RPM for 3 minutes at room temperature. The cells were resuspended in 200 µl FACS buffer and centrifugation repeated at 4°C.

The cells were resuspended in 100 µl of Biotin labeled hK2 (1 µg/ml diluted in FACS buffer) and incubated on ice for 30 minutes. 100 µl of FACS buffer was added, and spun washed at 4°C. The spin wash was repeated after adding another 200 µl FACS buffer. Staining with 100 µl of master solution containing secondary antibody SA-PE (1:250), live dead fixable stain (1:500), αCD3, αCD4 and αCD8 antibodies was performed on ice for 30 minutes. 100 µl FACS buffer was added and spun wash at 4°C, discarded and re-suspended in 200 µl FACS buffer before spin washing at 4°C. The samples were resuspended in 100 µl FACS Buffer before analyzing by flow cytometry.

Cell harvest and freezing was performed as follows. The final cell count was determined. The culture was harvested and centrifuged at 300 x g for 10 minutes at room temperature. The culture was resuspended in a smaller volume of media to fit in a 50 ml conical tube. The tubes were placed in magnets at 4°C for 10 minutes to "de-bead". The cells were gently transferred from the tube to minimize disturbing the beads / magnet, and the exact volume recorded. Counting was repeated. Centrifugation was performed at 300 x g for 10 minutes, with the supernatant discarded. Cells were frozen in CS-10 CryoStor® cell cryopreservation media in a cooling container. The containers were immediately transferred to -80°C for 24-48 hours before permanent storage in liquid Nitrogen. The results are shown in **Figure 11B**, and confirm hK2 CAR expression on the surface of the transduced T cells. A summary of the percentage of hK2 CAR + T cells (% positive) detected by novel KL2B413 HL&LH and rehumanized 11B6 KL2B359 HL&LH CARS analyzed is provided. As shown, different clones have different CAR expression level, ranges from 45.1% to 59.9%. All CAR T cells were normalized to the equal CAR+ T cells for subsequent functional assays.

## Example 10: Generation of anti-hK2 antibodies and scFvs

**Antibody generation from humanization of parental m11B6 antibody.**

A parental mouse anti-HK2 antibody, m11B6 has been described in Väisänen et al (Clinical Chemistry 50:9, 1607–1617 (2004)). Humanized 11B6 (referred herein to as

hu11B6) has been generated and described in U.S. Pat. No. 9,345,782 and U.S. Pat. No. 10,100,125.

Engineering of hu11B6 were initiated to generate additional anti-HK2 antibodies with improved properties, such as improved thermostability. Residue positions were identified in hu11B6 frameworks which could potentially be altered to improve thermostability of hu11B6 using modeling. The positions identified were residues P41, I49, M70, and A88 in the VH and S80, L82, A88 and Y91 in the VL (residue numbering according to the amino acid sequences of hu11B6_VH of **SEQ ID NO: 5** and hu11B6_VL of **SEQ ID NO: 2**).

Binary combinatorial scFv libraries were generated in the orientation VH-linker-VL in which one of the variable regions represented the combinatorial library and the second one being the parental hu11B6 VH or VL. Linker sequence of **GGSEGKSSGSGSESKSTGGS (SEQ ID NO: 7)** was used to conjugate the VH/VL regions. The engineered scFvs were expressed in E *coli* and the produced scFvs in the supernatants were tested for binding to human hK2 by ELISA and compared to the binding of hu11B6. Any new variants exhibiting binding comparable to hu11B6 were consolidated and further tested for binding to human hK2 after incubation of the supernatants at 55°C, 60°C, and 65°C for 10 minutes. The molecules which retained comparable binding to hu11B6 after incubation at 55°C, 60°C, and 65°C and improved thermostability were matrixed in both orientations (VH-linker-VL; VL-linker-VH) and converted to mammalian scFvs for further characterization. The matrixed scFvs were also incorporated into CAR constructs and further characterized as further described in Example 11.

In addition, another humanization of parental mouse 11B6 was performed following the approach outlined by Singh et al (MAbs. 2015;7(4):778-91). with extensive germ line variation and careful screening of the variants for enhanced thermal stability. Based on sequence conservation, the human heavy chain germline IGHV4-30 and the light chain germline IGKV3D-11, were chosen for framework adaption. A binary scFv library was constructed with residues comprising a select set of somatic hypermutation sites and mouse/human germline variations. The variants were cloned and expressed in E. coli as described above. The supernatants were screened at different temperatures in single point ELISA for enhanced thermal stability. A mouse/human chimeric 11B6 scFv was used as

parental control. Clone KL2B359 which maintained binding activity similar to murine 11B6 and a Tm value of 67°C was converted to scFv-Fc and CAR-T for additional profiling. The measured affinity ($K_D$) of KL2B359 to hK2 by SPR was ~0.7 – 1nM. HCF3-LCD6, HCG5-LCB7, KL2B357, KL2B358 and KL2B360 also resulted from this campaign and were further characterized for functionality.

**Antibody generation using transgenic mice (Ablexis®) and transgenic rats (OmniRat®) expressing human immunoglobulin loci.**

The OmniRat® contains a chimeric human/rat IgH locus (comprising 22 human $V_{HS}$, all human D and $J_H$ segments in natural configuration linked to the rat $C_H$ locus) together with fully human IgL loci (12 Vκs linked to Jκ-Cκ and 16 Vλs linked to Jλ-Cλ). (see e.g., Osborn, et al. (2013) J Immunol 190(4): 1481-1490). Accordingly, the rats exhibit reduced expression of rat immunoglobulin, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity chimeric human/rat IgG monoclonal antibodies with fully human variable regions. The preparation and use of OmniRat®, and the genomic modifications carried by such rats, is described in WO14/093908.

Ablexis® mice generate antibodies having human variable domains linked to human CH1 and CL domains, chimeric human/mouse hinge region, and mouse Fc regions. Ablexis Kappa Mouse and Lambda Mouse strains are distinguished by which of their heavy chains are human or mouse as noted below. Antibodies produced by the Kappa Mouse lack sequence derived from mouse $V_H$, $D_H$ and $J_H$ exons and mouse Vκ, Jκ and Cκ exons. The endogenous mouse Igλ is active in the Kappa Mouse. The human Igκ chains comprise approximately 90-95% of the naïve repertoire and mouse Igλ chains comprise approximately 5-10% of the naïve repertoire in this strain. Antibodies produced by the Lambda Mouse lack sequence derived from mouse $V_H$, $D_H$ and $J_H$ exons and mouse Vλ, Jλ and Cλ exons. The endogenous mouse Igκ is active in the Lambda Mouse. The human Igλ chains comprise approximately 40% of the naïve repertoire and mouse Igκ chains comprise approximately 60% of the naïve repertoire. The preparation and use of Ablexis®, and the genomic modifications carried by such mice, is described in WO11/123708.

Ablexis mice and OmniRats rats were immunized with soluble full length KLK2 protein (human Kallikrein-2 6-His protein).

**human Kallikrein-2 6-His protein**

VPLIEGRIVGGWECEKHSQPWQVAVYSHGWAHCGGVLVHPQWVLTAAHCLKKN
SQVWLGRHNLFEPEDTGQRVPVSHSFPHPLYNMSLLKHQSLRPDEDSSHDLMLLR
LSEPAKITDVVKVLGLPTQEPALGTTCYASGWGSIEPEEFLRPRSLQCVSLHYSEKV
TEFMLCAGLWTGGKDTCGGDSGGPLVCNGVLQGITSWGPEPCALPEKPAVYTKV
VHYRKWIKDTIAANPHHHHHH (SEQ ID NO: 319)

Lymphocytes from Ablexis mice and OniRats rats were extracted from lymph nodes and fusions performed by cohorts. Cells were combined and sorted for CD138 expression. Hybridoma screening was performed in high throughput miniaturized MSD format using soluble hK2 antigen. Approximately >300 samples were identified to be hK2 binders. The binding of >300 anti-hKLK2 supernatant samples to human KLK2 protein was measured by single cycle kinetics method by Biacore 8K SPR. Additionally the supernatant samples were tested for binding to human KLK3 protein as well. In parallel, supernatants were also tested for binding to KLK2 expressing cell lines VCap and negative cell line DU145 by Flow Cytometry. Selected cell binders were moved forward to scFv conversion in both VH-VL and VL/VH orientation and thermal stability tests as described above. KL2B413, KL2B30, KL2B53 and KL2B242 resulted from the Ablexis mice immunization campaign. KL2B467 and KL2B494 resulted from the OmniRat immunization campaign.

Antibodies generated through the various immunization and humanization campaigns described above were expressed in a fab format, a mAb format, a scFv format in the VH-linker-VL orientation or a scFv format in VL-linker-VH orientation and were further analyzed as described below. The linker sequence of SEQ ID NO: 7 described above was used to conjugate the VH/VL regions.

## Example 11. Structural characterization of anti KLK2 antibodies

Sequences of antibody variable domains and scFv antibody fragments which showed highest performance in intracellular assay are provided herein. Variable domains were

expressed in a Fab format, a scFv format in the VH-linker-VL orientation or a scFv format in VL-linker-VH orientation.

**Variable domains VH, VL and CDRs**

**Table 4** shows the VH and VL amino acid sequences of selected anti-hK2 antibodies. **Table 5** shows the Kabat HCDR1, HCDR2 and HCDR3 of selected anti-hK2 selected antibodies. **Table 6** shows the Kabat LCDR1, LCDR2 and LCDR3 of the selected anti-hK2 antibodies. **Table 7** shows the AbM HCDR1, HCDR2 and HCDR3 of selected anti-hK2 antibodies. **Table 8** shows the AbM LCDR1, LCDR2 and LCDR3 of the anti-hK2. **Table 9** summarizes the variable domain sequence and SEQ ID NO of selected hK2 antibodies. **Table 10** shows the protein and DNA SEQ ID NOs for the VH and VL regions.

**Table 4. VH and VL amino acid sequences of selected anti-hK2 antibodies.**

| mAb name | VH name | VH amino acid Sequence | VH SEQ ID NO: | VL name | VL amino acid sequence | VL SEQ ID NO: |
|---|---|---|---|---|---|---|
| m11B6 | m11B6_VH | DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIRQFPGNRLEWMGYISYSGSTTYSPSLKSRFSITRDTSKNQFFLQLNSVTPEDTATYFCATGYYYGSGFWGQGTLVTVSS | 317 | m11B6_VL | DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHWYRQKPGQPPKLLIYAASNVESGVPARFSGSGSGTDFSLNIQPVEEDDFSMYFCQQTRKVPYTFGGGTKLEIK | 318 |
| h11B6 | hu11B6_VH | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVSS | 5 | hu11B6_VL | DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIK | 2 |
| HCF3-LCD6 | HCF3_VH | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTIS | 6 | LCD6_VL | DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTI | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | RDTSKNQFSLKL SSVTPVDTAVY YCATGYYYGSG FWGQGTLVTVS S | | | QSVQAEDVSVYFC QQTRKVPYTFGQG TKLEIK | |
| HCG5-LCB7 | HCG5_V H | QVQLQESGPGL VKPSDTLSLTCA VSGNSITSDYAW NWIRQFPGKGLE WMGYISYSGST TYNPSLKSRVTI SRDTSKNQFSLK LSSVTPVDTAVY YCATGYYYGSG FWGQGTLVTVS S | 4 | LCB7_VL | DIVLTQSPDSLAVS LGERATINCKASE SVEYFGTSLMHW YQQKPGQPPKLLI YAASNRESGVPDR FSGSGSGTDFTLTI SSVQAEDVAVYY CQQTRKVPYTFGQ GTKLEIK | 3 |
| KL2B357 | KL2B357_VH | QVQLQESGPGL VKPSQTLSLTCT VSGNSITSDYAW NWIRQFPGKGLE WIGYISYSGSTT YNPSLKSRVTIS RDTSKNQFSLKL SSVTAADTAVY YCATGYYYGSG FWGQGTLVTVS S | 140 | KL2B357_ VL | DIVLTQSPDSLAVS LGERATINCRASES VEYFGTSLMHWY QQKPGQPPKLLIY AASNVESGVPDRF SGSGSGTDFTLTIS SLQAEDVAVYFCQ QTRKVPYTFGGGT KVEIK | 147 |
| KL2B358 | KL2B358_VH | QVQLQESGPGL VKPSQTLSLTCT VSGNSITSDYAW NWIRQPPGKGLE WIGYISYSGSTT YNPSLKSRVTIS RDTSKNQFSLKL SSVTAADTAVY YCATGYYYGSG FWGQGTLVTVS S | 141 | KL2B358_ VL | EIVLTQSPATLSLS PGERATLSCRASE SVEYFGTSLMHW YQQKPGQPPRLLI YAASNVESGIPAR FSGSGSGTDFTLTI SSVEPEDFAVYFC QQTRKVPYTFGGG TKVEIK | 75 |
| KL2B359 | KL2B359_VH | QVQLQESGPGL VKPSQTLSLTCT VSGNSITSDYAW NWIRQFPGKRLE WIGYISYSGSTT YNPSLKSRVTIS RDTSKNQFSLKL SSVTAADTAVY YCATGYYYGSG FWGQGTLVTVS S | 77 | KL2B359_ VL | EIVLTQSPATLSLS PGERATLSCRASE SVEYFGTSLMHW YQQKPGQPPRLLI YAASNVESGIPAR FSGSGSGTDFTLTI SSVEPEDFAVYFC QQTRKVPYTFGGG TKVEIK | 75 |

| | | | | | | |
|---|---|---|---|---|---|---|
| KL2B360 | KL2B360_VH | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS | 140 | KL2B360_VL | EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK | 75 |
| KL2B413 | KL2B413_VH | EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGHYGMDVWGQGTTVTVSS | 76 | KL2B413_VL | EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK | 74 |
| KL2B30 | KL2B30_VH | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS | 142 | KL2B30_VL | DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK | 148 |
| KL2B53 | KL2B53_VH | EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYYSCARESGWSHYYYYGMDVWGQGTMVTVSS | 143 | KL2B53_VL | DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK | 149 |
| KL2B242 | KL2B242_VH | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYW | 144 | KL2B242_VL | SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVL | 150 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | GWFDPWGQGTLVTVSS | | | | |
| KL2B467 | KL2B467_VH | QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSS | 145 | KL2B467_VL | QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTV | 151 |
| KL2B494 | KL2B494_VH | QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSS | 146 | KL2B494_VL | SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL | 152 |

**Table 5. Kabat HCDR1, HCDR2 and HCDR3 amino acid sequences of selected anti-KLK2 antibodies.**

| | Kabat HCDR1 | | Kabat HCDR2 | | Kabat HCDR3 | |
|---|---|---|---|---|---|---|
| mAb name | Sequence | SEQ ID NO: | Sequence | SEQ ID NO: | Sequence | SEQ ID NO: |
| m11B6 | SDYAWN | 63 | YISYSGSTTYSPSLKS | 64 | GYYYGSGF | 66 |
| hu11B6 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| HCF3-LCD6 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| HCG5-LCB7 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |

| | | | | | | |
|---|---|---|---|---|---|---|
| KL2B357 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| KL2B358 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| KL2B359 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| KL2B360 | SDYAWN | 63 | YISYSGSTTYNPSLKS | 65 | GYYYGSGF | 66 |
| KL2B413 | SYWMT | 314 | NIKQDGSERYYVDSVKG | 315 | DQNYDILTGHYGMDV | 311 |
| KL2B30 | SYYWS | 102 | YIYYSGSTNYNPSLKS | 103 | TTIFGVVTPNFYYGMDV | 104 |
| KL2B53 | SYDIH | 107 | IISYDGSKKDYTDSVKG | 108 | ESGWSHYYYYGMDV | 109 |
| KL2B242 | SYYWS | 102 | RLYVSGFTNYNPSLKS | 112 | DSGNYWGWFDP | 113 |
| KL2B467 | YYGMH | 115 | FISYDGSNKYYADSVKG | 116 | LPYSGSYWAFDY | 117 |
| KL2B494 | HYAMS | 120 | TIGGSGGSTYYADSVKG | 121 | PHIVMVTALLYDGMDV | 122 |

**Table 6. Kabat LCDR1, LCDR2 and LCDR3 amino acid sequences of selected anti-hK2 antibodies.**

| | Kabat LCDR1 | | Kabat LCDR2 | | Kabat LCDR3 | |
|---|---|---|---|---|---|---|
| mAb name | Sequence | SEQ ID NO | Sequence | SEQ ID NO | Sequence | SEQ ID NO |
| m11B6 | RASESVEYFGTSLMH | 67 | AASNVES | 69 | QQTRKVPYT | 71 |
| hu11B6 | KASESVEYFGTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| HCF3-LCD6 | KASESVEYFGTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| HCG5-LCB7 | KASESVEYFGTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| KL2B357 | RASESVEYFGTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B358 | RASESVEYFGTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B359 | RASESVEYFGTSLMH | 67 | AASNVES | 69 | QQTRKVPYT | 71 |
| KL2B360 | RASESVEYFGTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B413 | RASQGISSYLS | 312 | ATSTLQS | 313 | QQLNSYPRT | 91 |
| KL2B30 | RASQGISSYLA | 128 | AASTLQS | 129 | QQLNSYPLT | 130 |

| | | | | | | |
|---|---|---|---|---|---|---|
| KL2B53 | RASQDISNYLA | 125 | AASTLHS | 131 | QKYNSAPYT | 132 |
| KL2B242 | SGDQLGENYAC | 133 | QDSKRPS | 134 | QAWDNSIVV | 135 |
| KL2B467 | GGDNIGSKSVH | 136 | DNSDRPS | 137 | QVWDSSSDHPVV | 138 |
| KL2B494 | GGNNIGSKSVH | 97 | DDSDRPS | 127 | QVWDSSSDHVV | 139 |

**Table 7. AbM HCDR1, HCDR2 and HCDR3 amino acid sequences of selected anti-hK2 antibodies.**

| | AbM HCDR1 | | AbM HCDR2 | | AbM HCDR3 | |
|---|---|---|---|---|---|---|
| mAb name | Sequence | SEQ ID NO: | Sequence | SEQ ID NO | Sequence | SEQ ID NO: |
| m11B6 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| hu11B6 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| HCF3-LCD6 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| HCG5-LCB7 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| KL2B357 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| KL2B358 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| KL2B359 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| KL2B360 | GNSITSDYAWN | 72 | YISYSGSTT | 73 | GYYYGSGF | 66 |
| KL2B413 | GFTFSSYWMT | 309 | NIKQDGSERY | 310 | DQNYDILTGHYGMDV | 311 |
| KL2B30 | GGSISSYYWS | 105 | YIYYSGSTN | 106 | TTIFGVVTPNFYYGMDV | 104 |
| KL2B53 | GFTFSSYDIH | 110 | IISYDGSKKD | 111 | ESGWSHYYYYGMDV | 109 |
| KL2B242 | GGSISSYYWS | 105 | RLYVSGFTN | 114 | DSGNYWGWFDP | 113 |
| KL2B467 | GFTFSYY | 118 | FISYDGSNKY | 119 | LPYSGSYWAFDY | 117 |
| KL2B494 | GFTFSHYAMS | 123 | TIGGSGGSTYY | 124 | PHIVMVTALLYDGMDV | 122 |

**Table 8. AbM LCDR1, LCDR2 and LCDR3 amino acid sequences of selected anti-hK2 antibodies.**

| | AbM LCDR1 | AbM LCDR2 | AbM LCDR3 |
|---|---|---|---|

| mAb name | Sequence | SEQ ID NO: | Sequence | SEQ ID NO | Sequence | SEQ ID NO: |
|---|---|---|---|---|---|---|
| m11B6 | RASESVEYF GTSLMH | 67 | AASNVES | 69 | QQTRKVPYT | 71 |
| hu11B6 | KASESVEYF GTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| HCF3-LCD6 | KASESVEYF GTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| HCG5-LCB7 | KASESVEYF GTSLMH | 68 | AASNRES | 70 | QQTRKVPYT | 71 |
| KL2B357 | RASESVEYF GTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B358 | RASESVEYF GTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B359 | RASESVEYF GTSLMH | 67 | AASNVES | 69 | QQTRKVPYT | 71 |
| KL2B360 | RASESVEYF GTSLMH | 67 | AASNVES | 126 | QQTRKVPYT | 71 |
| KL2B413 | RASQGISSY LS | 312 | ATSTLQS | 313 | QQLNSYPRT | 91 |
| KL2B30 | RASQGISSY LA | 128 | AASTLQS | 129 | QQLNSYPLT | 130 |
| KL2B53 | RASQDISNY LA | 125 | AASTLHS | 131 | QKYNSAPYT | 132 |
| KL2B242 | SGDQLGENY AC | 133 | QDSKRPS | 134 | QAWDNSIVV | 135 |
| KL2B467 | GGDNIGSKS VH | 136 | DNSDRPS | 137 | QVWDSSSDHP VV | 138 |
| KL2B494 | GGNNIGSKS VH | 97 | DDSDRPS | 127 | QVWDSSSDHV V | 139 |

**Table 9. Amino acid sequences and SEQ ID NO summary of the variable domains of selected anti-hK2 antibodies**

| **Antibody** | **Region** | **Amino acid sequence** | **SEQ ID NO:** |
|---|---|---|---|
| m11B6 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYSPSLKS | 64 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | RASESVEYFGTSLMH | 67 |
| | LCDR2 | AASNVES | 69 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (m11B6_VH) | DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDY AWNWIRQFPGNRLEWMGYISYSGSTTYSPSL | 317 |

| | | | |
|---|---|---|---|
| | | KSRFSITRDTSKNQFFLQLNSVTPEDTATYFCA TGYYYGSGFWGQGTLVTVSS | |
| | VL (m11B6_VL) | DIVLTQSPASLAVSLGQRATISCRASESVEYFG TSLMHWYRQKPGQPPKLLIYAASNVESGVPA RFSGSGSGTDFSLNIQPVEEDDFSMYFCQQTR KVPYTFGGGTKLEIK | 318 |
| h11B6 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | KASESVEYFGTSLMH | 68 |
| | LCDR2 | AASNRES | 70 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (hu11B6_VH) | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQPPGKGLEWIGYISYSGSTTYNPSL KSRVTMSRDTSKNQFSLKLSSVTAVDTAVYY CATGYYYGSGFWGQGTLVTVSS | 5 |
| | VL (hu11B6_VL) | DIVLTQSPDSLAVSLGERATINCKASESVEYFG TSLMHWYQQKPGQPPKLLIYAASNRESGVPD RFSGSGSGTDFTLTISSLQAEDVAVYYCQQTR KVPYTFGQGTKLEIK | 2 |
| HCF3-LCD6 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | KASESVEYFGTSLMH | 68 |
| | LCDR2 | AASNRES | 70 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (HCF3_VH) | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWIGYISYSGSTTYNPSL KSRVTISRDTSKNQFSLKLSSVTPVDTAVYYC ATGYYYGSGFWGQGTLVTVSS | 6 |
| | VL (LCD6_VL) | DIVLTQSPDSLAVSLGERATINCKASESVEYFG TSLMHWYQQKPGQPPKLLIYAASNRESGVPD | 1 |

| | | | |
|---|---|---|---|
| | | RFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTR KVPYTFGQGTKLEIK | |
| HCG5-LCB7 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | KASESVEYFGTSLMH | 68 |
| | LCDR2 | AASNRES | 70 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (HCG5_VH) | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWMGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTPVDTAVYY CATGYYYGSGFWGQGTLVTVSS | 4 |
| | VL (LCB7_VL) | DIVLTQSPDSLAVSLGERATINCKASESVEYFG TSLMHWYQQKPGQPPKLLIYAASNRESGVPD RFSGSGSGTDFTLTISSVQAEDVAVYYCQQTR KVPYTFGQGTKLEIK | 3 |
| KL2B357 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 100 or 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | RASESVEYFGTSLMH | 67 |
| | LCDR2 | AASNVES | 126 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (KL2B357_VH) | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDY AWNWIRQFPGKGLEWIGYISYSGSTTYNPSLK SRVTISRDTSKNQFSLKLSSVTAADTAVYYCA TGYYYGSGFWGQGTLVTVSS | 140 |
| | VL (KL2B_357_VL) | DIVLTQSPDSLAVSLGERATINCRASESVEYFG TSLMHWYQQKPGQPPKLLIYAASNVESGVPD RFSGSGSGTDFTLTISSLQAEDVAVYFCQQTR KVPYTFGGGTKVEIK | 147 |
| KL2B358 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |

| | | | |
|---|---|---|---|
| | LICDR1 | RASESVEYFGTSLMH | 67 |
| | LCDR2 | AASNVES | 126 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (KL2B358_VH) | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDY AWNWIRQPPGKGLEWIGYISYSGSTTYNPSLK SRVTISRDTSKNQFSLKLSSVTAADTAVYYCA TGYYYGSGFWGQGTLVTVSS | 141 |
| | VL (KL2B_358_VL) | EIVLTQSPATLSLSPGERATLSCRASESVEYFG TSLMHWYQQKPGQPPRLLIYAASNVESGIPAR FSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKV PYTFGGGTKVEIK | 75 |
| KL2B359 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | RASESVEYFGTSLMH | 67 |
| | LCDR2 | AASNVES | 69 |
| | LCDR3 | QQTRKVPYT | 71 |
| | VH (KL2B359_VH) | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDY AWNWIRQFPGKRLEWIGYISYSGSTTYNPSLK SRVTISRDTSKNQFSLKLSSVTAADTAVYYCA TGYYYGSGFWGQGTLVTVSS | 77 |
| | VL (KL2B_359_VL) | EIVLTQSPATLSLSPGERATLSCRASESVEYFG TSLMHWYQQKPGQPPRLLIYAASNVESGIPAR FSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKV PYTFGGGTKVEIK | 75 |
| KL2B360 | HCDR1 | SDYAWN | 63 |
| | HCDR2 | YISYSGSTTYNPSLKS | 65 |
| | HCDR3 | GYYYGSGF | 66 |
| | LICDR1 | RASESVEYFGTSLMH | 67 |
| | LCDR2 | AASNVES | 69 |
| | LCDR3 | QQTRKVPYT | 71 |

| | | | |
|---|---|---|---|
| | VH (KL2B360_VH) | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS | 140 |
| | VL (KL2B_360_VL) | EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK | 75 |
| KL2B413 | HCDR1 | SYWMT | 314 |
| | HCDR2 | NIKQDGSERYYVDSVKG | 315 |
| | HCDR3 | DQNYDILTGHYGMDV | 311 |
| | LICDR1 | RASQGISSYLS | 312 |
| | LCDR2 | ATSTLQS | 313 |
| | LCDR3 | QQLNSYPRT | 91 |
| | VH (KL2B413_VH) | EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGHYGMDVWGQGTTVTVSS | 76 |
| | VL (KL2B_413_VL) | EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK | 74 |
| KL2B30 | HCDR1 | SYYWS | 102 |
| | HCDR2 | YIYYSGSTNYNPSLKS | 103 |
| | HCDR3 | TTIFGVVTPNFYYGMDV | 104 |
| | LICDR1 | RASQGISSYLA | 128 |
| | LCDR2 | AASTLQS | 129 |
| | LCDR3 | QQLNSYPLT | 130 |
| | VH (KL2B30_VH) | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS | 142 |

| | | | |
|---|---|---|---|
| | VL (KL2B30_VL) | DIQMTQSPSFLSASVGDRVTITCRASQGISSYL AWYQQKPGKAPKFLIYAASTLQSGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQLNSYPLTF GGGTKVEIK | 148 |
| KL2B53 | HCDR1 | SYDIH | 107 |
| | HCDR2 | IISYDGSKKDYTDSVKG | 108 |
| | HCDR3 | ESGWSHYYYYGMDV | 109 |
| | LICDR1 | RASQDISNYLA | 125 |
| | LCDR2 | AASTLHS | 131 |
| | LCDR3 | QKYNSAPYT | 132 |
| | VH (KL2B53_VH) | EVQLVESGGGVVQPGRSLRLSCVASGFTFSSY DIHWVRQAPGKGLEWVAIISYDGSKKDYTDS VKGRFTISRDNSKNTLYLQMDSLRVED SAVY SCARESGWSHYYYYGMDVWGQGTMVTVSS | 143 |
| | VL (KL2B53_VL) | DIVMTQSPSSLSASVGDRVTITCRASQDISNYL AWYQQKPGKVPKFLIYAASTLHSGVPSRFSGS GSGTDFTLTISSLQPEDVATYYCQKYNSAPYT FGQGTRLEIK | 149 |
| KL2B242 | HCDR1 | SYYWS | 102 |
| | HCDR2 | RLYVSGFTNYNPSLKS | 112 |
| | HCDR3 | DSGNYWGWFDP | 113 |
| | LICDR1 | SGDQLGENYAC | 133 |
| | LCDR2 | QDSKRPS | 134 |
| | LCDR3 | QAWDNSIVV | 135 |
| | VH (KL2B242_VH) | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYY WSWLRQPAGSGLEWIGRLYVSGFTNYNPSLK SRVTLSLDPSRNQLSLKLSSVTAADTAVYYCA GDSGNYWGWFDPWGQGTLVTVSS | 144 |
| | VL (KL2B242_VL) | SYELTQPPSVSVSPGETASITCSGDQLGENYAC WYQQKPGQSPVLVIYQDSKRPSGIPERFSGSN SGNTATLTISGTQALDEADYYCQAWDNSIVVF GGGTKLTVL | 150 |
| KL2B467 | HCDR1 | YYGMH | 115 |

| | | | |
|---|---|---|---|
| | HCDR2 | FISYDGSNKYYADSVKG | 116 |
| | HCDR3 | LPYSGSYWAFDY | 117 |
| | LICDR1 | GGDNIGSKSVH | 136 |
| | LCDR2 | DNSDRPS | 137 |
| | LCDR3 | QVWDSSSDHPVV | 138 |
| | VH (KL2B467_VH) | QVQLVESGGGVVQPGRSLRLSCAASGFTFSYY GMHWVRQAPGKGLEWVAFISYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAHLPYSGSYWAFDYWGQGTQVTVSS | 145 |
| | VL (KL2B467_VL) | QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVH WYQQKPGQAPVLVVYDNSDRPSGIPERFSGS NSGTTATLTISRVEAGDEADYYCQVWDSSSD HPVVFGGGTKVTV | 151 |
| KL2B494 | HCDR1 | HYAMS | 120 |
| | HCDR2 | TIGGSGGSTYYADSVKG | 121 |
| | HCDR3 | PHIVMVTALLYDGMDV | 122 |
| | LICDR1 | GGNNIGSKSVH | 97 |
| | LCDR2 | DDSDRPS | 127 |
| | LCDR3 | QVWDSSSDHVV | 139 |
| | VH (KL2B494_VH) | QVQLVESGGGLVQPGGSLRLSCAASGFTFSHY AMSWVRQAPGKGLEWVSTIGGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKPHIVMVTALLYDGMDVWGQGTMVT VSS | 146 |
| | VL (KL2B494_VL) | SSELTQPPSVSVAPGQTARITCGGNNIGSKSVH WYQQKPGQAPVLVVYDDSDRPSGIPERFSGS NSGNTATLTISRVEAGDEADYYCQVWDSSSD HVVFGGGTKLTVL | 152 |

**Table 10. SEQ ID NO: DNA sequences of the VH and VL domains of selected hK2 antibodies.**

| Antibody | VH Protein SEQ ID NO: | VL Protein SEQ ID NO | VH cDNA SEQ ID NO: | VL cDNA SEQ ID NO: |
|---|---|---|---|---|
| m11B6 | 317 | 318 | 320 | 326 |

| | | | | |
|---|---|---|---|---|
| hu11B6 | 5 | 2 | 321 | 327 |
| HCF3-LCD6 | 6 | 1 | 322 | 328 |
| HCG5-LCB7 | 4 | 3 | 323 | 329 |
| KL2B357 | 140 | 147 | 153 | 161 |
| KL2B358 | 141 | 75 | 154 | 162 |
| KL2B359 | 77 | 75 | 324 | 330 |
| KL2B360 | 140 | 75 | 155 | 163 |
| KL2B413 | 76 | 74 | 325 | 331 |
| KL2B30 | 142 | 148 | 156 | 164 |
| KL2B53 | 143 | 149 | 157 | 165 |
| KL2B242 | 144 | 150 | 158 | 166 |
| KL2B467 | 145 | 151 | 159 | 167 |
| KL2B494 | 146 | 152 | 160 | 168 |

**Consensus VH and VL sequences**

**Figure 17A** shows the sequence alignment of the VH domains of mu11B6, hu11B6, KL2B357, KL2B358, KL2B359, KL2B360, HCF3 and HCG5. FIG.2 shows the sequence alignment of the VL domains of mu11B6, hu11B6, KL2B357, KL2B358, KL2B359, KL2B360, LDC6 and LCB7. Consensus amino acid sequence of SEQ ID NO: 344 and SEQ ID NO:345 were determined for the VH and VL domains, respectively. HCDR and LCDR residues are underlined.

**SEQ ID NO: 344**

QVQLQESGPGLVKPS$X_1$TLSLTC$X_2$VSGNSITSDYAWNWIRQ$X_3$PGKGLEW$X_4$GYIS YSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVT$X_5X_6$DTAVYYCATGYYYGSGF WGQGTLVTVSS

Where,

X1 is D or Q;

X2 is A or T;

X3 is P or F;

X4 is I or M;

X5 is A or P; or

X6 is V or A.

**SEQ ID NO: 345**

$X_1$IVLTQSP$X_{2X3}$L$X_4X_5$S$X_6$GERATX$_6$X$_8$C$X_9$ASESVEYFGTSLMHWYQQKPGQPP$X_{10}$ LLIYAASN$X_{11}$ESGX$_{12}$P$X_{13}$RFSGSGSGTDFTLTI$X_{14}$SLQ$X_{15}$EDX$_{16}$AVYX$_{17}$CQQTRKV PYTFG X$_{18}$GTKX19EIK

X1 is D or E;
X2 is D or A;
X3 is S or T;
X4 is A or S;
X5 is V or L;
X6 is L or P;
X7 is I or L;
X8 is N or S;
X9 is R or K;
X10 is K or R;
X11 is V or R;
X12 is V or I;
X13 is A or D;
X14 is Q or S;
X15 is P or A;
X16 is F or V;
X17 is Y or F;
X18 is Q or G; and
X19 is L or V.

**Fab-Fc and scFvs**

The hK2 specific VH/VL regions were engineered as VH-CH1-linker CH2-CH3 and VL-CL and expressed as IgG2 or IgG4 or were engineered as scFvs in either the VH-Linker-VL or VL-linker-VH orientations. The linker that is used in the scFv was the linker of **SEQ ID NO: 7** described above. The scFv were used to generate bispecific antibodies as described in Example 7 or to generated CAR as described in Example 11.

**Table 11** shows the HC amino acid sequences of selected anti-hK2 antibodies in the mAb format. **Table 12** shows the LC amino acid sequences of selected anti-hK2 antibodies in a mAb. **Table 13** summaries the HC and LC DNA SEQ ID NOs of selected anti-hK2 antibodies in the mAb format. **Table 14** shows the amino acid sequences of selected scFvs in VH-linker-VL or VL-linker-VH orientation.

**Table 11. Amino acid sequence of the HC (VH-CH1-linker CH2-CH3 ) of selected anti-hK2antibodies in a mAb format.**

| KLK2 HEAVY CHAIN | HC PROTEIN SEQ ID NO: | HC AMINO ACID SEQUENCE |
|---|---|---|
| m11B6_HC | 332 | DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIR QFPGNRLEWMGYISYSGSTTYSPSLKSRFSITRDTSKNQF FLQLNSVTPEDTATYFCATGYYYGSGFWGQGTLVTVSS AKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTL TWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQ SITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLL GGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQIS WFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDW MSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLP PPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELN YKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSV VHEGLHNHHTTKSFSRTPGK |
| h11B6_HC | 334 | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIR QPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQ FSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK |
| KL2B30_HC | 185 | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQ PPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFS LKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWG QGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE GNVFSCSVMHEALHNHYTQKSLSLSLGK |
| K2B53_HC | 187 | EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVR QAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKN TLYLQMDSLRVEDSAVYSCARESGWSHYYYYGMDVW GQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS |

| | | |
|---|---|---|
| | | QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS<br>VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQ<br>PREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW<br>ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE<br>GNVFSCSVMHEALHNHYTQKSLSLSLGK |
| KL2B242_HC | 189 | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQ<br>PAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQL<br>SLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQGTL<br>VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE<br>PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS<br>SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE<br>AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE<br>VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL<br>HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ<br>VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG<br>QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFS<br>CSVMHEALHNHYTQKSLSLSLGK |
| KL2B467_HC | 191 | QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWV<br>RQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNS<br>KNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYW<br>GQGTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV<br>KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV<br>VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH<br>TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVV<br>SVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR<br>VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA<br>KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA<br>VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR<br>WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK |
| KL2B494_HC | 193 | QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVR<br>QAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSK<br>NTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMD<br>VWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALG<br>CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL<br>SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTC<br>VVVSVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS<br>TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI<br>SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS<br>DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK<br>SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK |

**Table 12. Amino acid sequences of the LC (VL-CL) of selected anti-hK2 antibodies in a mAb (Fab-Fc) format.**

| KLK2 LIGHT CHAIN | LC PROTEIN SEQ ID NO: | LC AMINO ACID SEQUENCE |
|---|---|---|

| | | |
|---|---|---|
| m11B6_LC | 333 | DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHW YRQKPGQPPKLLIYAASNVESGVPARFSGSGSGTDFSLNI QPVEEDDFSMYFCQQTRKVPYTFGGGTKLEIKRADAAP TVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGS ERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRNEC |
| h11B6_LC | 335 | DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHW YQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGEC |
| KL2B30_LC | 186 | DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQK PGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQP EDFATYYCQQLNSYPLTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC |
| KL2B53_LC | 188 | DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQK PGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQP EDVATYYCQKYNSAPYTFGQGTRLEIKRTVAAPSVFIFP PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC |
| KL2B242_LC | 190 | SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKP GQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQA LDEADYYCQAWDNSIVVFGGGTKLTVLGQPKAAPSVTL FPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS |
| KL2B467_LC | 192 | QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKP GQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEA GDEADYYCQVWDSSSDHPVVFGGGTKVTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS |
| KL2B494_LC | 194 | SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKP GQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEA GDEADYYCQVWDSSSDHVVFGGGTKLTVLGQPKAAPS VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS |

**Table 13. SEQ ID Nos of the cDNA sequences of HC and LC of selected hK2 antibodies**

| Antibody | HC Protein SEQ ID NO: | LC Protein SEQ ID NO: | HC cDNA SEQ ID NO: | LC cDNA SEQ ID NO: |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| m11B6 | 332 | 333 | 336 | 337 |
| hu11B6 | 334 | 335 | 338 | 339 |
| KL2B30 | 185 | 186 | 195 | 196 |
| KL2B53 | 187 | 188 | 197 | 198 |
| KL2B242 | 189 | 190 | 199 | 200 |
| KL2B467 | 191 | 192 | 201 | 202 |
| KL2B494 | 193 | 194 | 203 | 204 |

**Table 14. Amino acid sequences of the variable domain of selected anti-hK2 scFvs antibodies in VH-linker-VL (HL) or in VL-linker-VH (LH) format.**

| scFv name | Acronym | Amino acid sequence of scFv | SEQ ID NO: |
|---|---|---|---|
| scFv1 | HCG5_LDC6_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWMGYISYSGSTTYNP SLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY YCATGYYYGSGFWGQGTLVTVSSGGSEGKS SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTIQSV QAEDVSVYFCQQTRKVPYTFGQGTKLEIK | 8 |
| scFv2 | HCG5_hu11B6_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWMGYISYSGSTTYNP SLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY YCATGYYYGSGFWGQGTLVTVSSGGSEGKS SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTISSLQ AEDVAVYYCQQTRKVPYTFGQGTKLEIK | 9 |
| scFv3 | HCF3_hu11B6_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWIGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTPVDTAVYY CATGYYYGSGFWGQGTLVTVSSGGSEGKSS GSGSESKSTGGSDIVLTQSPDSLAVSLGERATI NCKASESVEYFGTSLMHWYQQKPGQPPKLLI YAASNRESGVPDRFSGSGSGTDFTLTISSVQA EDVAVYYCQQTRKVPYTFGQGTKLEIK | 10 |
| scFv4 | HCG5_LCB7_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQFPGKGLEWMGYISYSGSTTYNP SLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY YCATGYYYGSGFWGQGTLVTVSSGGSEGKS SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTISSVQ AEDVAVYYCQQTRKVPYTFGQGTKLEIK | 11 |
| scFv5 | LCD6_HCG5_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF GTSLMHWYQQKPGQPPKLLIYAASNRESGVP | 12 |

| | | | |
|---|---|---|---|
| | | DRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQT<br>RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS<br>TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN<br>SITSDYAWNWIRQFPGKGLEWMGYISYSGST<br>TYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD<br>TAVYYCATGYYYGSGFWGQGTLVTVSS | |
| scFv6 | hu11B6_HCF3_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF<br>GTSLMHWYQQKPGQPPKLLIYAASNRESGVP<br>DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQT<br>RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS<br>TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN<br>SITSDYAWNWIRQFPGKGLEWIGYISYSGSTT<br>YNPSLKSRVTISRDTSKNQFSLKLSSVTPVDT<br>AVYYCATGYYYGSGFWGQGTLVTVSS | 13 |
| scFv7 | hu11B6_HCG5_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF<br>GTSLMHWYQQKPGQPPKLLIYAASNRESGVP<br>DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQT<br>RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS<br>TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN<br>SITSDYAWNWIRQFPGKGLEWMGYISYSGST<br>TYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD<br>TAVYYCATGYYYGSGFWGQGTLVTVSS | 14 |
| scFv8 | LCB7_HCF3_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF<br>GTSLMHWYQQKPGQPPKLLIYAASNRESGVP<br>DRFSGSGSGTDFTLTISSVQAEDVAVYYCQQ<br>TRKVPYTFGQGTKLEIKGGSEGKSSGSGSESK<br>STGGSQVQLQESGPGLVKPSDTLSLTCAVSG<br>NSITSDYAWNWIRQFPGKGLEWIGYISYSGST<br>TYNPSLKSRVTISRDTSKNQFSLKLSSVTPVD<br>TAVYYCATGYYYGSGFWGQGTLVTVSS | 15 |
| scFv9 | LCB7_HCG5_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF<br>GTSLMHWYQQKPGQPPKLLIYAASNRESGVP<br>DRFSGSGSGTDFTLTISSVQAEDVAVYYCQQ<br>TRKVPYTFGQGTKLEIKGGSEGKSSGSGSESK<br>STGGSQVQLQESGPGLVKPSDTLSLTCAVSG<br>NSITSDYAWNWIRQFPGKGLEWMGYISYSGS<br>TTYNPSLKSRVTISRDTSKNQFSLKLSSVTPV<br>DTAVYYCATGYYYGSGFWGQGTLVTVSS | 16 |
| scFv10 | LCD6_HCF3_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF<br>GTSLMHWYQQKPGQPPKLLIYAASNRESGVP<br>DRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQT<br>RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS<br>TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN<br>SITSDYAWNWIRQFPGKGLEWIGYISYSGSTT<br>YNPSLKSRVTISRDTSKNQFSLKLSSVTPVDT<br>AVYYCATGYYYGSGFWGQGTLVTVSS | 17 |
| scFv11 | hu11B6_LCB7_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD<br>YAWNWIRQPPGKGLEWIGYISYSGSTTYNPS<br>LKSRVTMSRDTSKNQFSLKLSSVTAVDTAVY<br>YCATGYYYGSGFWGQGTLVTVSSGGSEGKS | 18 |

| | | | |
|---|---|---|---|
| | | SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTISSVQ AEDVAVYYCQQTRKVPYTFGQGTKLEIK | |
| scFv12 | hu11B6_LCD6_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQPPGKGLEWIGYISYSGSTTYNPS LKSRVTMSRDTSKNQFSLKLSSVTAVDTAVY YCATGYYYGSGFWGQGTLVTVSSGGSEGKS SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTIQSV QAEDVSVYFCQQTRKVPYTFGQGTKLEIK | 19 |
| scFv13 | hu11B6_HL | QVQLQESGPGLVKPSDTLSLTCAVSGNSITSD YAWNWIRQPPGKGLEWIGYISYSGSTTYNPS LKSRVTMSRDTSKNQFSLKLSSVTAVDTAVY YCATGYYYGSGFWGQGTLVTVSSGGSEGKS SGSGSESKSTGGSDIVLTQSPDSLAVSLGERA TINCKASESVEYFGTSLMHWYQQKPGQPPKL LIYAASNRESGVPDRFSGSGSGTDFTLTISSLQ AEDVAVYYCQQTRKVPYTFGQGTKLEIK | 20 |
| scFv14 | LCD6_hu11B6_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF GTSLMHWYQQKPGQPPKLLIYAASNRESGVP DRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQT RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN SITSDYAWNWIRQPPGKGLEWIGYISYSGSTT YNPSLKSRVTMSRDTSKNQFSLKLSSVTAVD TAVYYCATGYYYGSGFWGQGTLVTVSS | 21 |
| scFv15 | hu11B6_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF GTSLMHWYQQKPGQPPKLLIYAASNRESGVP DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQT RKVPYTFGQGTKLEIKGGSEGKSSGSGSESKS TGGSQVQLQESGPGLVKPSDTLSLTCAVSGN SITSDYAWNWIRQPPGKGLEWIGYISYSGSTT YNPSLKSRVTMSRDTSKNQFSLKLSSVTAVD TAVYYCATGYYYGSGFWGQGTLVTVSS | 22 |
| scFv16 | LCB7_hu11B6_LH | DIVLTQSPDSLAVSLGERATINCKASESVEYF GTSLMHWYQQKPGQPPKLLIYAASNRESGVP DRFSGSGSGTDFTLTISSVQAEDVAVYYCQQ TRKVPYTFGQGTKLEIKGGSEGKSSGSGSESK STGGSQVQLQESGPGLVKPSDTLSLTCAVSG NSITSDYAWNWIRQPPGKGLEWIGYISYSGST TYNPSLKSRVTMSRDTSKNQFSLKLSSVTAV DTAVYYCATGYYYGSGFWGQGTLVTVSS | 23 |
| scFv17 | KL2B413_HL | EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMTWVRQAPGKGLEWVANIKQDGSERYY VDSVKGRFTISRDNAKNSLYLQMNSLRAEDT | 340 |

| | | | |
|---|---|---|---|
| | | AVYYCARDQNYDILTGHYGMDVWGQGTTV TVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPS FLSASVGDRVTITCRASQGISSYLSWYQQKPG KAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLT ISSLQPEDFATYYCQQLNSYPRTFGQGTKVEI K | |
| scFv18 | KL2B413_LH | EIVLTQSPSFLSASVGDRVTITCRASQGISSYL SWYQQKPGKAPKLLIYATSTLQSGVPSRFSGS GSGTEFTLTISSLQPEDFATYYCQQLNSYPRT FGQGTKVEIKGGSEGKSSGSGSESKSTGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYW MTWVRQAPGKGLEWVANIKQDGSERYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDQNYDILTGHYGMDVWGQGTTVTV SS | 341 |
| scFv19 | KL2B359_HL | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSD YAWNWIRQFPGKRLEWIGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTAADTAVYY CATGYYYGSGFWGQGTLVTVSSGGSEGKSS GSGSESKSTGGSEIVLTQSPATLSLSPGERATL SCRASESVEYFGTSLMHWYQQKPGQPPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK | 342 |
| scFv20 | KL2B359_LH | EIVLTQSPATLSLSPGERATLSCRASESVEYFG TSLMHWYQQKPGQPPRLLIYAASNVESGIPA RFSGSGSGTDFTLTISSVEPEDFAVYFCQQTR KVPYTFGGGTKVEIKGGSEGKSSGSGSESKST GGSQVQLQESGPGLVKPSQTLSLTCTVSGNSI TSDYAWNWIRQFPGKRLEWIGYISYSGSTTY NPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS | 343 |
| scFv21 | KL2B357_HL | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSD YAWNWIRQFPGKGLEWIGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTAADTAVYY CATGYYYGSGFWGQGTLVTVSSGGSEGKSS GSGSESKSTGGSDIVLTQSPDSLAVSLGERATI NCRASESVEYFGTSLMHWYQQKPGQPPKLLI YAASNVESGVPDRFSGSGSGTDFTLTISSLQA EDVAVYFCQQTRKVPYTFGGGTKVEIK | 169 |
| scFv22 | KL2B357_LH | DIVLTQSPDSLAVSLGERATINCRASESVEYF GTSLMHWYQQKPGQPPKLLIYAASNVESGVP DRFSGSGSGTDFTLTISSLQAEDVAVYFCQQT RKVPYTFGGGTKVEIKGGSEGKSSGSGSESKS TGGSQVQLQESGPGLVKPSQTLSLTCTVSGN SITSDYAWNWIRQFPGKGLEWIGYISYSGSTT YNPSLKSRVTISRDTSKNQFSLKLSSVTAADT AVYYCATGYYYGSGFWGQGTLVTVSS | 170 |
| scFv23 | KL2B358_HL | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSD YAWNWIRQPPGKGLEWIGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTAADTAVYY | 171 |

| | | | |
|---|---|---|---|
| | | CATGYYYGSGFWGQGTLVTVSSGGSEGKSS GSGSESKSTGGSEIVLTQSPATLSLSPGERATL SCRASESVEYFGTSLMHWYQQKPGQPPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK | |
| scFv24 | KL2B358_LH | EIVLTQSPATLSLSPGERATLSCRASESVEYFG TSLMHWYQQKPGQPPRLLIYAASNVESGIPA RFSGSGSGTDFTLTISSVEPEDFAVYFCQQTR KVPYTFGGGTKVEIKGGSEGKSSGSGSESKST GGSQVQLQESGPGLVKPSQTLSLTCTVSGNSI TSDYAWNWIRQPPGKGLEWIGYISYSGSTTY NPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS | 172 |
| scFv25 | KL2B360_HL | QVQLQESGPGLVKPSQTLSLTCTVSGNSITSD YAWNWIRQFPGKGLEWIGYISYSGSTTYNPS LKSRVTISRDTSKNQFSLKLSSVTAADTAVYY CATGYYYGSGFWGQGTLVTVSSGGSEGKSS GSGSESKSTGGSEIVLTQSPATLSLSPGERATL SCRASESVEYFGTSLMHWYQQKPGQPPRLLI YAASNVESGIPARFSGSGSGTDFTLTISSVEPE DFAVYFCQQTRKVPYTFGGGTKVEIK | 173 |
| scFv26 | KL2B360_LH | EIVLTQSPATLSLSPGERATLSCRASESVEYFG TSLMHWYQQKPGQPPRLLIYAASNVESGIPA RFSGSGSGTDFTLTISSVEPEDFAVYFCQQTR KVPYTFGGGTKVEIKGGSEGKSSGSGSESKST GGSQVQLQESGPGLVKPSQTLSLTCTVSGNSI TSDYAWNWIRQFPGKGLEWIGYISYSGSTTY NPSLKSRVTISRDTSKNQFSLKLSSVTAADTA VYYCATGYYYGSGFWGQGTLVTVSS | 174 |
| scFv27 | KL2B30_HL | QVQLQESGPGLVKPSETLSLTCTVSGGSISSY YWSWIRQPPGKGLEWIGYIYYSGSTNYNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYY CAGTTIFGVVTPNFYYGMDVWGQGTTVTVS SGGSEGKSSGSGSESKSTGGSDIQMTQSPSFL SASVGDRVTITCRASQGISSYLAWYQQKPGK APKFLIYAASTLQSGVPSRFSGSGSGTEFTLTI SSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK | 175 |
| scFv28 | KL2B30_LH | DIQMTQSPSFLSASVGDRVTITCRASQGISSYL AWYQQKPGKAPKFLIYAASTLQSGVPSRFSG SGSGTEFTLTISSLQPEDFATYYCQQLNSYPLT FGGGTKVEIKGGSEGKSSGSGSESKSTGGSQV QLQESGPGLVKPSETLSLTCTVSGGSISSYYW SWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSR VTISVDTSKNQFSLKLSSVTAADTAVYYCAG TTIFGVVTPNFYYGMDVWGQGTTVTVSS | 176 |
| scFv29 | KL2B53_HL | EVQLVESGGGVVQPGRSLRLSCVASGFTFSS YDIHWVRQAPGKGLEWVAIISYDGSKKDYT DSVKGRFTISRDNSKNTLYLQMDSLRVEDSA VYSCARESGWSHYYYYGMDVWGQGTMVT VSSGGSEGKSSGSGSESKSTGGSDIVMTQSPS | 177 |

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|---|---|---|---|
| | | SLSASVGDRVTITCRASQDISNYLAWYQQKP GKVPKFLIYAASTLHSGVPSRFSGSGSGTDFT LTISSLQPEDVATYYCQKYNSAPYTFGQGTR LEIK | |
| scFv30 | KL2B53_LH | DIVMTQSPSSLSASVGDRVTITCRASQDISNY LAWYQQKPGKVPKFLIYAASTLHSGVPSRFS GSGSGTDFTLTISSLQPEDVATYYCQKYNSAP YTFGQGTRLEIKGGSEGKSSGSGSESKSTGGS EVQLVESGGGVVQPGRSLRLSCVASGFTFSS YDIHWVRQAPGKGLEWVAIISYDGSKKDYT DSVKGRFTISRDNSKNTLYLQMDSLRVEDSA VYSCARESGWSHYYYYGMDVWGQGTMVT VSS | 178 |
| scFv31 | KL2B242_HL | QVQLQESGPGLVKPSETLSLTCTVSGGSISSY YWSWLRQPAGSGLEWIGRLYVSGFTNYNPS LKSRVTLSLDPSRNQLSLKLSSVTAADTAVY YCAGDSGNYWGWFDPWGQGTLVTVSSGGS EGKSSGSGSESKSTGGSSYELTQPPSVSVSPG ETASITCSGDQLGENYACWYQQKPGQSPVLV IYQDSKRPSGIPERFSGSNSGNTATLTISGTQA LDEADYYCQAWDNSIVVFGGGTKLTVL | 179 |
| scFv32 | KL2B242_LH | SYELTQPPSVSVSPGETASITCSGDQLGENYA CWYQQKPGQSPVLVIYQDSKRPSGIPERFSGS NSGNTATLTISGTQALDEADYYCQAWDNSIV VFGGGTKLTVLGGSEGKSSGSGSESKSTGGS QVQLQESGPGLVKPSETLSLTCTVSGGSISSY YWSWLRQPAGSGLEWIGRLYVSGFTNYNPS LKSRVTLSLDPSRNQLSLKLSSVTAADTAVY YCAGDSGNYWGWFDPWGQGTLVTVSS | 180 |
| scFv33 | KL2B467 HL | QVQLVESGGGVVQPGRSLRLSCAASGFTFSY YGMHWVRQAPGKGLEWVAFISYDGSNKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDT AVYYCAHLPYSGSYWAFDYWGQGTQVTVS SGGSEGKSSGSGSESKSTGGSQSVLTQPPSVS VAPGQTASITCGGDNIGSKSVHWYQQKPGQ APVLVVYDNSDRPSGIPERFSGSNSGTTATLTI SRVEAGDEADYYCQVWDSSSDHPVVFGGGT KVTV | 181 |
| scFv34 | KL2B467 LH | QSVLTQPPSVSVAPGQTASITCGGDNIGSKSV HWYQQKPGQAPVLVVYDNSDRPSGIPERFSG SNSGTTATLTISRVEAGDEADYYCQVWDSSS DHPVVFGGGTKVTVGGSEGKSSGSGSESKST GGSQVQLVESGGGVVQPGRSLRLSCAASGFT FSYYGMHWVRQAPGKGLEWVAFISYDGSNK YYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCAHLPYSGSYWAFDYWGQGTQVT VSS | 182 |
| scFv35 | KL2B494_HL | QVQLVESGGGLVQPGGSLRLSCAASGFTFSH YAMSWVRQAPGKGLEWVSTIGGSGGSTYYA DSVKGRFTISRDNSKNTLYLQMNSLRAEDTA | 183 |

| | | | |
|---|---|---|---|
| | | VYYCAKPHIVMVTALLYDGMDVWGQGTMV TVSS<br>GGSEGKSSGSGSESKSTGGSSSELTQPPSVSV APGQTARITCGGNNIGSKSVHWYQQKPGQAP VLVVYDDSDRPSGIPERFSGSNSGNTATLTIS RVEAGDEADYYCQVWDSSSDHVVFGGGTKL TVL | |
| scFv36 | KL2B494_LH | SSELTQPPSVSVAPGQTARITCGGNNIGSKSV HWYQQKPGQAPVLVVYDDSDRPSGIPERFSG SNSGNTATLTISRVEAGDEADYYCQVWDSSS DHVVFGGGTKLTVLGGSEGKSSGSGSESKST GGSQVQLVESGGGLVQPGGSLRLSCAASGFT FSHYAMSWVRQAPGKGLEWVSTIGGSGGST YYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCAKPHIVMVTALLYDGMDVWGQG TMVTVSS | 184 |

**Example 12. Biophysical characterization of anti-hK2 antibodies**

**Affinity and thermal stability of anti-hK2 antibodies.**

Affinity of selected hK2 antibodies for soluble hK2 was measured by surface plasmon resonance (SPR). SPR is a label-free technique to study the strength of an interaction between two binding partners by measuring the change in mass upon complex formation and dissociation. Antibodies were captured on a sensor chip coated with an anti-Fc antibody followed by injection of soluble hK2 at various concentrations and specified association and dissociation times. Post dissociation, the surface was regenerated with an appropriate solution to prepare for the next interaction. Kinetic information (on-rate and off-rate constants) were extracted by fitting sensorgrams to the 1:1 Langmuir model. Binding affinity ($K_D$) are reported as the ratio of rate constants ($k_{off}/k_{on}$). $K_D$ values of selected hK2 antibodies are listed in **Table 15.**

Thermal stability was determined by Differential Scanning Fluorimetry (NanoDSF) using an automated Prometheus instrument. NanoDSF was used to measure $T_m$ of molecules at a concentration of 0.5 mg/mL in Phosphate Buffered Saline, pH 7.4. Measurements were made by loading samples into 24 well capillary from a 384 well sample plate. Duplicate runs were performed for each sample. The thermal scans span from 20°C to 95°C at a rate of 1.0°C/minute. Intrinsic tryptophan and tyrosine fluorescence were monitored at the

emission wavelengths of 330 nm and 350 nm, and the F350/F330 nm ratio were plotted against temperature to generate unfolding curves. Measured Tm values are listed in **Table 15**.

**Table 15. $K_D$ and Tm of selected molecules**

| Molecule | $K_D$ (nM) | Tm (°C) |
|---|---|---|
| KL2B413 (scFv) | 34.3 | 67 |
| KL2B359 (scFv) | 0.7 – 1 | 67 |
| KL2B30 (Fab) | 0.460 | >70 |
| KL2B242 (Fab) | 0.040 | >70 |
| KL2B53 (Fab) | 0.080 | >70 |
| KL2B467 (Fab) | 0.078 | >70 |
| KL2B494 (Fab) | 0.053 | >70 |

KL2B413 scFv generated from the Ablexis immunization campaign had a thermal stability (Tm) of 67°C as measured by Nano DSF and a binding affinity ($K_D$) to human hK2 of about 34 nM. Clone KL2B359 obtained for the re-humanization campaign and which had maintained a binding affinity similar to murine 11B6 was converted to scFv-Fc and CAR-T for additional profiling. KL2B359 scFv shows a Tm of 67°C and a binding affinity ($K_D$) to hK2 of ~0.7 – 1nM. KL2B30, KL2B242, KL2B53, KL2B467 and KL2B494 Fab showed binding affinities below 0.5 nM and Tm values above 70°C.

**Epitope mapping**

The epitope on selected KL2B antibodies was determined by hydrogen-deuterium exchange mass spectrometry (HDX-MS). Human KLK2 antigen was used for epitope mapping experiment.

Briefly, purified the KLK2 antigen was incubated with and without anti-KLK2 antibodies in deuterium oxide labeling buffer. The hydrogen-deuterium exchange (HDX) mixture

was quenched at different time point by the addition of 8 M urea, 1M TCEP, pH 3.0. The quenched sample was passed over an immobilized pepsin/FPXIII column at 600 µL/min equilibrated with buffer A (1% acetonitrile, 0.1% FA in H2O) at room temperature. Peptic fragments were loaded onto a reverse phase trap column at 600 µL/min with buffer A and desalted for 1 min (600 µL buffer A). The desalted fragments were separated by a C18 column with a linear gradient of 8% to 35% buffer B (95% acetonitrile, 5% H2O, 0.0025% TFA) at 100 µL/min over 20 min and analyzed by mass spectrometry. Mass spectrometric analyses were carried out using an LTQ™ Orbitrap Fusion Lumos mass spectrometer (Thermo Fisher Scientific) with the capillary temperature at 275 °C, resolution 150,000, and mass range (m/z) 300 – 1,800. BioPharma Finder 3.0 (Thermo Fisher Scientific) was used for the peptide identification of non-deuterated samples prior to the HDX experiments. HDExaminer version 2.5 (Sierra Analytics, Modesto, CA) was used to extract centroid values from the MS raw data files for the HDX experiments.

Incubation of hK2 antibodies, hu11B6, KL2B494, KL2B467, KL2B30, KL2B413 and KL2B53 with soluble hK2 protein resulted in different patterns of hydrogen exchange and overall protection. The protected segments were mapped onto the sequence of hK2 antigen to visualize the binding epitopes (**Figure 17B**). KL2B494, KL2B467 and KL2B30 bound to a common sequence consisting of residues 173-178 (**SEQ ID NO: 346**, KVTEF) and residue 230-234 (**SEQ ID NO: 347**, HYRKW). KL2B53 showed a different pattern of protection and bound to a sequence consisting of residues 27-32 (Seq ID NO: **348**, SHGWAH), 60-75 (**SEQ ID NO: 349**, RHNLFEPEDTGQRVP) and 138-147 (**SEQ ID NO: 350**, GWGSIEPEE).

**Example 13. Generation and characterization of additional scFvs CAR constructs**

The ectodomain of 11B6 cloned as scFv did not retain binding at elevated temperature (55°C) and hence additional campaigns were initiated to generate new humanized antibodies from the parental 11B6.

hK2 CARs containing thermally stabilized scFvs derived from the antibody 11B6 were generated. The description and SEQ ID NOs: of the CAR constructs containing thermally

stabilized scFvs are provided in **Table 16**. The names in the description refer back to the VH or the VL chains identified above, 20AA refers to the 20 amino acid long linker between the VH/VL pairs in the scFv. The scFv in the CARs were cloned in either VH-L-VL or VL-L-VH orientation.

The generated scFvs KL2B413_HL, KL2B413_LH, KL2B359_HL and KL2B359_LH were also incorporated into CAR constructs and further characterized. **Table 16** shows the generated CAR constructs and their SEQ ID NOs. The signal sequence used was MAWVWTLLFLMAAAQSIQA (SEQ ID NO: 24)

**Table 16.**

| Name of CAR construct | Description of scFv in the CAR | SEQ ID NO: of scFv amino acid sequence I the CAR | SEQ ID NO: of full ECD domain of CAR (including signal sequence) | SEQ ID NO: of CAR amino acid sequence |
|---|---|---|---|---|
| CAR1 | HL_HCG5_LCD6_20AA (scFv1) | 8 | 273 | 46 |
| CAR2 | HL_HCG5_LCh11B6_20AA (scFv2) | 9 | 274 | 47 |
| CAR3 | HL_HCF3_LCB7_20AA (scFv3) | 10 | 275 | 48 |
| CAR4 | HL_HCG5_LCB7_20AA (scFv4) | 11 | 276 | 49 |
| CAR5 | LH_LCD6_HCG5_20AA (scFv5) | 12 | 277 | 50 |
| CAR6 | LH_LCHumanized_HCF3_20AA (scFv6) | 13 | 278 | 51 |
| CAR7 | LH_LCHumanized_HCG5_20AA (scFv7) | 14 | 279 | 52 |
| CAR8 | LH_LCB7_HCF3_20AA (scFv8) | 15 | 280 | 53 |
| CAR9 | LH_LCB7_HCG5_20AA (scFv9) | 16 | 281 | 54 |
| CAR10 | LH_LCD6_HCF3_20AA (scFv10) | 17 | 282 | 55 |
| CAR11 | HL_HCHumanized_LCB7_20AA (scFv11) | 18 | 283 | 56 |
| CAR12 | HL_HCHumanized_LCD6_20AA (scFv12) | 19 | 284 | 57 |
| CAR13 | HL_HCHumanized_LCHumanized_20AA (scFv13) | 20 | 285 | 58 |
| CAR14 | LH_LCD6_HCHumanized_20AA (scFv14) | 21 | 286 | 59 |
| CAR15 | LH_LCHumanized_HCHumanized_20AA (scFv15) | 22 | 287 | 60 |

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|---|---|---|---|---|
| CAR16 | LH_LCB7_HCHumanized_20AA (scFv16) | 23 | 288 | 61 |
| CAR17 | KL2B413_HL (scFv17) | 340 | 289 | 82 |
| CAR18 | KL2B413_LH (scFv18) | 341 | 290 | 83 |
| CAR19 | KL2B359_HL (scFv19) | 342 | 291 | 84 |
| CAR20 | KL2B359_LH (scFv20) | 343 | 292 | 85 |
| CAR21 | KL2B357 HL (scFv21) | 169 | 319 | 205 |
| CAR22 | KL2B357 LH (scFv22) | 170 | 320 | 206 |
| CAR23 | KL2B358 HL (scFv23) | 171 | 321 | 207 |
| CAR24 | KL2B358 LH (scFv24) | 172 | 322 | 208 |
| CAR25 | KL2B360 HL (scFv25) | 173 | 323 | 209 |
| CAR26 | KL2B360 LH (scFv26) | 174 | 324 | 210 |
| CAR27 | KL2B30 HL (scFv27) | 175 | 325 | 211 |
| CAR28 | KL2B30 LH (scFv28) | 176 | 326 | 212 |
| CAR29 | KL2B53 HL (scFv29) | 177 | 327 | 213 |
| CAR30 | KL2B53 LH (scFv30) | 178 | 328 | 214 |
| CAR31 | KL2B242 HL (scFv31) | 179 | 329 | 215 |
| CAR32 | KL2B242 LH (scFv32) | 180 | 330 | 216 |
| CAR33 | KL2B467 HL (scFv33) | 181 | 331 | 217 |
| CAR34 | KL2B467 LH (scFv34) | 182 | 332 | 218 |
| CAR35 | KL2B494 HL (scFv35) | 183 | 333 | 219 |
| CAR36 | KL2B494 LH (scFv36) | 184 | 334 | 220 |
| LCHumanized refers to hu11B6_VL.<br>HCHumanized refers to hu11B6_VH | | | | |

**Example 14: Identification of different scFv-based CAR with antigen-independent activation via Jurkat-Lucia™ NFAT cells.**

Nuclear factor of activated T-cells (NFAT) is a family of transcription factors first identified as a regulator of immune cells. Without wishing to be bound by theory, T cell activation leads to calcium influx, which activates calcineurin that dephosphorylates serine rich nuclear localization signal at the N-terminus of NFAT, leading to nuclear import of NFAT. Tonic signaling due to scFv clustering could be subsequently detected by Firefly luciferase driven by NFAT promoter in JNL reporter cell line.

Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed JNL cells), were transduced with the various CAR constructs. Binding between the CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. Novel hK2 KL2B413 and rehumanized 11B6 CAR

clones were evaluated in the JNL reporter assay for antigen-dependent activity according to the following protocol.

Lentiviral transduction was performed as follows. JNL cells were harvested and resuspended to 1E6/ml. 500 µl JNL cells and lentiviral virus at MOI of 3 were added, and mixed by pipetting up and down. The mixture was placed in the 37°C incubator for 24 hours. Then, 500 µl of JNL media was added to each well. Culturing was continued in the 37°C incubator. The cells were transferred to a T25 flask on day 4. At day 5-6, transduction validation was performed. 150 µl of cells was harvested to examine CAR expression via appropriate detection reagent for the specific CAR of interest (e.g. biotin-hK2 Protein is used to detect hK2 CAR). The JNL cells were maintained at $5x10^5$/ml until there were enough cells to freeze down or use for the JNL assay described below.

A JNL assay was performed as follows. Co-culture with target cell lines was undertaken at the effector to target ratio of 2:1. JNL cells were spun down to remove any secreted luciferase in the medium, and resuspended in fresh media at $4x10^5$/ml. The JNL cells were harvested. Both antigen positive and antigen negative target cell lines were prepared at 2E5/ml. Then, 100 µl JNL was added to 100 µl target cells. For the JNL only control, 100 µl of media was added instead of target cells. For the positive control, JNL cells only or CAR JNL cells were added to 1x Cell Stimulation Cocktail, and incubated in a 37°C incubator for 24 hours. 150 µl of supernatant was harvested into a 96-well plate and centrifuged to remove cells. 100 µl of supernatant was transferred from the plate to a solid bottom black plate, followed by addition of 100 µl QUANTI-luc lucia detection reagent and incubation at room temperature for 5 minutes before reading with Envision multiplate reader.

Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed JNL cells) were transduced with various hK2 CAR constructs. Expression was determined by biotinylated hK2 followed by streptavidin-conjugated PE. The data are shown in **Figure 12A**. CAR expression in transduced JNL cells was confirmed for the selected clones, with 46–50% of cells expression on rehumanized 11B6 KL2B359 CARs and 73.7-96% of cells on KL2B413 CARs.

The data in **Figure 12B** shows that binding between the hK2 CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. JNL cells containing the indicated CAR clones and JNL cells (UTD) were co-cultured with target cells lines (VCap, LNCap/Hk2, LNCap, C4-2B, 22Rv1 or DU145 cells) and luciferase activity was measured as luminescence intensity. Clones were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells. No antigen-dependent activation was found for the novel KL2B413 and rehumanized 11B6 HL&LH CARs.

**Example 15: HK2 CAR-T cells were evaluated in the real-time IncuCyte killing assay for antigen-dependent cytotoxicity.**

HK2 CAR-T cells were co-incubated with HK2+ VCaP cells and HK2- DU145 cells for 96 hours. The effector-to-target (ET) ratio was calculated based on CAR expression data shown in **Figures 11A-11B**. Target cells were stably expressing a red nuclear dye, which was measured by IncuCyte imaging system in a real-time fashion. The data is shown in **Figure 13A** for HK2 CAR-T cells co-incubated with HK2+ VCaP cells, and in **Figure 13B** for HK2 CAR-T cells co-incubated with HK2- DU145 cells. In these figures, tumor cell growth inhibition (%) = (Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Example 16. Characterization of CAR-T cells transduced with KL2B413_HL, KL2B413_LH, KL2B359_HL or KL2B359_LH.**

**Activation of CAR-T cells is antigen-dependent**

The generated CAR-T cells were evaluated in the JNL reporter assay for antigen-dependent activity as described in Example 4. Briefly, Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed JNL cells) were transduced with CAR17 (KL2B413_HL), CAR18 (KL2B413_LH), CAR19 (KL2B359_HL) or CAR20 (KL2B359_LH) constructs. Expression of each CAR was determined by biotinylated hK2 followed by streptavidin-conjugated PE. CAR expression in transduced JNL cells was confirmed for the selected clones with 46–50% of cells expressing KL2B359-based CARs and 73.7-96% of cells expressing KL2B413-based CARs as shown in **Figure 6**. The percent JNL cells expressing each CAR was following: KL2B413_HL: 73.7%, KL2B413_LH: 93.6%, KL2B359_HL: 46%, KL2B359_LH: 50.8%.

Binding between the hK2 CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. To that end, JNL cells transduced with the test CAR constructs or untransduced JNL cells (UTD) were co-cultured with target cells lines (VCap, LNCap/hK2 (LNCaP cells recombinantly expressing hK2), LNCaP, C4-2B, 22Rv1 or DU145 cells) and luciferase activity was measured as luminescence intensity. Constructs were considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells. No antigen-dependent activation was found for the tested CAR constructs. **Figure 13A** shows the RLU (relative light units) resulting from binding of CAR-T cells to test target cells ad indicated in the Figure.

**CAR-T cells produce cytokines upon antigen stimulation**

IFN-γ produced by cytotoxic T cells is critical for exerting immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*. To determine whether hK2 CAR-modified human T cells were able to recognize and become activated by hK2 positive tumor cells, primary T cells transduced with indicated CAR clones and control untransduced T cells (UTD) were co-cultured with target cells lines (LNCaP/hK2, LNCaP, C4-2B, 22Rv1 or DU145 cells)

and supernatant were collected for IFN-γ concentration measurement. As shown in **Figure 14**, CAR-T cells transduced with hK2 CARs cells secreted IFN-γ during co-culture with LNCaP cells recombinantly expressing hK2 (LNCap/hK2) cells and also during co-culture with very low hK2-expressing C4-2B and LNCap cells but not hK2-negative DU145 cells. Mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures is shown in **Figure 14**.

**CAR-T cells proliferate in antigen-dependent manner**

CAR-T cells were evaluated for their proliferation using T-cell proliferation assay protocol described in Example 4. hK2 CAR-T and untransduced (UTD) T cells were labelled with CellTrace Violet(CTV; 5μM) and co-cultured with hK2 positive VCap and hK2 negative DU145 cells. Five days post co-culture, cells were harvested and stained with CD3, CD25, NearIR live/dead Dye and hK2 CAR. Flow cytometric analysis was performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes were identified by live CD3, and the frequencies of CAR-T cells with CTV dye dilution and activation marker CD25 were determined. By gating on CD3+ T cells, the hK2 positive Vcap cells but not hK2 negative DU145 cells promoted proliferation of each tested CAR-T cell line, as shown in **FIGS. 10C, 10D, and 10E,** and upregulation of activation marker CD25 as shown in **Figure 11B** and **Figure 12A**. T cells only without any stimulation did not proliferate and CD3/28 beads stimulated T cells displayed equivalent proliferation pattern. hK2 CAR+ T cells proliferated more robustly than CD3/28 beads positive control after 5 days of coculture with VCap cells. Different tested CAR-T cells had different proliferation activity and displayed different CAR-T cells counts. The percentage of proliferating T cells and CD25 expressing T cells was based on mean absolute cell count +/- SEM from duplicate.

**Example 17: Th1 cytokine IFN-gamma production of antigen-stimulated CAR-T Cells.**

Without wishing to be bound by theory, IFN-γ produced by cytotoxic T cells is critical for exerting immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*.

To determine whether hK2 CAR-modified human T cells were able to recognize and activated by hK2 (+) tumor cells, primary T cells containing the indicated CAR clones and control untransduced T cells (UTD) were co-cultured with target cells lines (LNCap/Hk2, LNCap, C4-2B, 22Rv1 or DU145 cells) and supernatant were collected for IFN-g concentration measurement. The data are shown in **Figure 14** as the mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures. As shown, hK2 CAR modified T cells secrete IFN-gamma during co-culture with hK2-expressing LNCap/hK2 cells, even very low Hk2 expressing C4-2B and LNCap cells but not hK2-negative DU145 cells. Undisclosed control CAR secreted a much higher amount of IFN- γ due to the much higher antigen expression level than hK2.

**Example 18: CD107a Degranulation assay to evaluate hK2 CAR T cells' antitumor activity.**

Without wishing to be bound by theory, tumor cells can be recognized and killed by cytotoxic lymphocytes, such as CD8+ T lymphocytes and natural killer (NK) cells, mainly through the immune secretion of lytic granules that kill target cells. This process involves the fusion of the granule membrane with the cytoplasmic membrane of the immune effector cell, resulting in surface exposure of lysosomal-associated proteins that are typically present on the lipid bilayer surrounding lytic granules, such as CD107a. Therefore, membrane expression of CD107a constitutes a marker of immune cell activation and cytotoxic degranulation.

The degranulation assay was performed as follows. Target cells ($5 \times 10^4$) were cocultured with an equal number of effector cells in 0.1ml per well in a 96-well plate. Control wells contained T cells alone. Anti-CD107a (5µl per well) was added in addition to 1µl/sample of monensin (BD Biosciences), followed by incubation for 4 hours at 37°C. Cells were

washed two times with PBS, stained for expression of the hK2 CAR, CD3, and CD8 and analyzed on a flow cytometer BD Fortessa. The data are shown in **Figure 15**.

As shown, the presence of hK2 antigen on Vcap cells leads to an increase in CD107A+ hK2 CAR(+) T cells, but not in hK2 CAR(-) and UTD T cells measured by flow cytometry. Only the background staining(<2%) was seen in the CAR T cells without tumor cell stimulation. Phorbol 12-myristate 13-acetate (PMA) in combination with ionomycin (eBioscience™ Cell Stimulation Cocktail; 500X) was a consistent inducer of CD107a cell surface expression in this 4-hour cell culture model, which was used as a positive control. The results shown in **Figure 15** are for representative donor T cells and are reproducible in multiple donors.

**Example 19: T-cell proliferation is an important *in vitro* parameter of *in vivo* immune function.**

To further evaluate the function of novel KL2B413 and rehumanized 11B6 (KL2B359) CAR T cells and to assist in picking the top candidate construct, CAR T cells were labeled with CellTrace™ Violet (CTV; 5uM) for the T cells proliferation assay. The following protocol was followed, with the results shown in **Figures 16A-16D**.

Tumor cells Vcap and DU145 were collected and washed twice with PBS. The cells were resuspended in 10E6/ml in PBS containing 100ug/ml Mitomycin C (MMC) for 1.5 hours in a 37°C incubator to block proliferation of tumor cells. 20 µL DMSO was added to a vial of CTV staining solution. Then, 5 µl of solution was diluted into 5mL (1:1000) of PBS (warmed to 37°C) to yield a 5 µM staining solution. 2E6 T cells were counted and collected, washed with PBS twice, and then resuspended in 4E6/ml (0.5ml). An equal volume (0.5 ml) of CTV staining solution was added. The cells were incubated for 20 minutes at 37°C. After 20 minutes, 4 ml PRMI+20% FBS was added to the cells to absorb any unbound dye, and the cells were incubated for 5 minutes. The cells were centrifuged for 5 minutes at 400 x g, followed by resuspension of the cell pellet in pre-warmed RPMI+10%FBS medium. The T cells were counted, and1E5 cells(100µl) were seeded in a 96-well flat bottom-plate.

In the meantime, MMC treated tumor cells hK2(+) VCap and HK2(-) DU145 were collected and counted post 1.5 hours, and then resuspended in 1E6/ml. 1E5 cells (100µl) were co-cultured with T cells in 96-well plate. T cells alone and T cells added in a 3:1 CD3/28 beads to cells ratio were used as negative and positive controls, respectively. After five days of co-culture, all the cells were collected from each well. The cells were centrifuged and washed for 5 minutes at 400 x g twice, and stained with hK2CAR, CD3, CD8 and CD25, live/dead (Near-IR) in 96-well U bottom plate. After washing, all cells were fixed for 10 minutes using BD Cytofix™ Fixation Buffer (50µl FACS buffer + 50µl Fixation Buffer) in 100µl. Stained samples were analyzed by multicolor flow cytometry after the end of the incubation period.

Flow cytometric analysis was performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes were identified by live CD3, and the frequencies of CAR+T cells with CTV dye dilution and activation marker CD25 were determined.

To prepare a CTV histogram, the CTV undiluted gate was set to encompass the far-right peak (CTV bright) of T cells cultured alone, and the CTV diluted gate to capture the rest of the population. This setting was applied to all samples. A statistic was added to include absolute # of cells in the CTV diluted population. A table was created with this statistic, followed by export of data (cell counts) to Excel for reformatting before transferring to Prism.

**Figures 16A-16D** show the results of a hK2 CAR T cell proliferation assay. By gating on CD3+ T cells, as shown in **Figures 16A-16B**, the hK2(+) Vcap cells but not hK2(-) DU145 cells promoted the proliferation of all CAR constructs engineered T cells and upregulation of activation marker CD25, as shown in **Figures 16C-16D**. CD3/28 beads stimulated T cells were used as positive controls, and T cells only were used as negative controls. T cells only without any stimulation do not proliferate and CD3/28 beads stimulated T cells displayed equivalent proliferation pattern. As shown, hK2 CAR+ T cells proliferate more robustly than the CD3/28 beads positive control after 5 days of coculture with VCap cells. Different CAR construct-engineered T cells have different proliferation activity and displayed different CAR+ T cells counts. The summary of percentage of

proliferating T cells and CD25 expressing T cells based on mean absolute cell count +/- SEM from duplicate is shown in **Figures 16B** and **16D**.

**Example 20: Construction and expression of hK2 scFv CARs**

hK2 CAR constructs comprising the following scFv sequences are constructed:

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| **KL2B357 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTY<br>NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG<br>SEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQ<br>KPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTF<br>GGGTKVEIK<br>(SEQ ID NO: 221) |
| **KL2B357 LH:**<br><br>DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNVES<br>GVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSG<br>SGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWI<br>GYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ<br>GTLVTVSS<br>(SEQ ID NO: 222) |
| **KL2B358 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTY<br>NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG<br>SEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQK<br>PGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGG<br>TKVEIK<br>(SEQ ID NO: 223) |

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| **KL2B358 LH:**<br><br>EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESG IPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSGSG SESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGY ISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT LVTVSS<br>(SEQ ID NO: 224) |
| **KL2B360 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTY NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG SEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQK PGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGG TKVEIK<br>(SEQ ID NO: 225) |
| **KL2B360 LH:**<br><br>EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESG IPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSGSG SESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGY ISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT LVTVSS<br>(SEQ ID NO: 226) |
| **KL2B30 HL:**<br><br>QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGT TVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSFLSASVGDRVTITCRASQGISSYLAW |

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| YQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPL TFGGGTKVEIK<br>(SEQ ID NO: 227) |
| **KL2B30 LH:**<br><br>DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK GGSEGKSSGSGSESK STGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGS TNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVW GQGTTVTVSS<br>(SEQ ID NO: 228) |
| **KL2B53 HL:**<br><br>EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGSKKD YTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGMDVWGQG TMVTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPSSLSASVGDRVTITCRASQDISNYLA WYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSA PYTFGQGTRLEIK<br>(SEQ ID NO: 229) |
| **KL2B53 LH:**<br><br>DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPS RFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSEGKSSGSGSES KSTGGSEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISY DGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGM DVWGQGTMVTVSS<br>(SEQ ID NO: 230) |
| **KL2B242 HL:** |

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| QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGFTNYN<br>PSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQGTLVTVS<br>SGGSEGKSSGSGSESKSTGGSSYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKP<br>GQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGG<br>GTKLTVL<br>(SEQ ID NO: 231) |
| **KL2B242 LH:**<br><br>SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGIPERF<br>SGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGSEGKSSGSGSES<br>KSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVS<br>GFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQG<br>TLVTVSS<br>(SEQ ID NO: 232) |
| **KL2B467 HL:**<br><br>QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYDGSNK<br>YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGT<br>QVTVSSGGSEGKSSGSGSESKSTGGSQSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHW<br>YQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSS<br>SDHPVVFGGGTKVTV<br>(SEQ ID NO: 233) |
| **KL2B467 LH:**<br><br>QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPER<br>FSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVGGSEGKSSGSG<br>SESKSTGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVA<br>FISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF<br>DYWGQGTQVTVSS<br>(SEQ ID NO: 234) |

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| **KL2B494 HL:**<br><br>QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGSGGST<br>YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVW<br>GQGTMVTVSSGGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQTARITCGGNNIGSKS<br>VHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQV<br>WDSSSDHVVFGGGTKLTVL<br>(SEQ ID NO: 235) |
| **KL2B494 LH:**<br><br>SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPER<br>FSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGGSEGKSSGSG<br>SESKSTGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVS<br>TIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL<br>YDGMDVWGQGTMVTVSS<br>(SEQ ID NO: 236) |

The hK2 CAR constructs comprised the following sequences:

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| **KL2B357 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTY<br>NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG<br>SEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQ<br>KPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTF<br>GGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPL<br>AGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR<br>VKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL<br>YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 205) |

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| **KL2B357 LH:**<br><br>DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNVES<br>GVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSG<br>SGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWI<br>GYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQ<br>GTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLA<br>GTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRV<br>KFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY<br>NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 206) |
| **KL2B358 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTY<br>NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG<br>SEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQK<br>PGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGG<br>TKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT<br>CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF<br>SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE<br>LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 207) |
| **KL2B358 LH:**<br><br>EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESG<br>IPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSGSG<br>SESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGY<br>ISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT<br>LVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT<br>CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF |

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| SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE<br>LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 208) |
| **KL2B360 HL:**<br><br>QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTY<br>NPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSSGG<br>SEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQK<br>PGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGG<br>TKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT<br>CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF<br>SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE<br>LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 209) |
| **KL2B360 LH:**<br><br>EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESG<br>IPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGSEGKSSGSG<br>SESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGY<br>ISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT<br>LVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT<br>CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKF<br>SRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE<br>LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 210) |
| **KL2B30 HL:**<br><br>QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYN<br>PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGT<br>TVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSFLSASVGDRVTITCRASQGISSYLAW |

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| YQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPL TFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWA PLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCE LRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE GLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 211) |
| **KL2B30 LH:**<br><br>DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSR FSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK GGSEGKSSGSGSESK STGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGS TNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVW GQGTTVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 212) |
| **KL2B53 HL:**<br><br>EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGSKKD YTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGMDVWGQG TMVTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPSSLSASVGDRVTITCRASQDISNYLA WYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSA PYTFGQGTRLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC ELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 213) |
| **KL2B53 LH:** |

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| DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPS<br>RFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSEGKSSGSGSES<br>KSTGGSEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISY<br>DGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYGM<br>DVWGQGTMVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY<br>IWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEG<br>GCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN<br>PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP<br>PR<br>(SEQ ID NO: 214) |
| **KL2B242 HL:**<br><br>QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGFTNYN<br>PSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQGTLVTVS<br>SGGSEGKSSGSGSESKSTGGSSYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKP<br>GQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGG<br>GTKLTVLTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG<br>TCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVK<br>FSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN<br>ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR<br>(SEQ ID NO: 215) |
| **KL2B242 LH:**<br><br>SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGIPERF<br>SGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGSEGKSSGSGSES<br>KSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVS<br>GFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQG<br>TLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAG<br>TCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVK<br>FSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN<br>ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR |

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| (SEQ ID NO: 216) |
| **KL2B467 HL:**<br><br>QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYDGSNK YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGT QVTVSSGGSEGKSSGSGSESKSTGGSQSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHW YQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSS SDHPVVFGGGTKVTVTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDI YIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEE GGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR<br>(SEQ ID NO: 217) |
| **KL2B467 LH:**<br><br>QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPER FSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVGGSEGKSSGSG SESKSTGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVA FISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF DYWGQGTQVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYI WAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNP QEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP R<br>(SEQ ID NO: 218) |
| **KL2B494 HL:**<br><br>QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGSGGST YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVW GQGTMVTVSSGGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQTARITCGGNNIGSKS |

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| VHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQV<br>WDSSSDHVVFGGGTKLTVLTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD<br>FACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP<br>EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP<br>RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM<br>QALPPR<br>(SEQ ID NO: 219) |
| **KL2B494 LH:**<br><br>SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPER<br>FSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGGSEGKSSGSG<br>SESKSTGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVS<br>TIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL<br>YDGMDVWGQGTMVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDF<br>ACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFP<br>EEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP<br>RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM<br>QALPPR<br>(SEQ ID NO: 220) |

Dynabeads Human T-Expander CD3/CD28 stimulated T cells are subjected to electroporation, then washed three times with OPTI-MEM (Invitrogen), and resuspended in OPTI-MEM at the final concentration of 50E6/ml. Subsequently, 0.1 ml of the cells (5E6) are mixed with 10ug of IVT CAR encoding RNA and electroporated in a 2-mm Gap cuvette (Harvard Apparatus BTX, Holliston, MA, USA) using BTX ECM830 (Harvard Apparatus BTX, Holliston, MA, USA) by pressing the "pulse" button one time. (Settings: 500 Volts, 750 µsec Pulse Length and single(1) pulse, 100mSec interval.) Post electroporation, the T cells are transferred to a 6-well plate and immediately put back into a 37°C incubator. Primary human T cells are electroporated with no mRNA (MOCK) or 10µg of mRNA expressing either the hK2 scFv CAR or irrelevant control CAR. 24 hours post-

electroporation CAR surface expression is measured by flow cytometry following staining with 2 μg/ml biotinylated L-protein and streptavidin-conjugated PE, or biotinylated hK2 (1 μg/ml) and streptavidin-conjugated PE.

Twenty-four hours post electroporation, the T cells are counted. 1E5 T cells are collected for each. The cells are washed with FACS buffer twice using 200 μL/well of FACS buffer for microtiter plates, with the supernatant discarded. All wells are stained with 100 μl staining buffer containing Protein L (Genscript, Cat. No. M000971:500;2ug/ml), and incubated for at least 30 minutes at 4°C while being protected from light. The cells are washed by adding FACS Buffer twice, using 150 μL/well for microtiter plates with FACS buffer. Centrifugation at 400x g is performed for 4 minutes at room temperature. The supernatant is then discarded. All wells are stained with 100 μl Streptavidin-R-Phycoerythrin (SA-PE;1:250) and Live/dead Fixable Near-IR Dead Cell Stain dye (1:1000), incubated for at least 30 minutes at 4°C while being protected from light. The cells are then ready for flow cytometry analysis.

Observation of protein L staining is seen for the hK2 CARs, whereas only the background staining (~5.5%) is seen in the control T cells that were T cells without mRNA electroporation. CAR expression on primary human T cells also can be detected via J&J internal biotin-labeled recombinant KLK2 protein followed by SA-PE. As shown, T cells efficiently express hK2 CARs as measured by flow cytometry, whereas only the background staining is seen in the control T cells that are T cells without mRNA electroporation or undisclosed control CAR (non-hK2 specific).

**Example 21: Tumor cell killing by hK2 CAR-T cells**

Co-culture for CellTrace Violet (CTV, Thermo Fisher Scientific Catalog number: C34557) based cytotoxicity assay using flow cytometer is performed as follows.

The T cells are prepared as follows. Twenty-four hours post EP, T cells are counted and resuspended at the concentration needed for the most concentrated/desired E:T. The T cells are added at 100 μl/well of assay ($2x10^6$ cells/ml; plated 100 μl in a 10:1 E:T ratio, i.e., 2E5 T cells per 2E4 target cells). A stock of the 10:1 E:T concentration is made, with

two-fold serial dilutions made with complete T cell media (Optimizer w/CTS, 5% Human Serum, 1% GlutaMax) to 0.3125:1. The T cells are plated (100ul/well) in triplicate using a 96 well round bottom tissue culture treated plate.

CTV labeled target cells are prepared as follows. 20 µL DMSO is added to a vial of CTV staining solution. This stock solution is diluted into 20 mL of PBS (warmed to 37°C) for a 5 µM staining solution. 10E6 tumor cells are collected, washed with PBS twice and resuspended in 4E6/ml (2.5ml). An equal volume (2.5ml) of CTV staining solution is added. The cells are incubated for 20 minutes in a 37°C incubator. 40 ml PRMI+20% FBS are added to the cells to absorb any unbound dye. The cells are incubated for 5 minutes. The cells are centrifuged for 5 minutes at 400 x g. The cell pellet is resuspended in pre-warmed RPMI+10%FBS medium. In the meantime, T cells are seeded at the desired E/T ratio described above. hK2+ tumor cell lines and a hK2- tumor cell line are recounted, and then the cells are resuspended in 2E5/ml and 100ul in duplicate. The cells are co-incubated with labelled tumor cell lines in a flat-bottom 96-well plate.

A cytotoxicity assay is performed as follows using a flow cytometer. After 20 hours of co-culture, all of the cells are transferred to a U-bottom 96-well plate and washed. After 20 hours of co-culture all of the cells are collected from a flat-bottom 96-well plate and transferred to a U-bottom 96-well plate, and then washed. 30 µl of 0.25% trypsin is added to all the wells and incubated for 5 minutes in a 37°C incubator. After 5 minutes, all of the tumor cells are collected to a U-bottom 96-well plate. The cells are centrifuged and washed for 5 minutes at 400 x g twice. The cell pellet is then resuspended in diluted (1:1000) LIVE/DEAD™ Fixable Near-IR staining dye (100 µl). The cells are incubated for 30 mins at 4 °C, and washed with FACS buffer twice by centrifuging the cells for 5 minutes at 400 x g. After washing, all of the cells are fixed for 10 minutes using 100 µl of BD Cytofix™ Fixation Buffer (50ul FACS buffer +50ulFixation Buffer). The cells are centrifuged and washed for 5 minutes at 400 x g once. The cell pellet is resuspended in FACS buffer. Stained samples are analyzed by multicolor flow cytometry after the end of the incubation period. The percentage of cytotoxic activity is calculated using the following equation:

% specific death = % Near IR+CTV+(dead) cells - % spontaneous Near IR +CTV+ / (100% - % spontaneous Near IR +CTV+ (dead) cells) x 100%.

Twenty-four hours after transient transfection, target cells (hK2positive Vcap and hK2 negative DU145 cells) are labeled with Cell Trace Violet (CTV) fluorescent dye and then co-cultured with hK2 CAR-T cells. Mock T cells serve as negative effector controls. Cells are co-cultured for 20 hours at the effector-to-target cell (E/T) ratios ranging from 0.3125:1 to 10:1. The percent killing is measured as the ratio of the absolute number of live (viability dye negative) target (CTV positive) cells remaining in the co-culture relative to the number of live target cells cultured without CAR-T cells. As shown, hK2 CAR T cells specifically and efficiently lyse the hK2(+) human cancer cell lines, but not hK2(-) cells at E/T ratios of 10:1 to 0.3125:1, whereas only the background cytotoxicity is seen in the T cells that were Mock or hK2 CAR.

hK2 CAR-T cells are also tested for real-time cytotoxicity using xCELLigence as a real-time cell analysis system as a potency assay for immune cell-mediated cytolysis of target cells.

50 µL of target cancer cell culturing media is added to each well of the 96-well E-Plates (ACEA Biosciences), and the background impedance is measured and displayed as a Cell Index. Then, adherent target cells hK2(+) and hK2(-) are dissociated and seeded at a density of 5E4 (VCap), 5E3 cells/well of the E-Plate in a volume of 100 µL, and allowed to passively adhere on the electrode surface. Post seeding, the E-Plate is kept at ambient temperature inside a laminar flow hood for 30 minutes and then transferred to the RTCA MP instrument inside a cell culture incubator. Data recording is initiated immediately at 15-minute intervals for the entire duration (96 hours) of the experiment.

At the time treatment is applied (24 hours post cancer cells seeding), data acquisition is paused, 50 µL of media is removed from each well, and effector CAR-T cells are added at different effector to target (E:T) ratios in a volume of 50 µL. hK2(+) CAR-T and undisclosed control CAR (non- hK2 specific) T cells are resuspended. Two-fold dilutions are then performed in duplicate in a 96-well plate (from 5:1 to 0.156:1 E/T ratio). Target plus Mock effector controls (no RNA electroporation T cells) are also added to the target cells.

Target cells hK2(+) and hK2(-) are incubated with Mock, 10µg mRNA electroporated (24 hours post transfection) into hK2(+) and hK2(-) CAR-T cells at different E/T ratios for approximately 72 hours. Normalized cell index (CI) plots for hK2(+) and hK2(-) are generated. When seeded alone, target cells adhered to the plate and proliferated, increasing the CI readout.

**Example 22: Cytokine production by hK2 CAR-T cells**

IFN-γ produced by cytotoxic T cells allows for exertion of immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*. To determine whether hK2 CAR-T cells are able to recognize and be activated by hK2 (+) tumor cells, the supernatant was collected from xCELLigence-based killing assay, as described in Example 21. After about 70 hours co-culture, the supernatant was collected and assayed by ELISA according to the directions provided with the ELISA kit (Human IFN-γ ELISA MAX™ Deluxe, BioLegend, Cat#:430106).

IFN-γ production of antigen-stimulated CAR-T cells occurs. hK2 CAR and control CAR-T cells secreted IFN-γ during co-culture with hK2-expressing cells in an E:T ratio-dependent manner, but not during co-culture with hK2-negative cells. Undisclosed control CAR secreted much higher amount of IFN- γ due to the much higher antigen expression level than hK2.

**Example 21: Tumor cell killing by hK2 CAR-T cells**

hK2 CAR-T cells are evaluated in the real-time IncuCyte tumor killing assay for antigen-dependent cytotoxicity. hK2 CAR-T cells are co-incubated with target cells for 88 hours at effector:target ratio of 1:1 or 0.5:1 which was calculated based on CAR expression data. Target cells are identified that are stably expressing a red nuclear dye as measured by IncuCyte imaging system in a real-time fashion. The following calculation is performed: Tumor cell growth inhibition (%) = (Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%).

**Example 22: Cytokine production by hK2 CAR-T cells**

Supernatant is collected from overnight (approximately 20 hours) co-culture of hK2CAR-T cells with cells at 1:1 of E/T ratio and was analyzed using 13-plex Milliplex Human High Sensitivity T cell kit (HSTCMAG28SPMX13). hK2 CAR modified T cells secreted cytokines during co-culture with hK2-expressing cells, but minimal for un-transduced T cells (UTD). The results of cytokine release by hK2 CAR-T cells.

Supernatant was collected from overnight (approximately 20 hours) co-culture of hK2 CAR-T cells with cells at 1:1 of E/T ratio. hK2 CAR-T cells secreted IFN-γ during co-culture with hK2-expressing cells, but not during co-culture with hK2-negative cells. CD3/28 beads stimulated T cells and T cells only were used as positive and negative controls, respectively. IFN-γ release by hK2 CAR-T cells. Mean IFN-γ concentration ± SD (pg/ml) from duplicate cultures is shown. Different thermally stabilized CAR-T cells produced different amount of IFN- γ when co-culture with hK2 (+) cells.

**Example 23: Proliferation of hK2 CAR-T cells**

hK2 CAR-T cells are evaluated in a proliferation assay. T-cell proliferation is an important *in vitro* parameter of *in vivo* immune function. To further evaluate the function of hK2 CAR-T cells, the hK2 CAR -T cells are labeled with CTV to assess T cells proliferation.

hK2 CAR-T and un-transduced (UTD) T cells are labelled with CellTrace Violet (CTV; 5μM) and co-cultured with hK2(+) and hK2(-) cells. Five days post co-culture, cells are harvested and stained with CD3, CD25, NearIR live/dead Dye and hK2 CAR. Flow cytometric analysis is performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes are identified by live CD3, and the frequencies of CAR-T cells with CTV dye dilution and activation marker CD25 are determined. By gating on hK2 CAR+ T cells, as shown, the hK2 (+) cells but not hK2 (-) cells promote the all CAR constructs. CD3/28 beads stimulated T cells and T cells only are used as positive and negative controls, respectively. T cells only without any stimulation do not proliferate and CD3/28 beads stimulated T cells displayed equivalent proliferation pattern. hK2CAR-T cells proliferated more robustly than CD3/28 beads positive control after 5 days of co-culture with cells. Different CAR constructs engineered T cells have different proliferation activity and

displayed different CAR-T cells counts. The CAR-T cells counts are based on mean absolute cell count +/- SEM from three technical replicates.

The protocol is performed as follows. The tumor cells are collected, washed twice with PBS, and resuspended in 10E6/ml in PBS containing 100ug/ml Mitomycin C (MMC) for 1.5 hours in a 37°C incubator so as to block tumor cells proliferation. 20 µL of DMSO is added to a vial of CTV staining solution. 5 µl of the solution is diluted into 5mL (1:1000) PBS (warmed to 37°C) to provide a 5 µM staining solution. The 2E6 T cells are counted, collected, washed with PBS twice, and resuspended in 4E6/ml (0.5ml). An equal volume (0.5 ml) of CTV staining solution is added. The cells are incubated for 20 minutes at 37°C. Then, 4 ml PRMI+20% FBS is added to the cells to absorb any unbound dye. The cells are incubated for 5 minutes, and centrifuged for 5 minutes at 400 x g. The cell pellet is resuspended in pre-warmed RPMI+10%FBS medium. The T cells are counted, and 1E5 cells (100ul) are seeded in 96-wells flat bottom-plate.

In the meantime, MMC-treated tumor cells are collected and counted after 1.5 hours, and then resuspended at 1E6/ml. 1E5 of the cells (100 µl) are cocultured with T cells in a 96-well plate. T cells alone, and T cells added 3:1 CD3/28 beads to cells ratio, are used as negative and positive controls, respectively.

After 5 days of co-culture, all of the cells are collected from each well. The cells are centrifuged and washed for 5 minutes at 400 x g twice, then stained hK2 CAR, CD3, CD8 and CD25, live/dead (Near-IR) in 96-well U bottom plate. After washing, all cells are fixed for 10 minutes using 100 µl BD Cytofix™ Fixation Buffer (50ul FACS buffer +50ulFixation Buffer). The stained samples are analyzed by multicolor flow cytometry after the end of the incubation period.

Data analysis is performed as follows. A CTV histogram is prepared. The CTV undiluted gate is set to encompass the far-right peak (CTV bright) of T cells cultured alone, and the CTV diluted gate to capture the rest of the population. This is applied to all samples.

**Example 24: Characterization of CAR-T cells transduced with various constructs described herein.**

The generated CAR-T cells are evaluated in the JNL reporter assay for antigen-dependent activity. Briefly, Jurkat cells containing the luciferase gene driven by the signaling-responsive NFAT promoter (termed JNL cells) are transduced with any construct comprising one or more nucleic acid sequences of SEQ ID NOS: 153-160, 161-168, 195-204, 320-325, 326-331, and 336-339.

Alternatively, the construct may comprise a nucleic acid sequence encoding:

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

Expression of each CAR is determined by biotinylated hK2 followed by streptavidin-conjugated PE.

Binding between the hK2 CAR construct and its cognate cellular antigen (hK2 on target cells) leads to luciferase expression in the JNL cells. To that end, JNL cells transduced with the test CAR constructs or untransduced JNL cells (UTD) are co-cultured with target tumor cell lines and luciferase activity was measured as luminescence intensity. Constructs are considered active when the luminescence intensity exceeded 1.5-fold the level of UTD cells in the presence of antigen-expressing cells.

**CAR-T cells mediate tumor cell killing in antigen-dependent manner**

CAR-T cells are transduced with CAR17, CAR18, CAR19 and CAR20 are co-incubated with hK2 positive cells and hK2 negative cells for 96 hours at effector-to-target (ET) ratio of 1:1 or 0.5:1 which was calculated based on CAR expression on T cells. Target cells stably express a red nuclear dye, which is measured by IncuCyte imaging system in a real-time fashion. Tumor cell growth inhibition (TGI) (%) = (Initial Viable Target Cell Number-Current Viable Target Cell Number)/Initial Viable Cell Number*100 (%). Tested CAR-T cells may achieve approximately 100% TGI whereas the untransduced control may

not demonstrate any TGI. No TGI may be observed with the tested CAR-T cells in hK2 negative cells.

**CAR-T cells produce cytokines upon antigen stimulation**

IFN-γ produced by cytotoxic T cells is critical for exerting immune surveillance of tumors, which can directly inhibit proliferation and induce apoptosis of some malignancies *in vivo* and *in vitro*. To determine whether hK2 CAR-modified human T cells are able to recognize and become activated by hK2 positive tumor cells, primary T cells are transduced with indicated CAR clones and control untransduced T cells (UTD) were co-cultured with target cells lines and supernatant were collected for IFN-γ concentration measurement. CAR-T cells transduced with hK2 CARs cells secrete IFN-γ during co-culture with LNCaP cells recombinantly express hK2 cells and also during co-culture with very low hK2-expressing cells but not hK2-negative cells.

**CAR-T cells are activated and upregulate markers of degranulation in antigen-dependent manner**

Tumor cells can be recognized and killed by cytotoxic lymphocytes, such as CD8+ T lymphocytes and natural killer (NK) cells mainly through the immune secretion of lytic granules that kill the target tumor cells. This process involves the fusion of the granule membrane with the cytoplasmic membrane of the immune effector cell, resulting in surface exposure of lysosomal-associated proteins that are typically present on the lipid bilayer surrounding lytic granules, such as CD107a. Therefore, membrane expression of CD107a constitutes a marker of immune cell activation and cytotoxic degranulation.

The degranulation assay is performed as described below. Target cells ($5 \times 10^4$) are co-cultured with an equal number of effector cells in 0.1ml per well in a 96-well plate. Control wells contained T cells alone. Anti-CD107a (5µl per well) are added in addition to 1µl/sample of monensin (BD Biosciences) and incubated for 4 hours at 37°C. Cells are washed two times with PBS, stained for expression of the hK2 CAR, CD3, and CD8 and analyzed on a flow cytometer BD Fortessa.

**hK2 CAR-T cells proliferate in antigen-dependent manner**

CAR-T cells are evaluated for their proliferation using T-cell proliferation assay protocol described in Example 23. hK2 CAR-T and untransduced (UTD) T cells are labelled with CellTrace Violet(CTV; 5μM) and co-cultured with hK2 positive and hK2 negative cells. Five days post co-culture, cells are harvested and stained with CD3, CD25, NearIR live/dead Dye and hK2 CAR. Flow cytometric analysis is performed on a Fortessa flow cytometer with Flowjo software. Lymphocytes are identified by live CD3, and the frequencies of CAR-T cells with CTV dye dilution and activation marker CD25 were determined. The percentage of proliferating T cells and CD25 expressing T cells is based on mean absolute cell count +/- SEM from duplicate.

The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

While example embodiments have been particularly shown and described, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the embodiments encompassed by the appended claims.

SEQUENCE LISTING

**SEQ ID NO: 1 - VL 1 (LCD6)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 2 - VL 2 (LCHumanized)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 3 - VL 3 (LCB7)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 4 - VH 1 (HCG5)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSS

**SEQ ID NO: 5 - VH 2 (HCHumanized)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSS

**SEQ ID NO: 6 - VH 3 (HCF3)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGT
LVTVSS

**SEQ ID NO: 7 - Linker sequence**

GGSEGKSSGSGSESKSTGGS

**SEQ ID NO: 8 - scFV 1 (HL_HCG5_LCD6_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 9 - scFV 2 (HL_HCG5_LCHumanized_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 10 - scFV 3 (HL_HCF3_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDV
AVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 11 - scFV 4 (HL_HCG5_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 12 - scFV 5 (LH_LCD6_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 13 - scFV 6 (LH_LCHumanized_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 14 - scFV 7 (LH_LCHumanized_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 15 - scFV 8 (LH_LCB7_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 16 - scFV 9 (LH_LCB7_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW

IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 17 - scFV 10 (LH_LCD6_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 18 - scFV 11 (HL_HCHumanized_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 19 - scFV 12 (HL_HCHumanized_LCD6_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 20 - scFV 13 (HL_HCHumanized_LCHumanized_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 21 - scFV 14 (LH_LCD6_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 22 - scFV 15 (LH_LCHumanized_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 23 - scFV 16 (LH_LCB7_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG

GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 24 - Signal sequence**

MAWVWTLLFLMAAAQSIQA

**SEQ ID NO: 25 - CD8a-hinge**

TSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

**SEQ ID NO: 26 - CD8a-TM**

IYIWAPLAGTCGVLLLSLVITLYC

**SEQ ID NO: 27 - CD137**

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

**SEQ ID NO: 28 - CD3zeta**

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM
QALPPR

**SEQ ID NO: 29 - Extracellular antigen-binding domain 1 (HL_HCG5_LCD6_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 30 - Extracellular antigen-binding domain 2 (HL_HCG5_LCHumanized_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 31 - Extracellular antigen-binding domain 3 (HL_HCF3_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDV
AVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 32 - Extracellular antigen-binding domain 4 (HL_HCG5_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 33 - Extracellular antigen-binding domain 5 (LH_LCD6_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 34 - Extracellular antigen-binding domain 6 (LH_LCHumanized_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 35 - Extracellular antigen-binding domain 7 (LH_LCHumanized_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG

GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 36 - Extracellular antigen-binding domain 8 (LH_LCB7_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 37 - Extracellular antigen-binding domain 9 (LH_LCB7_HCG5_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 38 - Extracellular antigen-binding domain 10 (LH_LCD6_HCF3_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 39 - Extracellular antigen-binding domain 11**
**(HL_HCHumanized_LCB7_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 40 - Extracellular antigen-binding domain 12**
**(HL_HCHumanized_LCD6_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 41 - Extracellular antigen-binding domain 13**
**(HL_HCHumanized_LCHumanized_20AA)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 42 - Extracellular antigen-binding domain 14 (LH_LCD6_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 43 - Extracellular antigen-binding domain 15 (LH_LCHumanized_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 44 - Extracellular antigen-binding domain 16 (LH_LCB7_HCHumanized_20AA)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 45 - Intracellular signaling domain**

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYK
QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM
AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 46 - CAR 1 (HL_HCG5_LCD6_20AA; pDR000083431)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 47 - CAR 2 (HL_HCG5_LCHumanized_20AA; pDR000083432)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 48 - CAR 3 (HL_HCF3_LCB7_20AA; pDR000083436)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDV
AVYYCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 49 - CAR 4 (HL_HCG5_LCB7_20AA; pDR000083437)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYS
GSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 50 - CAR 5 (LH_LCD6_HCG5_20AA; pDR000083438)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 51 - CAR 6 (LH_LCHumanized_HCF3_20AA; pDR000083440)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 52 - CAR 7 (LH_LCHumanized_HCG5_20AA; pDR000083441)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG

AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 53 - CAR 8 (LH_LCB7_HCF3_20AA; pDR000083443)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 54 - CAR 9 (LH_LCB7_HCG5_20AA; pDR000083444)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 55 - CAR 10 (LH_LCD6_HCF3_20AA; pDR000083446)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTAVY
YCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 56 - CAR 11 (HL_HCHumanized_LCB7_20AA; pDR000083433)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAED
VAVYYCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 57 - CAR 12 (HL_HCHumanized_LCD6_20AA; pDR000083434)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG

TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAED
VSVYFCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 58 - CAR 13 (HL_HCHumanized_LCHumanized_20AA; pDR000083435)**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQG
TLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCKASESVE
YFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAED
VAVYYCQQTRKVPYTFGQGTKLEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 59 - CAR 14 (LH_LCD6_HCHumanized_20AA; pDR000083439)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV

QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 60 - CAR 15 (LH_LCHumanized_HCHumanized_20AA; pDR000083442)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 61 - CAR 16 (LH_LCB7_HCHumanized_20AA; pDR000083445)**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNW
IRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAV
YYCATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPV
QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 62 – human Kallikrein-2 sequence (signal sequence: amino acids 1-18)**

MWDLVLSIALSVGCTGAVPLIQSRIVGGWECEKHSQPWQVAVYSHGWAHCGGV
LVHPQWVLTAAHCLKKNSQVWLGRHNLFEPEDTGQRVPVSHSFPHPLYNMSLLK
HQSLRPDEDSSHDLMLLRLSEPAKITDVVKVLGLPTQEPALGTTCYASGWGSIEPE
EFLRPRSLQCVSLHLLSNDMCARAYSEKVTEFMLCAGLWTGGKDTCGGDSGGPL
VCNGVLQGITSWGPEPCALPEKPAVYTKVVHYRKWIKDTIAANP

**SEQ ID NO: 63 – heavy chain CDR1 sequence**

SDYAWN

**SEQ ID NO: 64 – heavy chain CDR2 sequence**

YISYSGSTTYSPSLKS

**SEQ ID NO: 65 – heavy chain CDR2 sequence**

YISYSGSTTYNPSLKS

**SEQ ID NO: 66 – heavy chain CDR3 sequence**

GYYYGSGF

**SEQ ID NO: 67 – light chain CDR1 sequence**

RASESVEYFGTSLMH

**SEQ ID NO: 68 – light chain CDR1 sequence**

KASESVEYFGTSLMH

**SEQ ID NO: 69 – light chain CDR2 sequence**

AASNVES

**SEQ ID NO: 70 – light chain CDR2 sequence**

AASNRES

**SEQ ID NO: 71 – light chain CDR3 sequence**

QQTRKVPYT

**SEQ ID NO: 72 – heavy chain CDR1 sequence**

GNSITSDYAWN

**SEQ ID NO: 73 – heavy chain CDR1 sequence**

YISYSGSTT

**SEQ ID NO: 74 – VL 4 (KL2B413)**

EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSG
VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK

**SEQ ID NO: 75 – VL 5 (KL2B359)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 76 - VH 4 (KL2B413)**

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQD
GSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGH
YGMDVWGQGTTVTVSS

**SEQ ID NO: 77 - VH 5 (KL2B359)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSS

**SEQ ID NO: 78 - Extracellular antigen-binding domain 17 (KL2B413_HL)**

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQD
GSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGH
YGMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPSFLSASVGDRVT
ITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSL
QPEDFATYYCQQLNSYPRTFGQGTKVEIK

**SEQ ID NO: 79 - Extracellular antigen-binding domain 18 (KL2B413_LH)**

EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSG
VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIKGGSEGKS
SGSGSESKSTGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPG
KGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC
ARDQNYDILTGHYGMDVWGQGTTVTVSS

**SEQ ID NO: 80 - Extracellular antigen-binding domain 19 (KL2B359-HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 81 - Extracellular antigen-binding domain 20 (KL2B359-LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAAS
NVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGG
SEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWI
RQFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 82 - CAR 17 (KL2B413_HL; pBD000091628)**

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQD
GSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGH
YGMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPSFLSASVGDRVT
ITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSL
QPEDFATYYCQQLNSYPRTFGQGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRP

AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF
MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 83 - CAR 18 (KL2B413_LH; pBD000091623)**

EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSG
VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIKGGSEGKS
SGSGSESKSTGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPG
KGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC
ARDQNYDILTGHYGMDVWGQGTTVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACR
PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF
MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 84 - CAR 19 (KL2B359-HL; pBD000091576)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 85 - CAR 20 (KL2B359-LH; pBD000091577)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 86 – heavy chain CDR1 sequence**

GFTFSSYW

**SEQ ID NO: 87 – heavy chain CDR2 sequence**

IKQDGSER

**SEQ ID NO: 88 – heavy chain CDR3 sequence**

ARDQNYDILTGHYGMDV

**SEQ ID NO: 89 – light chain CDR1 sequence**

QGISSY

**SEQ ID NO: 90 – light chain CDR2 sequence**

ATS

**SEQ ID NO: 91 – light chain CDR3 sequence**

QQLNSYPRT

**SEQ ID NO: 92 – heavy chain CDR1 sequence**

GNSITSDYA

**SEQ ID NO: 93 – heavy chain CDR2 sequence**

ISYSGST

**SEQ ID NO: 94 – heavy chain CDR3 sequence**

ATGYYYGSGF

**SEQ ID NO: 95 – light chain CDR1 sequence**

ESVEYFGTSL

**SEQ ID NO: 96 – light chain CDR2 sequence**

AAS

**SEQ ID NO: 97 – light chain CDR3 sequence**

GGNNIGSKSVH

**SEQ ID NO: 98 - Linker sequence**

GTSGSSGSGSGGSGSGGGG

**SEQ ID NO: 99 - Linker sequence**

GKPGSGKPGSGKPGSGKPGS

**SEQ ID NO: 100 - heavy chain CDR2 sequence**

YISYSGSTTYNPSLKS

**SEQ ID NO: 101 - heavy chain CDR1 sequence**

GNSITSDYAWN

**SEQ ID NO: 102 - heavy chain CDR1 sequence**

SYYWS

**SEQ ID NO: 103 - heavy chain CDR2 sequence**

YIYYSGSTNYNPSLKS

**SEQ ID NO: 104 - heavy chain CDR3 sequence**

TTIFGVVTPNFYYGMDV

**SEQ ID NO: 105 - heavy chain CDR1 sequence**

GGSISSYYWS

**SEQ ID NO: 106 - heavy chain CDR2 sequence**

YIYYSGSTN

**SEQ ID NO: 107 - heavy chain CDR1 sequence**

SYDIH

**SEQ ID NO: 108 - heavy chain CDR2 sequence**

IISYDGSKKDYTDSVKG

**SEQ ID NO: 109 - heavy chain CDR3 sequence**

ESGWSHYYYYGMDV

**SEQ ID NO: 110 - heavy chain CDR1 sequence**

GFTFSSYDIH

**SEQ ID NO: 111 - heavy chain CDR2 sequence**

IISYDGSKKD

**SEQ ID NO: 112 - heavy chain CDR2 sequence**

RLYVSGFTNYNPSLKS

**SEQ ID NO: 113 - heavy chain CDR3 sequence**

DSGNYWGWFDP

**SEQ ID NO: 114 - heavy chain CDR2 sequence**

RLYVSGFTN

**SEQ ID NO: 115- heavy chain CDR1 sequence**

YYGMH

**SEQ ID NO: 116 - heavy chain CDR2 sequence**

FISYDGSNKYYADSVKG

**SEQ ID NO: 117 - heavy chain CDR3 sequence**

LPYSGSYWAFDY

**SEQ ID NO: 118 - heavy chain CDR1 sequence**

GFTFSYY

**SEQ ID NO: 119 - heavy chain CDR2 sequence**

FISYDGSNKY

**SEQ ID NO: 120 - heavy chain CDR1 sequence**

HYAMS

**SEQ ID NO: 121 - heavy chain CDR2 sequence**

TIGGSGGSTYYADSVKG

**SEQ ID NO: 122 - heavy chain CDR3 sequence**

PHIVMVTALLYDGMDV

**SEQ ID NO: 123 - heavy chain CDR1 sequence**

GFTFSHYAMS

**SEQ ID NO: 124 - heavy chain CDR3 sequence**

TIGGSGGSTYY

**SEQ ID NO: 125 - light chain CDR1 sequence**

RASQDISNYLA

**SEQ ID NO: 126 - light chain CDR2 sequence**

AASNVES

**SEQ ID NO: 127 - light chain CDR3 sequence**

DDSDRPS

**SEQ ID NO: 128 - light chain CDR1 sequence**

RASQGISSYLA

**SEQ ID NO: 129 - light chain CDR2 sequence**

AASTLQS

**SEQ ID NO: 130 - light chain CDR3 sequence**

QQLNSYPLT

**SEQ ID NO: 131 - light chain CDR2 sequence**

AASTLHS

**SEQ ID NO: 132 - light chain CDR3 sequence**

QKYNSAPYT

**SEQ ID NO: 133 - light chain CDR1 sequence**

SGDQLGENYAC

**SEQ ID NO: 134 - light chain CDR2 sequence**

QDSKRPS

**SEQ ID NO: 135 - light chain CDR3 sequence**

QAWDNSIVV

**SEQ ID NO: 136 - light chain CDR1 sequence**

GGDNIGSKSVH

**SEQ ID NO: 137 - light chain CDR2 sequence**

DNSDRPS

**SEQ ID NO: 138 - light chain CDR3 sequence**

QVWDSSSDHPVV

**SEQ ID NO: 139 - light chain CDR3 sequence**

QVWDSSSDHVV

**SEQ ID NO: 140 – VH (KL2B357, KL2B357 and KL2B360))**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT LVTVSS

**SEQ ID NO: 142 – VH (KL2B30)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGST NYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGM DVWGQGTTVTVSS

**SEQ ID NO: 143 – VH (KL2B53)**

EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDG SKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYG MDVWGQGTMVTVSS

**SEQ ID NO: 144 – VH (KL2B242)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWG QGTLVTVSS

**SEQ ID NO: 145 – VH (KL2B467)**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF
DYWGQGTQVTVSS

**SEQ ID NO: 146 – VH (KL2B494)**

QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL
YDGMDVWGQGTMVTVSS

**SEQ ID NO: 147 – VL (KL2B357)**

DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 148 – VL (KL2B30)**

DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQS
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK

**SEQ ID NO: 149 – VL (KL2B53)**

DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK

**SEQ ID NO: 150 – VL (KL2B242)**

SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGI
PERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVL

**SEQ ID NO: 151 – VL (KL2B467)**

QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPS
GIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTV

**SEQ ID NO: 152 – VL (KL2B494)**

SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS
GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL

**SEQ ID NO: 153 – VH (KL2B357)**

CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCT
GTCTCTGACCTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAA
CTGGATTCGGCAGTTCCCTGGCAAGGGCCTTGAGTGGATCGGCTACATCTCCT
ACTCCGGTTCCACCACCTACAACCCCAGCCTGAAGTCCCGGGTCACCATCTCCC
GCGACACCTCCAAGAACCAGTTCTCCCTGAAGCTGTCCTCCGTGACCGCTGCT
GATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTCCGGCTTTTGG
GGACAGGGCACACTGGTTACCGTGTCTAGT

**SEQ ID NO: 154 – VH (KL2B358)**

CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCT
GTCTCTGACCTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAA
CTGGATTCGGCAGCCACCTGGCAAGGGCCTTGAGTGGATCGGCTACATCTCCT
ACTCCGGTTCCACCACCTACAACCCCAGCCTGAAGTCCCGGGTCACCATCTCCC
GCGACACCTCCAAGAACCAGTTCTCCCTGAAGCTGTCCTCCGTGACCGCTGCT
GATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTCCGGCTTTTGG
GGACAGGGCACACTGGTTACCGTGTCTAGT

**SEQ ID NO: 155 – VH (KL2B360)**

CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCT
GTCTCTGACCTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAA
CTGGATTCGGCAGTTCCCTGGCAAGGGCCTTGAGTGGATCGGCTACATCTCCT
ACTCCGGTTCCACCACCTACAACCCCAGCCTGAAGTCCCGGGTCACCATCTCCC
GCGACACCTCCAAGAACCAGTTCTCCCTGAAGCTGTCCTCCGTGACCGCTGCT
GATACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTCCGGCTTTTGG
GGACAGGGCACACTGGTTACCGTGTCTAGT

**SEQ ID NO: 156 – VH (KL2B30)**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCT
GTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTG
GATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGATATATCTATTACA
GTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTA
GACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGA
CACGGCCGTGTATTACTGTGCGGGGACTACGATTTTTGGAGTGGTTACCCCCA
ACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCA

**SEQ ID NO: 157 – VH (KL2B53)**

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT
GAGACTCTCCTGTGTAGCCTCTGGATTCACCTTCAGTAGTTATGACATACACTG
GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAATTATTTCATATG
ATGGAAGTAAAAAAGACTATACAGACTCCGTGAAGGGCCGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGGACAGCCTGAGAGTTGA
GGACTCGGCTGTGTATTCCTGTGCGAGAGAAAGTGGCTGGTCCCACTACTACT
ATTACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA

**SEQ ID NO: 158 – VH (KL2B242)**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCT
GTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTATTGGAGCTG
GCTCCGGCAGCCCGCCGGGTCGGGACTGGAGTGGATTGGGCGTTTATATGTCA
GTGGGTTCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCTTGTCACTA
GACCCGTCCAGGAACCAGTTGTCCCTGAAACTGAGTTCTGTGACCGCCGCGGA
CACGGCCGTATATTATTGTGCGGGAGATAGTGGGAACTACTGGGGTTGGTTCG
ACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

**SEQ ID NO: 159 – VH (KL2B467)**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTTACTATGGCATGCACTG
GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCATTTATATCATATG
ATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTG

AGGACACGGCTGTGTATTACTGTGCCCACCTCCCTTATAGTGGGAGCTACTGG
GCCTTTGACTACTGGGGCCAGGGAACCCAGGTCACCGTCTCTTCA

**SEQ ID NO: 160 – VH (KL2B494)**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTCATTATGCCATGAGCTG
GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTGGTGGTA
GTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCG
AGGACACGGCCGTATATTACTGTGCGAAACCTCATATTGTAATGGTGACTGCT
CTTCTCTACGACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTC
CTCA

**SEQ ID NO: 161 – VL (KL2B357)**

GACATCGTGCTGACCCAGTCTCCAGACTCTCTGGCTGTGTCTCTGGGCGAGAG
AGCCACCATCAACTGCAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTC
TGATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCTAAGCTGCTGATCTAC
GCCGCCTCCAACGTGGAATCTGGCGTGCCCGATAGATTTTCCGGCTCTGGCTCT
GGCACCGACTTTACCCTGACCATCAGCTCTCTGCAGGCCGAGGATGTGGCCGT
GTACTTCTGTCAGCAGACCCGGAAGGTGCCCTACACATTTGGCGGCGGAACAA
AGGTGGAAATCAAG

**SEQ ID NO: 162 – VL (KL2B358)**

GAGATCGTGCTGACCCAGTCTCCTGCCACACTGTCACTGTCTCCAGGCGAGAG
AGCCACCCTCTCTTGTAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTCT

GATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCTAGACTGCTGATCTACG
CCGCCTCCAACGTCGAATCTGGCATCCCCGCTAGATTCTCCGGCTCTGGCTCTG
GCACAGACTTTACCCTGACCATCTCCTCCGTGGAACCCGAGGATTTCGCTGTGT
ACTTTTGCCAGCAGACCCGGAAGGTGCCCTACACATTTGGCGGCGGAACAAAG
GTGGAAATCAAG

**SEQ ID NO: 163 – VL (KL2B360)**

GAGATCGTGCTGACCCAGTCTCCTGCCACACTGTCACTGTCTCCAGGCGAGAG
AGCCACCCTCTCTTGTAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTCT
GATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCTAGACTGCTGATCTACG
CCGCCTCCAACGTCGAATCTGGCATCCCCGCTAGATTCTCCGGCTCTGGCTCTG
GCACAGACTTTACCCTGACCATCTCCTCCGTGGAACCCGAGGATTTCGCTGTGT
ACTTTTGCCAGCAGACCCGGAAGGTGCCCTATACATTTGGCGGCGGAACAAAG
GTGGAAATCAAG

**SEQ ID NO: 164 – VL (KL2B30)**

GACATCCAGATGACCCAGTCTCCTTCCTTCCTGTCTGCATCTGTAGGAGACAGA
GTCACCATCACTTGCCGGGCCAGTCAGGGCATTAGCAGTTATTTAGCCTGGTAT
CAGCAAAAACCAGGGAAAGCCCCTAAGTTCCTGATCTATGCTGCATCCACTTT
GCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCA
CTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCAAC
AGCTTAATAGTTACCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAA

**SEQ ID NO: 165 – VL (KL2B53)**

GACATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG
AGTCACCATCACTTGCCGGGCGAGTCAGGACATTAGCAATTATTTAGCCTGGT
ATCAGCAGAAACCAGGGAAAGTTCCTAAGTTCCTGATCTATGCTGCATCCACT
TTGCACTCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTC
ACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAA
AAGTATAACAGTGCCCCGTACACTTTTGGCCAAGGGACACGACTGGAGATTAA
A

**SEQ ID NO: 166 – VL (KL2B242)**

TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGAGAGACAGC
CAGCATCACCTGCTCTGGAGATCAATTGGGGGAAAATTATGCTTGCTGGTATC
AGCAGAAGCCAGGCCAGTCCCCTGTGTTGGTCATCTATCAAGATAGTAAGCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACAGCCAC
TCTGACCATCAGCGGGACCCAGGCTCTGGATGAGGCTGACTATTACTGTCAGG
CGTGGGACAACAGTATTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA

**SEQ ID NO: 167 – VL (KL2B467)**

CAGTCTGTGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCCGGGCAGACGGC
CAGTATTACCTGTGGGGGAGACAACATTGGAAGTAAAAGTGTGCACTGGTACC
AGCAGAAGCCAGGCCAGGCCCCTGTGCTGGTCGTCTATGATAATAGCGACCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGACCACGGCCAC
CCTGACCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGTCAGG
TGTGGGATAGTAGTAGTGATCATCCTGTGGTATTCGGCGGAGGGACCAAGGTC
ACCGTCCTA

**SEQ ID NO: 168 – VL (KL2B494)**

TCTTCTGAGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCAGGACAGACGGC
CAGGATTACCTGTGGGGGAAACAACATTGGAAGTAAAAGTGTGCACTGGTACC
AGCAGAAGCCAGGCCAGGCCCCTGTGCTGGTCGTCTATGATGATAGCGACCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACGGCCAC
CCTGACCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGTCAGG
TGTGGGATAGTAGTAGTGATCATGTGGTATTCGGCGGAGGGACCAAGCTGACC
GTCCTA

**SEQ ID NO: 169 – KL2B357 ScFv-HL**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCRASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDV
AVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 170 – KL2B357 ScFv-LH**

DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 171 – KL2B358 ScFv-HL**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT

LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 172 – KL2B358 ScFv-LH**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 173 – KL2B360 ScFv-HL**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 174 – KL2B360 ScFv-LH**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 175 – KL2B30 ScFv-HL**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGST
NYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGM
DVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSFLSASVGDRVTITC
RASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQP
EDFATYYCQQLNSYPLTFGGGTKVEIK

**SEQ ID NO: 176 – KL2B30 ScFv-LH**

DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQS
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIKGGSEGK
SSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGK
GLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTI
FGVVTPNFYYGMDVWGQGTTVTVSS

**SEQ ID NO: 177 – KL2B53 ScFv-HL**

EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDG
SKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVEDSAVYSCARESGWSHYYYYG
MDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPSSLSASVGDRVTI
TCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSL
QPEDVATYYCQKYNSAPYTFGQGTRLEIK

**SEQ ID NO: 178 – KL2B53 ScFv-LH**

DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSEGK

SSGSGSESKSTGGSEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPG
KGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVEDSAVYSCA
RESGWSHYYYYGMDVWGQGTMVTVSS

**SEQ ID NO: 179 – KL2B242 ScFv-HL**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF
TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWG
QGTLVTVSSGGSEGKSSGSGSESKSTGGSSYELTQPPSVSVSPGETASITCSGDQLG
ENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEAD
YYCQAWDNSIVVFGGGTKLTVL

**SEQ ID NO: 180 – KL2B242 ScFv-LH**

SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGI
PERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGSEGK
SSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAG
SGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAG
DSGNYWGWFDPWGQGTLVTVSS

**SEQ ID NO: 181 – KL2B467 ScFv-HL**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF
DYWGQGTQVTVSSGGSEGKSSGSGSESKSTGGSQSVLTQPPSVSVAPGQTASITCG
GDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEA
GDEADYYCQVWDSSSDHPVVFGGGTKVTV

**SEQ ID NO: 182 – KL2B467 ScFv-LH**

QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPS
GIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVGG
SEGKSSGSGSESKSTGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWV
RQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT
AVYYCAHLPYSGSYWAFDYWGQGTQVTVSS

**SEQ ID NO: 183 – KL2B494 ScFv-HL**

QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL
YDGMDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQTA
RITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTI
SRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL

**SEQ ID NO: 184 – KL2B494 ScFv-LH**

SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS
GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGG
SEGKSSGSGSESKSTGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWV
RQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA
VYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSS

**SEQ ID NO: 185 – KL2B30 HC IgG4**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGST
NYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGM
DVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE
SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSLGK

**SEQ ID NO: 186 – KL2B30 LC IgG4**

DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQS
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIKRTVAAP
SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

**SEQ ID NO: 187 – KL2B53 HC IgG4**

EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDG
SKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVEDSAVYSCARESGWSHYYYYG
MDVWGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR
VESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES
NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT
QKSLSLSLGK

**SEQ ID NO: 188 – KL2B53 LC IgG4**

DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKRTVAAP
SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS
KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

**SEQ ID NO: 189 – KL2B242 HC IgG4**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF
TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWG
QGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY
GPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI
EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL
SLGK

**SEQ ID NO: 190 – KL2B242 LC IgG4**

SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGI
PERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGQPKAA
PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQS
NNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

**SEQ ID NO: 191 – KL2B467 HC IgG4**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF
DYWGQGTQVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV
EPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK

**SEQ ID NO: 192 – KL2B467 LC IgG4**

QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPS
GIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVLG
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTT
PSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

**SEQ ID NO: 193 – KL2B494 HC IgG4**

QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL
YDGMDVWGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVSV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK

**SEQ ID NO: 194 – KL2B494 LC IgG4**

SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS
GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGQ
PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTP
SKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

**SEQ ID NO: 195 – KL2B30 HC DNA**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCT
GTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTACTGGAGCTG
GATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGATATATCTATTACA
GTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTA
GACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGA
CACGGCCGTGTATTACTGTGCGGGGACTACGATTTTTGGAGTGGTTACCCCCA
ACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC
TCAGCTTCCACCAAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGC
ACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGA
ACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCT
TCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG
TGCCCTCCAGCAGCTTGGGCACGAAAACCTACACTTGCAACGTAGATCACAAG
CCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATG
CCCACCATGCCCAGCACCTGAGGCCGCCGGGGGACCATCAGTCTTCCTGTTCC
CCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGC
GTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGT
GGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTC
AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCT
GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCA
TCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTA

CACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCT
GCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAT
GGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG
GCTCCTTCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGATGGCAGGAG
GGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
ACAGAAGAGCCTCTCCCTGTCTCTGGGTAAA

**SEQ ID NO: 196 – KL2B30 LC DNA**

GACATCCAGATGACCCAGTCTCCTTCCTTCCTGTCTGCATCTGTAGGAGACAGA
GTCACCATCACTTGCCGGGCCAGTCAGGGCATTAGCAGTTATTTAGCCTGGTAT
CAGCAAAAACCAGGGAAAGCCCCTAAGTTCCTGATCTATGCTGCATCCACTTT
GCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCA
CTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCAAC
AGCTTAATAGTTACCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAA
CGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTG
AAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAG
GCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGG
AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCAC
CCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
GTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGA
GTGT

**SEQ ID NO: 197 – KL2B53 HC DNA**

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT
GAGACTCTCCTGTGTAGCCTCTGGATTCACCTTCAGTAGTTATGACATACACTG
GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAATTATTTCATATG
ATGGAAGTAAAAAAGACTATACAGACTCCGTGAAGGGCCGATTCACCATCTCC

AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGGACAGCCTGAGAGTTGA
GGACTCGGCTGTGTATTCCTGTGCGAGAGAAAGTGGCTGGTCCCACTACTACT
ATTACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCT
TCCACCAAGGGCCCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC
GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT
GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGG
CTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT
CCAGCAGCTTGGGCACGAAAACCTACACTTGCAACGTAGATCACAAGCCCAGC
AACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACC
ATGCCCAGCACCTGAGGCCGCCGGGGGACCATCAGTCTTCCTGTTCCCCCCAA
AACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTG
GTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAG
CACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCC
TGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG
GTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC
AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAGGCTAACCGTGGACAAGAGCAGATGGCAGGAGGGGA
ATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAG
AAGAGCCTCTCCCTGTCTCTGGGTAAA

**SEQ ID NO: 198 – KL2B53 LC DNA**

GACATCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG
AGTCACCATCACTTGCCGGGCGAGTCAGGACATTAGCAATTATTTAGCCTGGT
ATCAGCAGAAACCAGGGAAAGTTCCTAAGTTCCTGATCTATGCTGCATCCACT
TTGCACTCTGGGGTCCCATCTCGGTTCAGTGGCAGTGGATCTGGGACAGATTTC
ACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCAACTTATTACTGTCAA

AAGTATAACAGTGCCCCGTACACTTTTGGCCAAGGGACACGACTGGAGATTAA
ACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT
GAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGA
GGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAG
GAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCA
CCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA
AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG
AGTGT

**SEQ ID NO: 199 – KL2B242 HC DNA**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCT
GTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTTACTATTGGAGCTG
GCTCCGGCAGCCCGCCGGGTCGGGACTGGAGTGGATTGGGCGTTTATATGTCA
GTGGGTTCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCTTGTCACTA
GACCCGTCCAGGAACCAGTTGTCCCTGAAACTGAGTTCTGTGACCGCCGCGGA
CACGGCCGTATATTATTGTGCGGGAGATAGTGGGAACTACTGGGGTTGGTTCG
ACCCCTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCTTCCACCAAGGGC
CCATCCGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGC
CGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT
GGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTG
GGCACGAAAACCTACACTTGCAACGTAGATCACAAGCCCAGCAACACCAAGG
TGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCATGCCCAGCA
CCTGAGGCCGCCGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGA
CACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGA
GCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGT
GCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGTACCGT
GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAGGAGTA
CAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAACCATCT

CCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCCCATCC
CAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT
TCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA
CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTA
CAGCAGGCTAACCGTGGACAAGAGCAGATGGCAGGAGGGGAATGTCTTCTCA
TGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTC
CCTGTCTCTGGGTAAA

**SEQ ID NO: 200 – KL2B242 LC DNA**

TCCTATGAGCTGACTCAGCCACCCTCAGTGTCCGTGTCCCCAGGAGAGACAGC
CAGCATCACCTGCTCTGGAGATCAATTGGGGGAAAATTATGCTTGCTGGTATC
AGCAGAAGCCAGGCCAGTCCCCTGTGTTGGTCATCTATCAAGATAGTAAGCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACAGCCAC
TCTGACCATCAGCGGGACCCAGGCTCTGGATGAGGCTGACTATTACTGTCAGG
CGTGGGACAACAGTATTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA
GGTCAGCCCAAGGCTGCACCCAGTGTCACTCTGTTCCCGCCCTCCTCTGAGGA
GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGG
GAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAGGCGGGAGT
GGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGC
TATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCA
GGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGT
TCA

**SEQ ID NO: 201 – KL2B467 HC DNA**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTTACTATGGCATGCACTG
GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCATTTATATCATATG

ATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTG
AGGACACGGCTGTGTATTACTGTGCCCACCTCCCTTATAGTGGGAGCTACTGG
GCCTTTGACTACTGGGGCCAGGGAACCCAGGTCACCGTCTCTTCAGCCTCCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG
GTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGT
CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAG
CAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACA
CCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGC
CCACCGTGCCCAGCACCTGAAGCCGCCGGGGGACCGTCAGTCTTCCTCTTCCC
CCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG
TGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACA
ACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTAC
ACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG
CCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATG
GGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGG
CTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGATGGCAGCAGG
GGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG
CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

**SEQ ID NO: 202 – KL2B467 LC DNA**

CAGTCTGTGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCCGGGCAGACGGC
CAGTATTACCTGTGGGGGAGACAACATTGGAAGTAAAAGTGTGCACTGGTACC
AGCAGAAGCCAGGCCAGGCCCCTGTGCTGGTCGTCTATGATAATAGCGACCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGACCACGGCCAC

CCTGACCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGTCAGG
TGTGGGATAGTAGTAGTGATCATCCTGTGGTATTCGGCGGAGGGACCAAGGTC
ACCGTCCTAGGTCAGCCCAAGGCTGCACCCAGTGTCACTCTGTTCCCGCCCTCC
TCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTT
CTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAG
GCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGG
CCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTAC
AGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTA
CAGAATGTTCA

**SEQ ID NO: 203 – KL2B494 HC DNA**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTCATTATGCCATGAGCTG
GGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTGGTGGTA
GTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCC
AGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCG
AGGACACGGCCGTATATTACTGTGCGAAACCTCATATTGTAATGGTGACTGCT
CTTCTCTACGACGGTATGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTC
CTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAG
CACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG
AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACC
TTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC
GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAA
GCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAA
ACTCACACATGCCCACCGTGCCCAGCACCTGAAGCCGCCGGGGGACCGTCAGT
CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGA
GGTCACATGCGTGGTGGTGAGCGTGAGCCACGAAGACCCTGAGGTCAAGTTCA
ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA
GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACC

AGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAA
CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCT
GGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA
GATGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

**SEQ ID NO: 204 – KL2B494 LC DNA**

TCTTCTGAGCTGACTCAGCCACCCTCGGTGTCAGTGGCCCCAGGACAGACGGC
CAGGATTACCTGTGGGGGAAACAACATTGGAAGTAAAAGTGTGCACTGGTACC
AGCAGAAGCCAGGCCAGGCCCCTGTGCTGGTCGTCTATGATGATAGCGACCGG
CCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACGGCCAC
CCTGACCATCAGCAGGGTCGAAGCCGGGGATGAGGCCGACTATTACTGTCAGG
TGTGGGATAGTAGTAGTGATCATGTGGTATTCGGCGGAGGGACCAAGCTGACC
GTCCTAGGTCAGCCCAAGGCTGCACCCAGTGTCACTCTGTTCCCGCCCTCCTCT
GAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTA
CCCGGGAGCCGTGACAGTGGCCTGGAAGGCCGATAGCAGCCCCGTCAAGGCG
GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCA
GCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGC
TGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAG
AATGTTCA

**SEQ ID NO: 205 – CAR (KL2B357 HL and KL2B357 LH)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT

LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCRASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDV
AVYFCQQTRKVPYTFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYD
VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGH
DGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 207 – CAR (KL2B358 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 208 – CAR (KL2B358 LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL

DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 209 – CAR (KL2B360 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 210 – CAR (KL2B360 LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVL
DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG
LYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 211 – CAR (KL2B30 HL)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGST
NYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGM
DVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSFLSASVGDRVTITC
RASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQP
EDFATYYCQQLNSYPLTFGGGTKVEIKTSTPAPRPPTPAPTIASQPLSLRPEACRPA
AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR
PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE
EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG
KGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 212 – CAR (KL2B30 LH)**

DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQS
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK GGSEG
KSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPG
KGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGT
TIFGVVTPNFYYGMDVWGQGTTVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPA
AGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMR
PVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRRE
EYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG
KGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 213 – CAR (KL2B53 HL)**

EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDG
SKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYG
MDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPSSLSASVGDRVTI
TCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSL

QPEDVATYYCQKYNSAPYTFGQGTRLEIKTSTPAPRPPTPAPTIASQPLSLRPEACR
PAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF
MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 214 – CAR (KL2B53 LH)**

DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSEGK
SSGSGSESKSTGGSEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPG
KGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCA
RESGWSHYYYYGMDVWGQGTMVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRP
AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPF
MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR
REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 215 – CAR (KL2B242 HL)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF
TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWG
QGTLVTVSSGGSEGKSSGSGSESKSTGGSSYELTQPPSVSVSPGETASITCSGDQLG
ENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEAD
YYCQAWDNSIVVFGGGTKLTVLTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDV
LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD
GLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 216 – CAR (KL2B242 LH)**

SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGI
PERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGSEGK
SSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAG
SGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAG
DSGNYWGWFDPWGQGTLVTVSSTSTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDV
LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD
GLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 217 – CAR (KL2B467 HL)**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF
DYWGQGTQVTVSSGGSEGKSSGSGSESKSTGGSQSVLTQPPSVSVAPGQTASITCG
GDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEA
GDEADYYCQVWDSSSDHPVVFGGGTKVTVTSTPAPRPPTPAPTIASQPLSLRPEAC
RPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQP
FMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG
RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGER
RRGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 218 – CAR (KL2B467 LH)**

QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPS
GIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVGG
SEGKSSGSGSESKSTGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWV
RQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT
AVYYCAHLPYSGSYWAFDYWGQGTQVTVSSTSTPAPRPPTPAPTIASQPLSLRPEA
CRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQ
PFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNL
GRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGE
RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 219 – CAR (KL2B494 HL)**

QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL
YDGMDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQTA
RITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTI
SRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLTSTPAPRPPTPAPTIASQPLSL
RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL
YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY
NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 220 – CAR (KL2B494 LH)**

SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS
GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGG
SEGKSSGSGSESKSTGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWV
RQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA
VYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSSTSTPAPRPPTPAPTIASQPLSL

RPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLL
YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLY
NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIG
MKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

**SEQ ID NO: 221 – Extracellular antigen-binding domain (KL2B357 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDSLAVSLGERATINCRASESVEY
FGTSLMHWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDV
AVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 222 – Extracellular antigen-binding domain (KL2B357 LH)**

DIVLTQSPDSLAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIKG
GSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNW
IRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVY
YCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 223 – Extracellular antigen-binding domain (KL2B358 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 224 – Extracellular antigen-binding domain (KL2B358 LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 225 – Extracellular antigen-binding domain (KL2B360 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSG
STTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGT
LVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYF
GTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAV
YFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 226 – Extracellular antigen-binding domain (KL2B360 LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGS
EGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIR
QFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYC
ATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 227 – Extracellular antigen-binding domain (KL2B30 HL)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGST
NYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGTTIFGVVTPNFYYGM
DVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSFLSASVGDRVTITC
RASQGISSYLAWYQQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQP
EDFATYYCQQLNSYPLTFGGGTKVEIK

**SEQ ID NO: 228 – Extracellular antigen-binding domain (KL2B30 LH)**

DIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQS
GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK GGSEG
KSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPG
KGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGT
TIFGVVTPNFYYGMDVWGQGTTVTVSS

**SEQ ID NO: 229 – Extracellular antigen-binding domain (KL2B53 HL)**

EVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPGKGLEWVAIISYDG
SKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCARESGWSHYYYYG
MDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSDIVMTQSPSSLSASVGDRVTI
TCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSL
QPEDVATYYCQKYNSAPYTFGQGTRLEIK

**SEQ ID NO: 230 – Extracellular antigen-binding domain (KL2B53 LH)**

DIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLHS
GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIKGGSEGK
SSGSGSESKSTGGSEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIHWVRQAPG

KGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVED SAVYSCA
RESGWSHYYYYGMDVWGQGTMVTVSS

**SEQ ID NO: 231 – Extracellular antigen-binding domain (KL2B242 HL)**

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGF
TNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAGDSGNYWGWFDPWG
QGTLVTVSSGGSEGKSSGSGSESKSTGGSSYELTQPPSVSVSPGETASITCSGDQLG
ENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEAD
YYCQAWDNSIVVFGGGTKLTVL

**SEQ ID NO: 232 – Extracellular antigen-binding domain (KL2B242 LH)**

SYELTQPPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGI
PERFSGSNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVLGGSEGK
SSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWLRQPAG
SGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTAVYYCAG
DSGNYWGWFDPWGQGTLVTVSS

**SEQ ID NO: 233 – Extracellular antigen-binding domain (KL2B467 HL)**

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYD
GSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAF
DYWGQGTQVTVSSGGSEGKSSGSGSESKSTGGSQSVLTQPPSVSVAPGQTASITCG
GDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEA
GDEADYYCQVWDSSSDHPVVFGGGTKVTV

**SEQ ID NO: 234 – Extracellular antigen-binding domain (KL2B467 LH)**

QSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPS
GIPERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTVGG
SEGKSSGSGSESKSTGGSQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGMHWV
RQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT
AVYYCAHLPYSGSYWAFDYWGQGTQVTVSS

**SEQ ID NO: 235 – Extracellular antigen-binding domain (KL2B494 HL)**

QVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALL
YDGMDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGGSSSELTQPPSVSVAPGQTA
RITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTI
SRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL

**SEQ ID NO: 236 – Extracellular antigen-binding domain (KL2B494 LH)**

SSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSDRPS
GIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVLGG
SEGKSSGSGSESKSTGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMSWV
RQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTA
VYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSS

**SEQ ID NO: 237 - Linker sequence**

GGGSGGGS

**SEQ ID NO: 238 - Linker sequence**

GGGSGGGSGGGS

**SEQ ID NO: 239 - Linker sequence**

GGGSGGGSGGGSGGGS

**SEQ ID NO: 240 - Linker sequence**

GGGSGGGSGGGSGGGSGGGS

**SEQ ID NO: 241 - Linker sequence**

GGGGSGGGGSGGGGS

**SEQ ID NO: 242 - Linker sequence**

GGGGSGGGGSGGGGSGGGGS

**SEQ ID NO: 243 - Linker sequence**

GGGGSGGGGSGGGGSGGGGSGGGGS

**SEQ ID NO: 244 - Linker sequence**

GSTSGSGKPGSGEGSTKG

**SEQ ID NO: 245 - Linker sequence**

IRPRAIGGSKPRVA

**SEQ ID NO: 246 - Linker sequence**

GKGGSGKGGSGKGGS

**SEQ ID NO: 247 - Linker sequence**

GGKGSGGKGSGGKGS

**SEQ ID NO: 248 - Linker sequence**

GGGKSGGGKSGGGKS

**SEQ ID NO: 249 - Linker sequence**

GKGKSGKGKSGKGKS

**SEQ ID NO: 250 - Linker sequence**

GGGKSGGKGSGKGGS

**SEQ ID NO: 251 - Linker sequence**

GKPGSGKPGSGKPGS

**SEQ ID NO: 252 - Linker sequence**

GKPGSGKPGSGKPGSGKPGS

**SEQ ID NO: 253 - Linker sequence**

GKGKSGKGKSGKGKSGKGKS

**SEQ ID NO: 254 - Linker sequence**

STAGDTHLGGEDFD

**SEQ ID NO: 255 - Linker sequence**

GEGGSGEGGSGEGGS

**SEQ ID NO: 256 - Linker sequence**

GGEGSGGEGSGGEGS

**SEQ ID NO: 257 - Linker sequence**

GEGESGEGESGEGES

**SEQ ID NO: 258 - Linker sequence**

GGGESGGEGSGEGGS

**SEQ ID NO: 259 - Linker sequence**

GEGESGEGESGEGESGEGES

**SEQ ID NO: 260 - Linker sequence**

GSTSGSGKPGSGEGSTKG

**SEQ ID NO: 261 - Linker sequence**

PRGASKSGSASQTGSAPGS

**SEQ ID NO: 262 - Linker sequence**

GTAAAGAGAAGGAAAGAAG

**SEQ ID NO: 263 - Linker sequence**

GTSGSSGSGSGGSGSGGGG

**SEQ ID NO: 264 - Linker sequence**

GKPGSGKPGSGKPGSGKPGS

**SEQ ID NO: 265 - Linker sequence**

GSGS

**SEQ ID NO: 266 - Linker sequence**

APAPAPAPAP

**SEQ ID NO: 267 - Linker sequence**

APAPAPAPAPAPAPAPAPAP

**SEQ ID NO: 268 - Linker sequence**

AEAAAKEAAAKEAAAAKEAAAAKEAAAAKAAA

**SEQ ID NO: 269 – CAR hinge sequence**

EPKSCDKTHTCPPCP

**SEQ ID NO: 270 – CAR hinge sequence**

ERKCCVECPPCP

**SEQ ID NO: 271 – CAR hinge sequence**

ELKTPLGDTTHTCPRCP(EPKSCDTPPPCPRCP)3

**SEQ ID NO: 272 – CAR hinge sequence**

ESKYGPPCPSCP

**SEQ ID NO: 273 – Extracellular antigen-binding domain 1 (HL_HCG5_LCD6_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 274 – Extracellular antigen-binding domain 2 (HL_HCG5_LCHumanized_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 275 – Extracellular antigen-binding domain 3 (HL_HCF3_LCB7_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDTA
VYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDS
LAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPDR
FSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 276 – Extracellular antigen-binding domain 4 (HL_HCG5_LCB7_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTPVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 277 – Extracellular antigen-binding domain 5 (LH_LCD6_HCG5_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYF
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD

TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISR
DTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 278 – Extracellular antigen-binding domain 6 (LH_LCHumanized_HCF3_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD
TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 279 – Extracellular antigen-binding domain 7 (LH_LCHumanized_HCG5_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISR
DTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 280 – Extracellular antigen-binding domain 8 (LH_LCB7_HCF3_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD
TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 281 – Extracellular antigen-binding domain 9 (LH_LCB7_HCG5_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWMGYISYSGSTTYNPSLKSRVTISR
DTSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 282 – Extracellular antigen-binding domain 10 (LH_LCD6_HCF3_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYF
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD
TSKNQFSLKLSSVTPVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 283 – Extracellular antigen-binding domain 11 (HL_HCHumanized_LCB7_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTISSVQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 284 – Extracellular antigen-binding domain 12 (HL_HCHumanized_LCD6_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTIQSVQAEDVSVYFCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 285 – Extracellular antigen-binding domain 13 (HL_HCHumanized_LCHumanized_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAW
NWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDT
AVYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPD
SLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNRESGVPD
RFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIK

**SEQ ID NO: 286 – Extracellular antigen-binding domain 14 (LH_LCD6_HCHumanized_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTIQSVQAEDVSVYF
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSR
DTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 287 – Extracellular antigen-binding domain 15 (LH_LCHumanized_HCHumanized_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD

TLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSR
DTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 288 – Extracellular antigen-binding domain 16 (LH_LCB7_HCHumanized_20AA) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCKASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYY
CQQTRKVPYTFGQGTKLEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSD
TLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTMSR
DTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 289 – Extracellular antigen-binding domain 17 (KL2B413_HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMT
WVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAE
DTAVYYCARDQNYDILTGHYGMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGG
SEIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSG
VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIK

**SEQ ID NO: 290 – Extracellular antigen-binding domain 18 (KL2B413_LH) with signal peptide**

MAWVWTLLFLMAAAQSIQAEIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQ
QKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSY
PRTFGQGTKVEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGGLVQPGGSLRLSCA
ASGFTFSSYWMTWVRQAPGKGLEWVANIKQDGSERYYVDSVKGRFTISRDNAKN
SLYLQMNSLRAEDTAVYYCARDQNYDILTGHYGMDVWGQGTTVTVSS

**SEQ ID NO: 291 – Extracellular antigen-binding domain 19 (KL2B359-HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAW
NWIRQFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA
VYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATL
SLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFS
GSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 292 – Extracellular antigen-binding domain 20 (KL2B359-LH) with signal peptide**

MAWVWTLLFLMAAAQSIQAEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM
HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQ
TRKVPYTFGGGTKVEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLS
LTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSGSTTYNPSLKSRVTISRDTSK
NQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 293 – Extracellular antigen-binding domain (KL2B357 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAW
NWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA
VYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIVLTQSPDS
LAVSLGERATINCRASESVEYFGTSLMHWYQQKPGQPPKLLIYAASNVESGVPDR
FSGSGSGTDFTLTISSLQAEDVAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 294 – Extracellular antigen-binding domain (KL2B357 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVLTQSPDSLAVSLGERATINCRASESVEYFGTSL
MHWYQQKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYF
CQQTRKVPYTFGGGTKVEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQ
TLSLTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRD
TSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 295 – Extracellular antigen-binding domain (KL2B358 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAW
NWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA
VYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATL
SLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFS
GSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 296 – Extracellular antigen-binding domain (KL2B358 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQAEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM
HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQ
TRKVPYTFGGGTKVEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLS
LTCTVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSK
NQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 297 – Extracellular antigen-binding domain (KL2B360 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAW
NWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTA
VYYCATGYYYGSGFWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATL

SLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASNVESGIPARFS
GSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 298 – Extracellular antigen-binding domain (KL2B360 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQAEIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLM
HWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQ
TRKVPYTFGGGTKVEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLS
LTCTVSGNSITSDYAWNWIRQFPGKGLEWIGYISYSGSTTYNPSLKSRVTISRDTSK
NQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 299 – Extracellular antigen-binding domain (KL2B30 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWS
WIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTA
VYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSD
IQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKFLIYAASTLQSG
VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIK

**SEQ ID NO: 300 – Extracellular antigen-binding domain (KL2B30 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQADIQMTQSPSFLSASVGDRVTITCRASQGISSYLAWY
QQKPGKAPKFLIYAASTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNS
YPLTFGGGTKVEIKGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTCT
VSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSL
KLSSVTAADTAVYYCAGTTIFGVVTPNFYYGMDVWGQGTTVTVSS

**SEQ ID NO: 301 – Extracellular antigen-binding domain (KL2B53 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAEVQLVESGGGVVQPGRSLRLSCVASGFTFSSYDIH
WVRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNTLYLQMDSLRVE
DSAVYSCARESGWSHYYYYGMDVWGQGTMVTVSSGGSEGKSSGSGSESKSTGG
SDIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWYQQKPGKVPKFLIYAASTLH
SGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPYTFGQGTRLEIK

**SEQ ID NO: 302 – Extracellular antigen-binding domain (KL2B53 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQADIVMTQSPSSLSASVGDRVTITCRASQDISNYLAWY
QQKPGKVPKFLIYAASTLHSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNS
APYTFGQGTRLEIKGGSEGKSSGSGSESKSTGGSEVQLVESGGGVVQPGRSLRLSC
VASGFTFSSYDIHWVRQAPGKGLEWVAIISYDGSKKDYTDSVKGRFTISRDNSKNT
LYLQMDSLRVEDSAVYSCARESGWSHYYYYGMDVWGQGTMVTVSS

**SEQ ID NO: 303 – Extracellular antigen-binding domain (KL2B242 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWS
WLRQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQLSLKLSSVTAADTA
VYYCAGDSGNYWGWFDPWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSSYELTQ
PPSVSVSPGETASITCSGDQLGENYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSG
SNSGNTATLTISGTQALDEADYYCQAWDNSIVVFGGGTKLTVL

**SEQ ID NO: 304 – Extracellular antigen-binding domain (KL2B242 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQASYELTQPPSVSVSPGETASITCSGDQLGENYACWY
QQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQALDEADYYCQAWD
NSIVVFGGGTKLTVLGGSEGKSSGSGSESKSTGGSQVQLQESGPGLVKPSETLSLTC
TVSGGSISSYYWSWLRQPAGSGLEWIGRLYVSGFTNYNPSLKSRVTLSLDPSRNQL
SLKLSSVTAADTAVYYCAGDSGNYWGWFDPWGQGTLVTVSS

**SEQ ID NO: 305 – Extracellular antigen-binding domain (KL2B467 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGM
HWVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRA
EDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSSGGSEGKSSGSGSESKSTGGSQ
SVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWYQQKPGQAPVLVVYDNSDRPSGI
PERFSGSNSGTTATLTISRVEAGDEADYYCQVWDSSSDHPVVFGGGTKVTV

**SEQ ID NO: 306 – Extracellular antigen-binding domain (KL2B467 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQAQSVLTQPPSVSVAPGQTASITCGGDNIGSKSVHWY
QQKPGQAPVLVVYDNSDRPSGIPERFSGSNSGTTATLTISRVEAGDEADYYCQVW
DSSSDHPVVFGGGTKVTVGGSEGKSSGSGSESKSTGGSQVQLVESGGGVVQPGRS
LRLSCAASGFTFSYYGMHWVRQAPGKGLEWVAFISYDGSNKYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAHLPYSGSYWAFDYWGQGTQVTVSS

**SEQ ID NO: 307 – Extracellular antigen-binding domain (KL2B494 HL) with signal peptide**

MAWVWTLLFLMAAAQSIQAQVQLVESGGGLVQPGGSLRLSCAASGFTFSHYAMS
WVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAE
DTAVYYCAKPHIVMVTALLYDGMDVWGQGTMVTVSSGGSEGKSSGSGSESKST

GGSSSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVYDDSD
RPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTKLTVL

**SEQ ID NO: 308 – Extracellular antigen-binding domain (KL2B494 LH) with signal peptide**

MAWVWTLLFLMAAAQSIQASSELTQPPSVSVAPGQTARITCGGNNIGSKSVHWY
QQKPGQAPVLVVYDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVW
DSSSDHVVFGGGTKLTVLGGSEGKSSGSGSESKSTGGSQVQLVESGGGLVQPGGS
LRLSCAASGFTFSHYAMSWVRQAPGKGLEWVSTIGGSGGSTYYADSVKGRFTISR
DNSKNTLYLQMNSLRAEDTAVYYCAKPHIVMVTALLYDGMDVWGQGTMVTVS
S

**SEQ ID NO: 309 – heavy chain CDR1 sequence**

GFTFSSYWMT

**SEQ ID NO: 310 – heavy chain CDR2 sequence**

NIKQDGSERY

**SEQ ID NO: 311 – heavy chain CDR3 sequence**

DQNYDILTGHYGMDV

**SEQ ID NO: 312 – light chain CDR1 sequence**

RASQGISSYLS

**SEQ ID NO: 313 – light chain CDR2 sequence**

ATSTLQS

**SEQ ID NO: 314 – heavy chain CDR1 sequence**

SYWMT

**SEQ ID NO: 315 – heavy chain CDR2 sequence**

NIKQDGSERYYVDSVKG

**SEQ ID NO: 316 – heavy chain CDR2 sequence**

YISYSGSTTYSPSLKS

**SEQ ID NO: 317 – VH (m11B6)**

DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIRQFPGNRLEWMGYISYSG
STTYSPSLKSRFSITRDTSKNQFFLQLNSVTPEDTATYFCATGYYYGSGFWGQGTLV
TVSS

**SEQ ID NO: 318 – VL (m11B6)**

DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHWYRQKPGQPPKLLIYAASN
VESGVPARFSGSGSGTDFSLNIQPVEEDDFSMYFCQQTRKVPYTFGGGTKLEIK

**SEQ ID NO: 319 – human Kallikrein-2 6-His protein**

VPLIEGRIVGGWECEKHSQPWQVAVYSHGWAHCGGVLVHPQWVLTAAHCLKKN
SQVWLGRHNLFEPEDTGQRVPVSHSFPHPLYNMSLLKHQSLRPDEDSSHDLMLLR
LSEPAKITDVVKVLGLPTQEPALGTTCYASGWGSIEPEEFLRPRSLQCVSLHYSEKV

TEFMLCAGLWTGGKDTCGGDSGGPLVCNGVLQGITSWGPEPCALPEKPAVYTKV
VHYRKWIKDTIAANPHHHHHH

**SEQ ID NO: 320 – VH cDNA (m11B6)**

GATGTGCAGCTTCAGGAGTCTGGACCCGGACTTGTTAAACCAAGTCAGTCTCTG
TCCCTGACCTGTACCGTCACCGGCAACAGCATCACAAGCGATTACGCATGGAA
CTGGATCAGGCAGTTCCCTGGAAATCGACTCGAATGGATGGGCTACATTTCATA
CTCCGGTTCAACCACTTACTCTCCATCCTTGAAATCTAGGTTCAGCATCACCCG
TGATACCTCAAAGAACCAATTTTTTCTGCAACTGAATAGCGTAACTCCAGAGGA
CACAGCCACATATTTCTGCGCCACTGGGTATTACTATGGCTCAGGTTTCTGGGG
TCAGGGCACTCTCGTCACCGTCAGCAGC

**SEQ ID NO: 321 – VH cDNA (hu11B6)**

CAGGTCCAACTGCAAGAGAGCGGACCGGGCCTGGTAAAGCCATCCGACACATT
GTCCCTGACGTGTGCGGTAAGTGGAAACTCTATCACTAGCGACTATGCGTGGA
ATTGGATAAGACAACCGCCGGGCAAGGGGCTGGAATGGATAGGATATATCAGC
TATTCCGGTTCTACGACATACAATCCTTCCCTGAAAAGCAGAGTCACTATGTCA
CGCGACACGTCCAAGAATCAGTTCTCATTGAAATTGTCATCCGTAACGGCCGTT
GACACTGCGGTTTATTATTGCGCAACCGGATATTACTACGGCTCTGGTTTTTGG
GGACAGGGAACACTTGTTACTGTTAGTTCA

**SEQ ID NO: 322 – VH cDNA (HCF3-LCD6)**

CAGGTGCAGCTGCAGGAGAGCGGCCCAGGCCTGGTGAAGCCAAGCGACACCCT
GAGCCTGACCTGCGCCGTGAGCGGCAACAGCATCACCAGCGACTACGCCTGGA
ACTGGATCCGCCAGTTCCCAGGCAAGGGCCTGGAGTGGATCGGCTACATCAGC
TACAGCGGCAGCACCACCTACAACCCAAGCCTGAAGAGCCGCGTCACCATCAG
CCGCGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCCCTG

TGGACACCGCCGTGTACTACTGCGCCACCGGCTACTACTACGGCAGCGGCTTCT
GGGGCCAGGGCACCCTGGTGACCGTGAGCAGC

**SEQ ID NO: 323 – VH cDNA (HCG5-LCB7)**

CAGGTGCAGCTGCAGGAGAGCGGCCCAGGCCTGGTGAAGCCAAGCGACACCCT
GAGCCTGACCTGCGCCGTGAGCGGCAACAGCATCACCAGCGACTACGCCTGGA
ACTGGATCCGCCAGTTCCCAGGCAAGGGCCTGGAGTGGATGGGCTACATCAGC
TACAGCGGCAGCACCACCTACAACCCAAGCCTGAAGAGCCGCGTCACCATCAG
CCGCGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCCCTG
TGGACACCGCCGTGTACTACTGCGCCACCGGCTACTACTACGGCAGCGGCTTCT
GGGGCCAGGGCACCCTGGTGACCGTGAGCAGC

**SEQ ID NO: 324 – VH cDNA (KL2B359)**

CAGGTTCAGCTGCAAGAGTCTGGACCAGGCCTGGTCAAGCCCTCTCAGACCCT
GTCTCTGACCTGTACCGTGTCCGGCAACTCCATCACCTCTGACTACGCCTGGAA
CTGGATTCGGCAGTTCCCTGGCAAGCGCCTTGAGTGGATCGGCTACATCTCCTA
CTCCGGTTCCACCACCTACAACCCCAGCCTGAAGTCCCGGGTCACCATCTCCCG
CGACACCTCCAAGAACCAGTTCTCCCTGAAGCTGTCCTCCGTGACCGCTGCTGA
TACCGCCGTGTACTACTGTGCCACCGGCTACTACTACGGCTCCGGCTTTTGGGG
ACAGGGCACACTGGTTACCGTGTCTAGT

**SEQ ID NO: 325 – VH cDNA (KL2B413)**

GAGGTGCAACTTGTGGAGAGCGGCGGAGGTCTGGTCCAACCCGGAGGAAGTCT
CCGTCTCTCCTGTGCTGCTAGTGGCTTCACTTTCAGCTCATATTGGATGACATGG
GTGAGACAAGCCCCAGGAAAGGGGCTCGAGTGGGTAGCTAACATTAAACAGG
ACGGCTCCGAACGGTACTATGTTGATTCTGTGAAGGGACGGTTCACTATATCCA
GGGATAATGCAAAAAATTCACTCTATCTTCAAATGAACTCACTCAGAGCAGAG

GACACTGCCGTGTATTATTGCGCCAGGGATCAAAATTATGACATACTGACCGGT
CATTATGGAATGGATGTTTGGGGCCAGGGAACAACCGTTACCGTCTCAAGT

**SEQ ID NO: 326 – VL cDNA (m11B6)**

GACATTGTGCTGACACAGAGTCCAGCATCCTTGGCAGTATCTTTGGGGCAGCG
GGCAACAATTTCATGCCGTGCATCTGAAAGTGTGGAGTATTTTGGAACTTCTCT
TATGCACTGGTATCGCCAGAAGCCTGGGCAGCCTCCCAAACTCCTTATATATGC
CGCTTCCAACGTGGAGTCCGGAGTACCAGCACGCTTTTCCGGCTCTGGGTCCGG
CACAGACTTTTCCCTCAATATCCAACCTGTTGAAGAAGACGATTTTTCCATGTA
TTTTTGCCAACAGACACGCAAGGTTCCATATACATTCGGCGGCGGCACTAAACT
TGAGATCAAA

**SEQ ID NO: 327 – VL cDNA (hu11B6)**

GACATAGTCTTGACTCAGAGCCCGGATTCCCTTGCTGTGTCTCTGGGAGAACGA
GCTACGATCAACTGCAAGGCAAGTGAATCCGTAGAATACTTCGGGACATCATT
GATGCATTGGTATCAACAGAAACCGGGGCAACCGCCCAAATTGCTGATATATG
CGGCTAGTAATAGAGAATCAGGAGTACCGGATAGGTTTAGTGGTTCAGGATCA
GGTACAGATTTCACCCTGACAATAAGTAGCTTGCAAGCCGAAGACGTAGCAGT
GTATTACTGCCAACAAACCCGAAAGGTGCCATATACGTTTGGACAGGGTACAA
AGTTGGAAATCAAA

**SEQ ID NO: 328 – VL cDNA (HCF3-LCD6)**

GACATCGTGCTGACCCAGAGCCCAGACAGCCTGGCCGTGAGCCTGGGCGAGCG
CGCCACCATCAACTGCAAGGCCAGCGAGAGCGTGGAGTACTTCGGCACCAGCC
TGATGCACTGGTACCAGCAGAAGCCAGGCCAGCCACCAAAGCTGCTGATCTAC
GCTGCCAGCAACCGCGAGAGCGGCGTGCCAGACCGCTTCAGCGGCAGCGGCAG
CGGCACCGACTTCACCCTGACCATCCAGAGCGTGCAGGCCGAGGACGTCTCCG

TGTACTTCTGCCAGCAGACCCGCAAGGTGCCATACACCTTCGGCCAGGGCACC
AAGCTGGAGATCAAG

**SEQ ID NO: 329 – VL cDNA (HCG5-LCB7)**

GACATCGTGCTGACCCAGAGCCCAGACAGCCTGGCCGTGAGCCTGGGCGAGCG
CGCCACCATCAACTGCAAGGCCAGCGAGAGCGTGGAGTACTTCGGCACCAGCC
TGATGCACTGGTACCAGCAGAAGCCAGGCCAGCCACCAAAGCTGCTGATCTAC
GCTGCCAGCAACCGCGAGAGCGGCGTGCCAGACCGCTTCAGCGGCAGCGGCAG
CGGCACCGACTTCACCCTGACCATCAGCAGCGTGCAGGCCGAGGACGTCGCCG
TGTACTACTGCCAGCAGACCCGCAAGGTGCCATACACCTTCGGCCAGGGCACC
AAGCTGGAGATCAAG

**SEQ ID NO: 330 – VL cDNA (KL2B359)**

GAGATCGTGCTGACCCAGTCTCCTGCCACACTGTCACTGTCTCCAGGCGAGAGA
GCCACCCTCTCTTGTAGAGCCTCCGAGTCCGTGGAATACTTCGGCACCTCTCTG
ATGCACTGGTACCAGCAGAAGCCCGGCCAGCCTCCTAGACTGCTGATCTACGC
CGCCTCCAACGTCGAATCTGGCATCCCCGCTAGATTCTCCGGCTCTGGCTCTGG
CACAGACTTTACCCTGACCATCTCCTCCGTGGAACCCGAGGATTTCGCTGTGTA
CTTTTGCCAGCAGACCCGGAAGGTGCCCTACACATTTGGCGGCGGAACAAAGG
TGGAAATCAAG

**SEQ ID NO: 331 – VL cDNA (KL2B413)**

GAAATCGTACTGACCCAGTCCCCTTCTTTCTTGAGTGCATCAGTTGGGGATAGA
GTGACCATTACTTGTAGAGCATCTCAAGGTATTTCTTCATACTTGTCTTGGTATC
AACAAAAACCTGGCAAGGCACCCAAACTCTTGATCTACGCCACCTCTACATTG
CAAAGTGGGGTTCCTTCTAGGTTTTCAGGCTCCGGCTCTGGTACCGAGTTCACC
CTCACTATAAGCAGTCTCCAACCTGAAGATTTCGCTACTTATTATTGTCAGCAG
CTTAATTCTTATCCCCGAACCTTTGGTCAAGGAACTAAGGTCGAGATCAAA

**SEQ ID NO: 332 – m11B6 HC IgG4**

DVQLQESGPGLVKPSQSLSLTCTVTGNSITSDYAWNWIRQFPGNRLEWMGYISYSG
STTYSPSLKSRFSITRDTSKNQFFLQLNSVTPEDTATYFCATGYYYGSGFWGQGTLV
TVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHT
FPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPC
KCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV
HTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPK
GSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNT
EPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK

**SEQ ID NO: 333 – m11B6 LC IgG4**

DIVLTQSPASLAVSLGQRATISCRASESVEYFGTSLMHWYRQKPGQPPKLLIYAASN
VESGVPARFSGSGSGTDFSLNIQPVEEDDFSMYFCQQTRKVPYTFGGGTKLEIKRA
DAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTD
QDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRNEC

**SEQ ID NO: 334 – h11B6 HC IgG4**

QVQLQESGPGLVKPSDTLSLTCAVSGNSITSDYAWNWIRQPPGKGLEWIGYISYSG
STTYNPSLKSRVTMSRDTSKNQFSLKLSSVTAVDTAVYYCATGYYYGSGFWGQGT
LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
PGK

**SEQ ID NO: 335 – h11B6 LC IgG4**

DIVLTQSPDSLAVSLGERATINCKASESVEYFGTSLMHWYQQKPGQPPKLLIYAAS
NRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQTRKVPYTFGQGTKLEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

**SEQ ID NO: 336 – m11B6 HC DNA**

GATGTGCAGCTTCAGGAGTCTGGACCCGGACTTGTTAAACCAAGTCAGTCTCTG
TCCCTGACCTGTACCGTCACCGGCAACAGCATCACAAGCGATTACGCATGGAA
CTGGATCAGGCAGTTCCCTGGAAATCGACTCGAATGGATGGGCTACATTTCATA
CTCCGGTTCAACCACTTACTCTCCATCCTTGAAATCTAGGTTCAGCATCACCCG
TGATACCTCAAAGAACCAATTTTTTCTGCAACTGAATAGCGTAACTCCAGAGGA
CACAGCCACATATTTCTGCGCCACTGGGTATTACTATGGCTCAGGTTTCTGGGG
TCAGGGCACTCTCGTCACCGTCAGCAGCGCCAAAACAACAGCACCAAGTGTCT
ATCCACTGGCCCCTGTGTGTGGAGATACAACTGGCTCCTCGGTGACTCTAGGAT
GCCTGGTCAAGGGTTATTTCCCTGAGCCAGTGACCTTGACCTGGAACTCTGGAT
CCCTGTCCAGTGGTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACA
CCCTCAGCAGCTCAGTGACTGTAACCTCGAGCACCTGGCCCAGCCAGTCCATCA
CCTGCAATGTGGCCCACCCGGCAAGCAGCACCAAGGTGGACAAGAAAATTGAG
CCCAGAGGGCCCACAATCAAGCCCTGTCCTCCATGCAAATGCCCAGCACCTAA
CCTCTTGGGTGGACCATCCGTCTTCATCTTCCCTCCAAAGATCAAGGATGTACT
CATGATCTCCCTGAGCCCCATAGTCACATGTGTGGTGGTGGATGTGAGCGAGG
ATGACCCAGATGTCCAGATCAGCTGGTTTGTGAACAACGTGGAAGTACACACA
GCTCAGACACAAACCCATAGAGAGGATTACAACAGTACTCTCCGGGTGGTCAG
TGCCCTCCCCATCCAGCACCAGGACTGGATGAGTGGCAAGGAGTTCAAATGCA
AGGTCAACAACAAAGACCTCCCAGCGCCCATCGAGAGAACCATCTCAAAACCC
AAAGGGTCAGTAAGAGCTCCACAGGTATATGTCTTGCCTCCACCAGAAGAAGA
GATGACTAAGAAACAGGTCACTCTGACCTGCATGGTCACCGACTTCATGCCTG
AAGACATTTACGTGGAGTGGACCAACAACGGGAAAACAGAGCTAAACTACAA

GAACACTGAACCAGTCCTGGACTCTGATGGTTCTTACTTCATGTACAGCAAGCT
GAGAGTGGAAAAGAAGAACTGGGTGGAAAGAAATAGCTACTCCTGTTCAGTG
GTCCACGAGGGTCTGCACAATCACCACACGACTAAGAGCTTCTCCCGGACTCC
GGGTAAA

**SEQ ID NO: 337 – mu11B6 LC DNA**

GACATTGTGCTGACACAGAGTCCAGCATCCTTGGCAGTATCTTTGGGGCAGCG
GGCAACAATTTCATGCCGTGCATCTGAAAGTGTGGAGTATTTTGGAACTTCTCT
TATGCACTGGTATCGCCAGAAGCCTGGGCAGCCTCCCAAACTCCTTATATATGC
CGCTTCCAACGTGGAGTCCGGAGTACCAGCACGCTTTTCCGGCTCTGGGTCCGG
CACAGACTTTTCCCTCAATATCCAACCTGTTGAAGAAGACGATTTTTCCATGTA
TTTTTGCCAACAGACACGCAAGGTTCCATATACATTCGGCGGCGGCACTAAACT
TGAGATCAAACGGGCTGATGCTGCACCGACTGTGTCCATCTTCCCACCATCCAG
TGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTA
CCCCAAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAACGACAAAATG
GCGTCCTGAACAGTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCATG
AGCAGCACCCTCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTATAC
CTGTGAGGCCACTCACAAGACATCAACTTCACCCATTGTCAAGAGCTTCAACA
GGAATGAGTGT

**SEQ ID NO: 338 – hu11B6 HC DNA**

CAGGTCCAACTGCAAGAGAGCGGACCGGGCCTGGTAAAGCCATCCGACACATT
GTCCCTGACGTGTGCGGTAAGTGGAAACTCTATCACTAGCGACTATGCGTGGA
ATTGGATAAGACAACCGCCGGGCAAGGGGCTGGAATGGATAGGATATATCAGC
TATTCCGGTTCTACGACATACAATCCTTCCCTGAAAAGCAGAGTCACTATGTCA
CGCGACACGTCCAAGAATCAGTTCTCATTGAAATTGTCATCCGTAACGGCCGTT
GACACTGCGGTTTATTATTGCGCAACCGGATATTACTACGGCTCTGGTTTTTGG
GGACAGGGAACACTTGTTACTGTTAGTTCAGCCTCCACCAAGGGCCCATCGGTC
TTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGC

TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGG
CGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACT
CTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGAC
CTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAG
TTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTG
AACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC
TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA
TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTG
CAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAG
CCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAG
GAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC
CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTAC
AAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAG
CTCACCGTGGACAAGAGCAGATGGCAGCAGGGGAACGTCTTCTCATGCTCCGT
GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC
GGGTAAA

**SEQ ID NO: 339 – hu11B6 LC DNA**

GACATAGTCTTGACTCAGAGCCCGGATTCCCTTGCTGTGTCTCTGGGAGAACGA
GCTACGATCAACTGCAAGGCAAGTGAATCCGTAGAATACTTCGGGACATCATT
GATGCATTGGTATCAACAGAAACCGGGGCAACCGCCCAAATTGCTGATATATG
CGGCTAGTAATAGAGAATCAGGAGTACCGGATAGGTTTAGTGGTTCAGGATCA
GGTACAGATTTCACCCTGACAATAAGTAGCTTGCAAGCCGAAGACGTAGCAGT
GTATTACTGCCAACAAACCCGAAAGGTGCCATATACGTTTGGACAGGGTACAA
AGTTGGAAATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCAT
CTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACT
TCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCG
GGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACA

GCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTC
TACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTT
CAACAGGGGAGAGTGT

**SEQ ID NO: 340 – scFv 17 (KL2B413 HL)**

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKGLEWVANIKQD
GSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQNYDILTGHY
GMDVWGQGTTVTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPSFLSASVGDRVTIT
CRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGVPSRFSGSGSGTEFTLTISSLQP
EDFATYYCQQLNSYPRTFGQGTKVEIK

**SEQ ID NO: 341 – scFv 18 (KL2B413 LH)**

EIVLTQSPSFLSASVGDRVTITCRASQGISSYLSWYQQKPGKAPKLLIYATSTLQSGV
PSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPRTFGQGTKVEIKGGSEGKSSG
SGSESKSTGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWVRQAPGKG
LEWVANIKQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR
DQNYDILTGHYGMDVWGQGTTVTVSS

**SEQ ID NO: 342 – scFv 19 (KL2B359 HL)**

QVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQFPGKRLEWIGYISYSGS
TTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCATGYYYGSGFWGQGTL
VTVSSGGSEGKSSGSGSESKSTGGSEIVLTQSPATLSLSPGERATLSCRASESVEYFG
TSLMHWYQQKPGQPPRLLIYAASNVESGIPARFSGSGSGTDFTLTISSVEPEDFAVY
FCQQTRKVPYTFGGGTKVEIK

**SEQ ID NO: 343 – scFv 20 (KL2B359 LH)**

EIVLTQSPATLSLSPGERATLSCRASESVEYFGTSLMHWYQQKPGQPPRLLIYAASN
VESGIPARFSGSGSGTDFTLTISSVEPEDFAVYFCQQTRKVPYTFGGGTKVEIKGGSE
GKSSGSGSESKSTGGSQVQLQESGPGLVKPSQTLSLTCTVSGNSITSDYAWNWIRQF
PGKRLEWIGYISYSGSTTYNPSLKSRVTISRDTSKNQFSLKLSSVTAADTAVYYCAT
GYYYGSGFWGQGTLVTVSS

**SEQ ID NO: 344 VH consensus sequence**

QVQLQESGPGLVKPSX1TLSLTCX2VSGNSITSDYAWNWIRQX3PGKGLEWX4GYIS
YSGSTTYNPSLKSRVTMSRDTSKNQFSLKLSSVTX5X6DTAVYYCATGYYYGSGF
WGQGTLVTVSS

X1 is D or Q; X2 is A or T; X3 is P or F; X4 is I or M; X5 is A or P; or X6 is V or A.

HCDR residues are underlined.

**SEQ ID NO: 345 VL consensus sequence**

X1IVLTQSPX2X3LX4X5SX6GERATX6X8CX9ASESVEYFGTSLMHWYQQKPGQPPX10
LLIYAASNX11ESGX12PX13RFSGSGSGTDFTLTIX14SLQX15EDX16AVYX17CQQTRKV
PYTFG X18GTKX19EIK

X1 is D or E; X2 is D or A; X3 is S or T; X4 is A or S; X5 is V or L; X6 is L or P; X7 is I or L; X8 is N or S; X9 is R or K; X10 is K or R; X11 is V or R; X12 is V or I; X13 is A or D; X14 is Q or S; X15 is P or A; X16 is F or V; X17 is Y or F; X18 is Q or G; and X19 is L or V. LCDR residues are underlined.

**SEQ ID NO: 346 – epitope**

KVTEF

**SEQ ID NO: 347 – epitope**

HYRKW

**SEQ ID NO: 348 – epitope**

SHGWAH

**SEQ ID NO: 349 – epitope**

RHNLFEPEDTGQRVP

**SEQ ID NO: 350 – epitope**

GWGSIEPEE

# CLAIMS

What is claimed is:

1. A chimeric antigen receptor (CAR) comprising:

(a) an extracellular domain that specifically binds to the human Kallikrein-2 (hK2) antigen,

(b) a transmembrane domain, and

(c) an intracellular signaling domain optionally comprising at least one co-stimulatory domain.

2. The CAR of claim 1, further comprising

(d) a CD8a-hinge region,

wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide; and

wherein the intracellular signaling domain comprises a co-stimulatory domain comprising a TNF receptor superfamily member 9 (CD137) component and a primary signaling domain comprising a T-cell surface glycoprotein CD3 zeta chain (CD3z) component.

3. The CAR of claim 2, wherein

the CD8a-hinge region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 25, 269, 270, 271, or 272;

the transmembrane domain comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 26; and/or

the intracellular signaling domain comprises a co-stimulatory domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 27, and a primary signaling domain having an amino acid sequence that is at least 90% identical to SEQ ID NO: 28.

4. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 309, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 310, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 311;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 72, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 73, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 92, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 93, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 94;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 106, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 110, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 111, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 105, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 114, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 118, a heavy chain CDR2 having the amino acid

sequence of SEQ ID NO: 119, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 123, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 124, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122,

wherein the extracellular antigen-binding domain binds the hK2 antigen.

5. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139,

wherein the extracellular antigen-binding domain binds the hK2 antigen.

6. The CAR according to claim 4, wherein the extracellular antigen-binding domain further comprises:

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 95, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 96, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 137, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 139.

7. The CAR according to claim 6, wherein the extracellular antigen-binding domain comprises:

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 64, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 68, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 70, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 69, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 63, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 65, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 66, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 67, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 126, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 71;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 314, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 315, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO:

311, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 312, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 313, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 103, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 104, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 128, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 129, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 130;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 107, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 108, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 109, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 125, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 131, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 132;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 102, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 112, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 113, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 133, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 134, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 135;

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 115, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 116, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 117, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 136, a light chain CDR2 having the amino acid sequence

of SEQ ID NO: 137, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138; or

a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 120, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 121, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 122, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 97, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 127, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 138.

8. The CAR according to claim 6, wherein the extracellular antigen-binding domain comprises: a heavy chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 86, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 87, a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 88, and a light chain complementarity determining region 1 (CDR1) having the amino acid sequence of SEQ ID NO: 89, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 90, a light chain CDR3 having the amino acid sequence of SEQ ID NO: 91.

9. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises:

a light chain variable domain (VL) comprising an amino acid sequence selected from SEQ ID NOS: 1, 2, 3, 74, 75, 147, 148, 149, 150, 151, 152 and 318; and/or

a heavy chain variable domain (VH) comprising an amino acid sequence selected from SEQ ID NOS: 4, 5, 6, 76, 77, 140, 141, 142, 143, 144, 145, 146 and 317;

wherein the extracellular antigen-binding domain binds the human Kallikrein-2 (hK2) antigen.

10. The CAR of claim 9, wherein the extracellular antigen-binding domain comprises:

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 4;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 6;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 3 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 5;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 74 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 76;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 77;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 147 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 141;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 75 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 140;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 148 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 142;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 149 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 143;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 150 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 144;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 151 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 145;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 152 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 146;

a light chain variable region comprising an amino acid sequence of SEQ ID NO: 318 and a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 317.

11. The CAR of any of claims 1-10, wherein the extracellular antigen-binding domain comprises a single-chain variable fragment (scFv), the scFv comprising a light chain variable region (VL) and a heavy chain variable region (VH).

12. The CAR of claim 11, wherein the scFv comprises a linker polypeptide between the light chain variable region (VL) and the heavy chain variable region (VH).

13. The CAR of claim 12, wherein the linker polypeptide comprises an amino acid sequence of SEQ ID NO: 7.

14. The CAR of any of claims 11-13, wherein the scFv comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 8-23, 169-184 and 340-343.

15. The CAR of any of claims 1-14, wherein the extracellular antigen-binding domain comprises a signal polypeptide.

16. The CAR of claim 15, wherein the signal polypeptide comprises an amino acid sequence of SEQ ID NO: 24.

17. The CAR of any of claims 4-16, wherein the intracellular signaling domain comprises a polypeptide component selected from the group consisting of a TNF receptor superfamily member 9 (CD137) component, a T-cell surface glycoprotein CD3 zeta chain

(CD3z) component, a cluster of differentiation (CD27) component, a cluster of differentiation superfamily member component, and a combination thereof.

18. The CAR of claim 17, wherein the CD137 component comprises an amino acid sequence of SEQ ID NO: 27.

19. The CAR of claim 17 or claim 18, wherein the CD3z component comprises an amino acid sequence of SEQ ID NO: 28.

20. The CAR of any one of claims 17-19, wherein the intracellular signaling domain comprises an amino acid sequence of SEQ ID NO: 45, or, optionally, the intracellular signaling domain comprises a co-stimulatory domain comprising an amino acid sequence of SEQ ID NO: 27, and a primary signaling domain comprising an amino acid sequence of SEQ ID NO: 28.

21. The CAR of any of claims 4-20, wherein the transmembrane domain comprises a CD8a transmembrane region (CD8a-TM) polypeptide.

22. The CAR of claim 21, wherein the CD8a-TM polypeptide comprises an amino acid sequence of SEQ ID NO: 26.

23. The CAR of any of claims 4-22, further comprising a hinge region linking the transmembrane domain to the extracellular antigen-binding domain.

24. The CAR of claim 23, wherein the hinge region is a CD8a-hinge region.

25. The CAR of claim 24, wherein the CD8a-hinge region comprises an amino acid sequence of SEQ ID NO: 25, 269, 270, 271, or 272.

26. The CAR of any of claims 1-25, wherein the extracellular antigen-binding domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 29-44, 78-81, 221-236, and 273-308.

27. The CAR of any of claims 1-26, wherein the CAR comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 46-61, 82-85 and 205-220.

28. An isolated lymphocyte expressing the CAR of any of claims 1-27.

29. The isolated lymphocyte of claim 28, wherein the lymphocyte is a T lymphocyte.

30. The isolated lymphocyte of claim 28, wherein the lymphocyte is a natural killer (NK) cell.

31. An isolated nucleic acid molecule encoding the CAR of any of claims 1-27.

32. A vector comprising the nucleic acid molecule of claim 31.

33. A cell expressing the nucleic acid molecule of claim 31.

34. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of claims 28-30.

35. A pharmaceutical composition, comprising an effective amount of the lymphocyte of any of claims 28-30 and a pharmaceutically acceptable excipient.

36. The CAR of any of claims 1-27 or the pharmaceutical composition of claims 34 or 35 for use in therapy.

37. The CAR of any of claims 1-27 or the pharmaceutical composition of claims 34 or 35 for use in a method of treating a subject having cancer.

38. A method of treating a subject having cancer, the method comprising: administering a therapeutically effective amount of the lymphocyte of any of claims 28-30 to a subject in need thereof, whereby the lymphocyte induces killing of cancer cells in the subject.

39. The method of claim 38, or the CAR or the pharmaceutical composition for use in a method of claim 37, wherein the cancer is prostate cancer or androgen receptor-expressing breast cancer.

40. A method of targeted killing of a cancer cell, the method comprising: contacting the cancer cell with the lymphocyte of any of claims 28-30, whereby the lymphocyte induces killing of the cancer cell.

41. The method of claim 40, wherein the cancer cell is a prostate cancer cell or androgen receptor-expressing breast cancer cell.

42. A method of detecting the presence of cancer in a subject, comprising: contacting a cell sample obtained from the subject with the CAR of any one of claims 1-27, thereby forming a CAR-cell complex, and

detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.