COMPOSITIONS AND METHODS FOR TREATING MESOTHELIN POSITIVE CANCERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is claims benefit of priority to U.S. Provisional Application No. 63/085,971, filed on September 30, 2020, and U.S. Provisional Application No. 63/068,245, filed on August 20, 2020, each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The disclosure relates to the fields of adoptive cell therapy and cancer therapeutics.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0003] The sequence listing paragraph application contains a Sequence Listing which has been submitted in ASCII format via EFS-WEB and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 17, 2021 is named A2BI_019_03WO_SeqList_ST25.txt and is 1.08 MB in size.

BACKGROUND

[0004] Cell therapy is a powerful tool for the treatment of various diseases, particularly cancers. In conventional adoptive cell therapies, immune cells are engineered to express specific receptors, for example chimeric antigen receptors (CARs) or T cell receptors (TCRs), which direct the activity of the immune cells to cellular targets via interaction of the receptor with a ligand expressed by the target cell. Identification of suitable target molecules remains challenging, as many targets are expressed in normal tissues. This expression can lead to toxicity when the transplanted cells target normal tissues expressing target molecules. There is thus a need in the art for compositions and methods useful in the treatment of disease, particularly cancers, by adoptive cell therapy.

[0005] Mesothelin (MSLN) was proposed as a cancer target in 1992 (Chang et al. *Cancer Res* 52:181-86), yet there is still no viable therapy that utilizes MSLN. Not only is it expressed on most mesotheliomas but also large subsets of ovarian, cervical, uterine, gastric, pancreatic and lung adenocarcinomas. (Hassan et al. *J Clin Oncol* 34:4171-79) In normal

adults, MSLN is present only in mesothelium, a tissue that itself may be nonessential. Several investigational therapeutics directed at MSLN have been tested; for example, immunotoxin-conjugates, antibody-drug conjugates, bispecific antibodies, CAR-Ts, and a hybrid TCR-scFv.

[0006] All active systemically administered therapeutics have been toxic. Accordingly, there exists a need in the art for compositions and methods related to treatment of MSLN(+) cancers.

SUMMARY

[0007] Provided herein are compositions and methods related to treatment of MSLN(+) cancers. Advantageously, the compositions and methods disclosed herein may exploits loss of heterozygosity (LOH) to address MSLN(+) cancer. The compositions and methods disclosed herein may, in some cases, avoid systemic toxicity to normal tissues by pairing a MSLN-targeted activator receptor with a blocker receptor. Without being bound by theory, the difference in blocker antigen expression in tumor versus. normal tissues caused by LOH at the locus encoding the blocker antigen may confer high selectivity for tumor killing.

[0008] The disclosure provides immune cells comprising: (a) a first receptor, comprising an extracellular ligand binding domain specific to Mesothelin (MSLN); and (b) a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen lost in a MSLN + cancer cell, wherein the first receptor is an activator receptor responsive to MSLN; and wherein the second receptor is an inhibitory receptor responsive to the non-target antigen.

[0009] In some embodiments of the immune cells of the disclosure, the non-target antigen is lost in the MSLN+ cancer cell through loss of heterozygosity.

[0010] In some embodiments of the immune cells of the disclosure, the extracellular ligand binding domain of the second receptor specifically binds an allelic variant of a major histocompatibility complex (MHC) protein. In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds an allelic variant of an HLA-A, HLA-B, or HLA-C protein. In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11, HLA-B*07, or HLA-C*07. In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*02. In some embodiments, the extracellular ligand binding domain of the second receptor comprises complementarity determining regions

(CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of Table 6 or Table 7. In some embodiments, the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOS: 42-47 or of SEQ ID NOS: 48-53; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of SEQ ID NOS: 42-47 or SEQ ID NOS: 48-53. In some embodiments, the extracellular ligand binding domain of the second receptor comprises a polypeptide sequence selected from the polypeptide sequence disclosed in Table 5; or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the extracellular ligand binding domain of the second receptor comprises any one of SEQ ID NOS: 30-41, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0010a] Disclosed herein is an immune cell comprising: a) first receptor, comprising an extracellular ligand binding domain specific to Mesothelin (MSLN); and b) a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen lost in a MSLN+ cancer cell, wherein the first receptor is an activator receptor responsive to MSLN; and wherein the second receptor is an inhibitory receptor responsive to the non-target antigen, wherein the extracellular ligand binding domain of the second receptor specifically binds HLA-A*02, and wherein the extracellular ligand binding domain of the first receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOs: 535, 539, 542, 438, 454, and 533, and wherein the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs), wherein the CDR-L1 sequence is RSSQSIVHSNGNTYLE (SEQ ID NO: 42), the CDR-L2 sequence is KVSNRFSGVPAR, the CDR-L3 sequence is FQGSHVPRT (SEQ ID NO: 44), the CDR-H1 sequence is ASGYTFTSYHIH (SEQ ID NO: 45), the CDR-H2 sequence is WIYPGNVNTEYNEKFKGK (SEQ ID NO: 46), and the CDR-H3 sequence is EEITYAMDY (SEQ ID NO: 47), or wherein the extracellular ligand binding domain of the first receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOs: 535, 539, 542, 438, 454, and 488, and wherein the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs), wherein the CDR-L1 sequence is RSSQSIVHSNGNTYLE (SEQ ID NO: 42), the CDR-L2 sequence is KVSNRFSGVPAR, the CDR-L3 sequence is FQGSHVPRT (SEQ ID NO: 44), the CDR-H1 sequence is

ASGYTFTSYHIH (SEQ ID NO: 45), the CDR-H2 sequence is WIYPGNVNTEYNEKFKGK (SEQ ID NO: 46), and the CDR-H3 sequence is EEITYAMDY (SEQ ID NO: 47).

[0011] In some embodiments of the immune cells of the disclosure, the first receptor is a chimeric antigen receptor (CAR). In some embodiments, the extracellular ligand binding domain of the first receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 2; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the CDRs of Table 2. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a variable heavy (VH) portion comprising a sequence set forth in Table 3 and a variable light (VL) portion comprising a sequence set forth in Table 4; or a sequence having at least 80%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a variable heavy (VH) portion comprising SEQ ID NO: 233 or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto, and a variable light (VL) portion comprising SEQ ID NO: 279 or a sequence having 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a sequence selected from the group consisting of SEQ ID NOS: 3-6, 80 and 154-215, or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises an scFv sequence of SEQ ID NO: 171; or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0012] In some embodiments of the immune cells of the disclosure, the first receptor comprises a hinge domain, a transmembrane domain and an intracellular domain. In some embodiments, the hinge domain comprises a CD8α hinge domain. In some embodiments, the CD8α hinge domain comprises a sequence of SEQ ID NO: 7, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the transmembrane domain comprises a CD28 transmembrane domain. In some embodiments, the CD28 transmembrane domain comprises a sequence of SEQ ID NO: 11, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the intracellular domain comprises a CD28 co-stimulatory domain, a 4-1BB co-stimulatory domain, and a CD3ζ activation domain. In some embodiments, the intracellular domain comprises a sequence of SEQ ID NO: 285, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity

thereto. In some embodiments, the first receptor comprises a sequence of SEQ ID NO: 303, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0013] In some embodiments of the immune cells of the disclosure, the second receptor comprises a LILRB1 intracellular domain or a functional variant thereof. In some embodiments, the LILRB1 intracellular domain comprises a sequence at least 90%, at least 95%, at least 97%, at least 99%, or is identical to SEQ ID NO: 70. In some embodiments, the second receptor comprises a LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 90%, at least 95%, at least 97%, at least 99% or is identical to SEQ ID NO: 74. In some embodiments, the second receptor comprises a LILRB1 hinge domain or functional variant thereof. In some embodiments, the LILRB1 hinge domain comprises a sequence at least 90%, at least 95%, at least 97%, at least 99% or is identical to SEQ ID NO: 73. In some embodiments, the second receptor comprises a LILRB1 intracellular domain, a LILRB1 transmembrane domain, a LILRB1 hinge domain, a functional variant of any of these, or combinations thereof. In some embodiments, the LILRB1 hinge domain, LILRB1 intracellular domain and LILRB1 transmembrane domain comprises SEQ ID NO: 71 or a sequence at least 90%, at least 95%, at least 97%, at least 99% or is identical to SEQ ID NO: 71. In some embodiments, the second receptor comprises a sequence of SEQ ID NO: 348, or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto.

[0014] In some embodiments of the immune cells of the disclosure, the MSLN+ cancer cell is a mesothelioma cancer cell, an ovarian cancer cell, a cervical cancer cell, a colorectal cancer cell, an esophageal cancer cell, a head and neck cancer cell, a kidney cancer cell, an uterine cancer cell, a gastric cancer cell, a pancreatic cancer cell, a lung cancer cell, a colorectal cancer cell or a cholangiocarcinoma cell, or any cancer cell expressing MSLN. In some embodiments, the MSLN+ cancer cell is a mesothelioma cancer cell, an ovarian cancer cell, a cervical cell, a uterine cancer cell, a gastric cancer cell, a pancreatic cancer cell or a lung adenocarcinoma cell.

[0015] In some embodiments, the MSLN+ cancer cell is an epithelial cancer cell. Epithelial cancers are cancers that originate in the epithelial cells. In some embodiments, the MSLN+ epithelial cancer is a carcinoma.

[0016] In some embodiments of the immune cells of the disclosure, the MSLN+ cancer cell is a MSLN+/HLA-A*02– cancer cell that does not express HLA-A*02. In some embodiments, the MSLN+/HLA-A*02– cancer cell is derived from a MSLN+/HLA-A*02+

cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02. In some embodiments, the first receptor and the second receptor together specifically activate the immune cell in the presence of the MSLN+/HLA-A*02- cancer cell having loss of heterozygosity. In some embodiments, the first receptor and the second receptor together do not specifically activate the immune cell in the presence of an MSLN+ cell that has not lost HLA-A*02 by loss of heterozygosity.

[0017] In some embodiments of the immune cells of the disclosure, the immune cell is a T cell. In some embodiments, the T cell is a CD8+ CD4- T cell.

[0018] In some embodiments of the immune cells of the disclosure, expression and/or function of a MHC Class I gene has been reduced or eliminated. In some embodiments, the MHC Class I gene is beta-2-microglobulin (B2M). In some embodiments, the immune cells further comprise an interfering RNA, the interfering RNA comprising a sequence complementary to a sequence of a B2M mRNA. In some embodiments, the interfering RNA comprises a sequence selected from the group of sequences set forth in Table 13, or a sequence having at most 1, 2, 3, or 4 substitutions, insertions or deletions relative thereto. In some embodiments, the interfering RNA is capable of inducing RNAi-mediated degradation of the B2M mRNA. In some embodiments, the interfering RNA is a short hairpin RNA (shRNA). In some embodiments, the shRNA comprises: (a) a first sequence, having from 5' end to 3' end a sequence complementary to a sequence of the B2M mRNA; and (b) a second sequence, having from 5' end to 3' end a sequence complementary to the first sequence, wherein the first sequence and the second sequence form the shRNA. In some embodiments, the shRNA is encoded by a sequence comprising a sequence of GCACTCAAAGCTTGTTAAGATCGAAATCTTAACAAGCTTTGAGTGC (SEQ ID NO: 349) or GTTAACTTCCAATTTACATACCGAAGTATGTAAATTGGAAGTTAAC (SEQ ID NO: 350), or a sequence having at least 80%, at least 90%, or at least 95% identity thereto.

[0019] In some embodiments of the immune cells of the disclosure, expression and/or function of a MHC Class I gene has been reduced or eliminated. In some embodiments, the MHC Class I gene is beta-2-microglobulin (B2M). In some embodiments, the immune cells comprise one or more modifications to a sequence encoding B2M, wherein the one or more modifications reduce the expression and/or eliminate the function of B2M. In some embodiments, the one or more modifications comprise one or more inactivating mutations of the endogenous gene encoding B2M. In some embodiments, the one or more inactivating mutations comprise a deletion, an insertion, a substitution, or a frameshift mutation. In some embodiments, the one or more inactivating mutations are introduced with a nucleic acid

guided endonuclease in a complex with at least one guide In some embodiments e nucleic acid (gNA) that specifically targets a sequence of the endogenous gene encoding B2M. In some embodiments, the gNA comprises a sequence selected from the group of sequences set forth in Table 12, or a sequence having at most 1, 2, 3, or 4 substitutions, insertions or deletions relative thereto.

[0020] In some embodiments of the immune cells of the disclosure, expression and/or function of a MHC Class I gene has been reduced or eliminated. In some embodiments, the MHC Class I gene is HLA-A*02. In some embodiments, the immune cells comprise a polynucleotide comprising an interfering RNA, comprising a sequence complementary to a sequence of an HLA-A*02 mRNA. In some embodiments, the interfering RNA is capable of inducing RNA interference (RNAi)-mediated degradation of the HLA-A*02 mRNA. In some embodiments, the interfering RNA is a short hairpin RNA (shRNA) comprising: (a) a first sequence, having from 5' end to 3' end a sequence complementary to a sequence of the HLA-A*02 mRNA; and (b) a second sequence, having from 5' end to 3' end a sequence complementary to the first sequence, wherein the first sequence and the second sequence form the shRNA. In some embodiments, the shRNA comprises a sequence set forth in 14. In some embodiments, the immune cells comprise one or more modifications to a sequence of an endogenous gene encoding HLA-A*02, wherein the one or modifications reduce the expression and/or eliminate the function of HLA-A*02. In some embodiments, the one or more modifications comprise one or more inactivating mutations of the endogenous gene encoding HLA-A*02. In some embodiments, the one or more inactivating mutations are introduced with a nucleic acid guided endonuclease in a complex with at least one guide nucleic acid (gNA) that specifically targets a sequence of the endogenous gene encoding HLA-A*02. In some embodiments, the gNA comprises a sequence set forth in Table 11.

[0021] In some embodiments of the immune cells of the disclosure, the first receptor comprises a sequence of SEQ ID NO: 164, and the second receptor comprises a sequence of SEQ ID NO: 52, or sequences having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the immune cells comprise an shRNA encoded by a sequence comprising GCACTCAAAGCTTGTTAAGATCGAAATCTTAACAAGCTTTGAGTGC (SEQ ID NO: 349) or GTTAACTTCCAATTTACATACCGAAGTATGTAAATTGGAAGTTAAC (SEQ ID NO: 350) or a sequence having at least 80%, at least 90%, or at least 95% identity thereto. In some embodiments, the first receptor and second receptor are encoded by a single polynucleotide, and wherein the sequences encoding the first and second receptors are

separated by a sequence encoding a self-cleaving polypeptide. In some embodiments, the self-cleaving polypeptide comprises a T2A self-cleaving polypeptide comprising a sequence of GSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 351).

[0022] In some embodiments of the immune cells of the disclosure, the immune cells are autologous.

[0023] In some embodiments of the immune cells of the disclosure, the immune cells are allogeneic.

[0024] Disclosed herein is a pharmaceutical composition, comprising a therapeutically effective amount of the immune cells of the disclosure. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, diluent or excipient.

[0025] The disclosure provides a pharmaceutical composition, comprising a therapeutically effective amount of the immune cells of the disclosure for use as a medicament in the treatment of MSLN+ cancer.

[0026] The disclosure provides a polynucleotide or polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding: (a) a first receptor, comprising an extracellular ligand binding domain specific to Mesothelin (MSLN); and (b) a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen that has been lost in a MSLN+ cancer cell, wherein the first receptor is an activator receptor responsive to MSLN on the MSLN+ cancer cell; and wherein the second receptor is an inhibitory receptor responsive to the non-target antigen.

[0026a] Disclosed herein is a polynucleotide or polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding the first receptor and the second receptor for generating the immune cells of the disclosure, or a vector, comprising the one or more polynucleotides.

[0027] In some embodiments of the polynucleotide or polynucleotide system of the disclosure, the polynucleotide or polynucleotide system comprises one or more polynucleotides comprising polynucleotide sequences encoding the first receptor and the second receptor for use in generating the immune cells of the disclosure. In some embodiments, the polynucleotide or polynucleotide system comprises a sequence encoding an shRNA specific to B2M. In some embodiments, the sequences encoding the first receptor, the second receptor and the shRNA specific to B2M are encoded by the same polynucleotide. In some embodiments, (a) the sequence encoding the shRNA specific to B2M comprises GCACTCAAAGCTTGTTAAGATCGAAATCTTAACAAGCTTTGAGTGC (SEQ ID NO:

349) or GTTAACTTCCAATTTACATACCGAAGTATGTAAATTGGAAGTTAAC (SEQ ID NO: 350) or a sequence having at least 80%, at least 90%, or at least 95% identity thereto; (b) the sequence encoding the first receptor comprises a sequence encoding a polypeptide of SEQ ID NO: 303, or a sequence having at least 80%, at least 90%, or at least 95% identity thereto; and (c) the sequence encoding the second receptor comprises a sequence encoding a polypeptide of SEQ ID NO: 348, or a sequence having at least 80%, at least 90%, or at least 95% identity thereto.

[0028] The disclosure provides a vector, comprising the one or more polynucleotides of the disclosure.

[0029] The disclosure provides methods of killing a MSLN+ cancer cell having loss of heterozygosity at an MHC class I locus, comprising administering to the subject an effective amount of the immune cells or pharmaceutical composition of the disclosure.

[0030] The disclosure provides methods of treating MSLN+ cancer in a subject having a MSLN+ tumor having loss of heterozygosity at an MHC class I locus, comprising administering to the subject an effective amount of the immune cells or pharmaceutical composition of the disclosure.

[0031] The disclosure provides methods of treating a cancer in a subject comprising: (a) determining HLA-A genotype or expression of normal cells and a plurality of cancer cells of the subject; (b) optionally, determining the expression of MSLN in a plurality of cancer cells of the subject; and (c) administering to the subject an effective amount of the immune cells or pharmaceutical composition of the disclosure if the normal cells express HLA-A*02 and the plurality of cancer cells do not express HLA-A*02, and the plurality of cancer cells are MSLN-positive.

In some embodiments of the methods of the disclosure, the subject is a heterozygous HLA-A*02 patient with a malignancy that expresses MSLN (MSLN+) and has lost HLA-A*02 expression. In some embodiments, the subject is a heterozygous HLA-A*02 patient with recurrent unresectable or metastatic solid tumors that express MSLN and have lost HLA-A*02 expression. In some embodiments, the cancer comprises

mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma. In some embodiments, the cancer comprises mesothelioma, ovarian cancer, cervical cancer, uterine cancer, gastric cancer, pancreatic cancer or lung adenocarcinoma. In some embodiments, the cancer has relapsed in a subject. In some embodiments, the cancer is refractory to one or more prior administered anticancer therapies.

In some embodiments, the cancer is metastatic.

[0031a] Disclosed herein is the immune cell of the disclosure for use in the treatment of MSLN+ cancer, optionally wherein the MSLN+ cancer is an MSLN+ tumor having loss of heterozygosity at a locus encoding a non-target antigen; and/or wherein the MSLN+ cancer comprises MSLN+ cancer cells having loss of heterozygosity at an MHC class I locus, optionally wherein the cancer comprises mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma; and/or wherein the cancer cells comprise MSLN+/HLA-A*02–cancer cells that do not express HLA-A*02; optionally cancer cells derived from a MLSN+/HLA-A*02+ cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02.

[0031b] Disclosed herein is the use of the immune cell of the disclosure in the manufacture of a medicament for the treatment of MSLN+ cancer, optionally wherein the MSLN+ cancer is an MSLN+ tumor having loss of heterozygosity at a locus encoding a non-target antigen; and/or wherein the MSLN+ cancer comprises MSLN+ cancer cells having loss of heterozygosity at an MHC class I locus, optionally wherein the cancer comprises mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma; and/or wherein the cancer cells comprise MSLN+/HLA-A*02–cancer cells that do not express HLA-A*02; optionally cancer cells derived from a MLSN+/HLA-A*02+ cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02.

[0032] In some embodiments of the methods of the disclosure, the cancer cells comprise MSLN+/HLA-A*02– cancer cells that do not express HLA-A*02. In some embodiments, the MSLN+/HLA-A*02– cancer cells are derived from a MLSN+/HLA-A*02+ cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02. In some embodiments, the first receptor and the second receptor together specifically activate the immune cell in the presence of the MSLN+/HLA-A*02- cancer cells. In some embodiments, the first receptor and the second receptor together do not specifically activate the immune cell in the presence of a MSLN+ cell that has not lost HLA-A*02.

[0033] In some embodiments of the methods of the disclosure, administration of the immune cells or pharmaceutical composition reduces the size of a tumor in the subject. In some embodiments, the tumor is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%,

about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In some embodiments, the tumor is eliminated.

[0034] In some embodiments of the methods of the disclosure, administration of the immune cells or pharmaceutical composition arrests the growth of a tumor in the subject.

[0035] In some embodiments of the methods of the disclosure, administration of the immune cells or pharmaceutical composition reduces the number of tumors in the subject.

[0036] In some embodiments of the methods of the disclosure, administration of the immune cells or pharmaceutical composition results in selective killing of a cancer cell but not a normal cell in the subject. In some embodiments, at least about 60% of the cells killed are cancer cells, about 65% of the cells killed are cancer cells, about 70% of the cells killed are cancer cells, about 75% of the cells killed are cancer cells, about 80% of the cells killed are cancer cells, about 85% of the cells killed are cancer cells, about 90% of the cells killed are cancer cells, about 95% of the cells killed are cancer cells, or about 100% of the cells killed are cancer cells. In some embodiments, administration of the immune cell or pharmaceutical composition results in the killing of at least about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or all of the cancer cells of the subject.

[0037] In some embodiments of the methods of the disclosure, administration of the immune cell or the pharmaceutical composition results in fewer side effects for the subject than administration of an otherwise equivalent immune cell comprising the first activator receptor but no second inhibitory receptor.

[0038] The disclosure provides methods making a plurality of immune cells, comprising: (a) providing a plurality of immune cells, and (b) transforming the plurality of immune cells with the polynucleotide, polynucleotide system or vector of the disclosure.

[0039] The disclosure provides kits comprising the immune cells or pharmaceutical composition of the disclosure. In some embodiments, the kits further comprise instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 is a table showing expression of blocker candidate genes from the TCGA database. (*) indicates genes previously identified as being expressed in the mesothelium.

[0041] FIG. 2 is a plot showing Mesothelin (MSLN) expression in normal tissues.

[0042] FIG. 3 is a plot showing the expression of MSLN across TCGA cancers (with tumor and normal samples.) Abbreviations: BLCA (Bladder cancer), BRCA (Breast Cancer), CESC (Cervical squamous cell carcinoma and endocervical adenocarcinoma), CHOL

Cholangiocarcinoma), COAD (Colon adenocarcinoma), ESCA (Esophageal carcinoma), GBM (Glioblastoma multiforme), HNSC (Head and Neck squamous cell carcinoma), KICH (Kidney Chromophobe), KIRP (Kidney renal papillary cell carcinoma), LIHC (Liver hepatocellular carcinoma), LUAD (Lung adenocarcinoma), LUSC (Lung squamous cell carcinoma), PAAD (Pancreatic adenocarcinoma), PRAD (Prostate adenocarcinoma), PCPG (Pheochromocytoma and Paraganglioma), READ (Rectum adenocarcinoma), SARC (Sarcoma), SKCM (Skin Cutaneous Melanoma), THCA (Thyroid carcinoma), THYM (Thymoma), STAD (Stomach adenocarcinoma), UCEC (Uterine Corpus Endometrial Carcinoma).

[0043] FIG. 4 is a plot showing MSLN expression in CCLE cell lines.

[0044] FIG. 5 is a plot showing LRRN4 expression in normal tissues.

[0045] FIG. 6 is a plot showing the expression of LRRN4 across TCGA cancers (with tumor and normal samples).

[0046] FIG. 7 is a plot showing the expression of LRRN4 across TCGA tumors.

[0047] FIG. 8 is a plot showing expression of LRRN4 in CCLE cell lines.

[0048] FIG. 9 is a plot showing the distribution of 10 leucine rich repeat (LRR) and Fibronectin Type III domains relative to the transmembrane domain of LRRN4. Most of these domains are likely located on the cell surface.

[0049] FIG. 10A shows that a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor can inhibit activation of Jurkat cells in *cis* in a cell-free bead based assay.

[0050] FIG. 10B that a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor can inhibit activation of Jurkat cells by a MSLN scFv CAR using the leukemia cell line K562 as target cells.

[0051] FIG. 11 is a diagram (left) and a chart (right) showing that a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor can inhibit activation of Jurkat cells, as measured by fold induction of IFNγ, by a MSLN scFv CAR using a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor and HLA-A*02+ HeLa and SiHa cells as target cells.

[0052] FIG. 12 shows that a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor inhibits killing by MSLN CAR activators using HLA-A*02+ SiHa cells but not HLA-A*02- SiHa cells.

[0053] FIG. 13 is a diagram of the bioinformatics pipeline used to identify potential inhibitory receptor targets that are lost in cancer cells due to loss of heterozygosity.

[0054] FIG. 14 is a of the bioinformatics pipeline used to identify potential inhibitory receptor targets that are not expressed in cancer cells.

[0055] FIG. 15A is a pair of plots showing that the HLA-A*02 blocker inhibits MSLN CAR activators directed at MSLN, a high-density antigen. Jurkat cells transfected with MSLN LBD1-CAR or MSLN LBD1-CAR & A2-LIR-1 co-cultured with K562 cells expressing either MSLN or MSLN & HLA-A*02 shows blocking of activation by a high-density antigen with A2-LIR-1 blocker only in the presence of HLA-A*02.

[0056] FIG. 15B is a pair of plots showing that the HLA-A*02 blocker inhibits MSLN CAR activators directed at MSLN, a high-density antigen. Killing of endogenous MSLN+ HeLa cells by MSLN LBD1-CAR T cells is blocked in the presence of HLA-A*02 with the A2-LIR-1 blocker.

[0057] FIG. 15C is a pair of plots showing that the HLA-A*02 blocker inhibits MSLN CAR activators directed at MSLN, a high-density antigen. Killing of endogenous MSLN+ HeLa cells by MSLN LBD2-CAR T cells is shown. The effect of A2-LIR-1 blocker on T cell killing is in part controlled by the activator LBD, suggesting further optimization of the blocker module or pairs of activator/blockers may be required.

[0058] FIG. 16 is a series of plots showing that HLA-A*02 LIR1 inhibitory receptors (PA2.1, mouse and humanized) effectively block killing by T cells expressing MSLN Generation 3 CAR in the presence of HeLa cells that express MSLN and HLA-A*02. Top row: MSLN + HLA-A*02+ HeLa target cells; bottom row: MSLN+ HLA-A*02- HeLa cells (control). The murine SS1 generation 3 CAR (upper right, boxed) provides a better window than the humanized M5 and humanized SS1 CARs.

[0059] FIG. 17 is a series of plots showing that HLA-A*02 LIR1 inhibitory receptors (PA2.1, mouse and humanized) effectively block killing by T cells expressing MSLN Generation 3 CAR in the presence of MSLN+ HLA-A*02+ Capan-2 cells.

[0060] FIG. 18 is a pair of plots that shows that killing of MSLN + HLA-A*02+ HeLa cells (left) or HCT116 wild type (WT) cells that are natively MSLN + HLA-A*02+ by T cells expressing a 2nd generation CAR with a murine SS1 scFv is effectively blocked by an HLA-A*02 scFv LIR1 inhibitory receptor.

[0061] FIG. 19 is a series of fluorescence activated cell sorting (FACS) plots showing the expression of murine SS1 second generation CARs by T cells, with and without co-transduction of an HLA-A*02 scFv LIR-1 blocker.

[0062] FIG. 20A is a plot showing the effect of LIR-1 hinge on the ability of an HLA-A*02 inhibitory receptor to block activation of Jurkat cells by a KRAS TCR. H: hinge, T: transmembrane domain, ICD: intracellular domain, s: short. LIR-1 constructs are described in

more detail in FIG. 20B. Humanized PA2.1 and humanized BB7.2 with shorter LIR-1 hinge block similarly to original, longer hinge

[0063] FIG. 20B is a plot and a table showing EC50 shift (+/- HLA-A*02 target cells) for Jurkat cells expressing a KRAS TCR activator and the HLA-A*02 scFv LIR-1 inhibitory receptors shown in the table at bottom (SEQ ID NOs: 352-356).

[0064] FIG. 21A is a plot showing the effect of LIR-1 hinge on the ability of an HLA-A*02 inhibitory receptor to block activation of Jurkat cells by a KRAS TCR. H: hinge, TM: transmembrane domain, ICD: intracellular domain, s: short; tr: truncated. LIR-1 constructs are described in more detail in FIG. 21B. Mouse PA2.1 with slightly longer hinges function similarly to original LIR-1 hinge in T2-Jurkat assay.

[0065] FIG. 21B is a plot and a pair of tables showing EC50 shift (+/- HLA-A*02 target cells) for Jurkat cells expressing a KRAS TCR activator and the HLA-A*02 scFv LIR-1 inhibitory receptors shown in the table at bottom (SEQ ID NOs: 357-361), with lengths shown in the table at left.

[0066] FIG. 22A and FIG. 22B show the Tmod approach to achieve selective cytotoxicity with two targets (Tmod refers to immune cells expressing the combination of activator and inhibitory receptor). FIG. 22A shows the lung (and other vital organs) are surrounded by the MSLN(+) mesothelial lining, creating high risk of on-target, off-tumor toxicity for MSLN-targeted medicines. By selecting patients heterozygous for HLA-A*02 whose tumors have lost this allele via LOH, there is an opportunity to target MSLN-activated CAR-T cells to kill tumor cells specifically and spare normal mesothelium. FIG. 22B shows the molecular composition of MSLN-targeted Tmod constructs (Tmod refers to the paired activator and inhibitory receptors). The two receptors are co-expressed in a single construct and the encoded fusion protein is cleaved in the cell to generate the activator and blocker.

[0067] FIG. 23A, FIG. 23B, FIG. 23C, and FIG. 23D show the isolation and characterization of selective MSLN binders. On-target probe was labeled soluble MSLN (Acro Bio); off-target probe used for counterselection was a mixture of soluble CEA and EGFR proteins. FIG. 23A shows enrichment of IgG library. FIG. 23B shows enrichment of scFv library. FIG. 23C shows surface expression of MSLN CARs (Gen3) in Jurkat cells. Cells were transfected with CAR constructs and stained with Protein L or monomeric soluble MSLN (see Methods). Benchmark and CAR1-6 expression histograms are labeled. PE, phycoerythrin; NA, neutravidin; SA, streptavidin. “On-target NGS” corresponds to the cell populations that are collected and subjected to DNA sequencing to determine enrichment of individual idiotypes. FIG. 23D shows the characterization of MSLN binders in solid-state Jurkat cell assays with

MSLN protein attached to the surface (see Hamburger et al., 2020). 62 CAR constructs (Gen3) bearing different scFvs were transiently transfected in Jurkat cells to express CARs and a functional response to surface-bound recombinant human sMSLN (Acro Bio) was assessed after 6 hours. Most resulted in some degree of response.

[0068] FIG. 24A shows the sensitivity of MSLN CARs vs. benchmark CARs M5, SS1 and m912. All constructs were Gen3 except SS1 (Gen2). Jurkat cell dose-response (RLU) was measured to assess the sensitivity in a 6 hour co-culture assay: (1) Titrated MSLN-encoding mRNA was used to transfect HEK293 cells; (2) QIFIKIT (quantitative analysis kit, Agilent) was used to convert flow-cytometry based surface expression to MSLN molecules/cell; and, (3) The molecule/cell sensitivities (EC50) of 6 novel and three benchmark CARs were calculated from fitting the dose-response curves. For those CARs with sensitivities below the limit of detection of the assay, EC50 was reported as <3000 MSLN molecules/cell. Maximum signal (Emax) for each construct was also noted. Experiments were repeated 1-4 times.

[0069] FIG. 24B shows CAR3 selectivity. An example of MSLN CAR3 selectivity benchmarked against the M5 CAR. Activation of CARs in a Jurkat cell functional assay by MSLN(+) or MSLN(-) cell lines was measured. For MSLN(+) cell lines, variant MSLN(-) versions were generated by MSLN knockout for comparison For more detailed off-target characterization, see FIG. 32B.

[0070] FIG. 25A shows expression of MSLN in human cell lines assessed by staining with MSLN mAb and flow cytometry. K562 displayed some cross-reactivity to the anti-MSLN antibody, although no functional reactivity to CAR3 or M5 benchmark CAR was observed.

[0071] FIG. 25B shows plotted levels of MSLN and A*02 mRNA (CCLE) and protein (QIFIKIT) show correlation. Conversions between protein and mRNA levels were calculated using the standard curves (see Methods for Example 8, *infra*).

[0072] FIG. 26A shows a summary of cell lines used in this study. Quantification of surface densities of MSLN and A*02 in various cancer cell lines, and corresponding reported mRNA levels in normal lung tissue (GTEx). Surface MSLN and A*02 of engineered and wildtype tumor cell lines was quantified using a QIFIKIT (quantitative analysis kit, Agilent). Where cell line HLA-A haplotypes are heterozygous for A*02, the TPM values were divided by 2. Note that in certain cases the HLA-A allele copy number is not known. The TPM value of MS751 + transduced A*02 (438 TPM) was estimated from measurement of its surface A*02 protein level using the standard curve. Cell lines transduced with HLA-A*02 better mimic the A*02:MSLN ratio of normal lung tissue than cell lines expressing endogenous levels of the

proteins (bold black boxes). TPM, transcripts per million; na, not applicable; A*02: HLA-A*02.

[0073] FIG. 26B shows quantification of MSLN molecules/cell using QIFIKIT. Anti-human MSLN mouse antibody clone 618923 (R&D Systems) was used to stain ~100,000 cells. After washing the cells, anti-mouse IgG F(ab')2 secondary antibody (Invitrogen A21237) was used to stain both the cells and QIFI beads. The number of MSLN molecules on the surface was quantified using the QIFI antigen standard curve.

[0074] FIG. 27A shows the characterization of MSLN CAR Tmod constructs in Jurkat cell functional assays. Six HuTARG-derived MSLN activators (CAR1-6) and benchmark CARs M5 and SS1 activators were paired with A*02 blocker (closed circles) or empty vector control (open circles). Jurkat NFAT luciferase cells expressing the CAR +/- blocker were co-cultured with wild-type, endogenous MSLN(+) HeLa cells transfected with a titration of A*02:01 mRNA. The functional response (RLU) was assessed after a 6 hour co-culture. Titrated antigen molecules on the surface were quantified using the QIFIKIT. IC50 (molecules/cell) values are indicated in the figure. CAR1-6 are Gen3; CAR M5 and SS1 are Gen2.

[0075] FIG. 27B shows a 2-dimensional titration of MSLN and A*02 mRNA in MSLN(-) HeLa target cells to establish EC50 for the MSLN CAR3 Tmod construct in Jurkat cells. MSLN(-) HeLa target cells were transfected with serially diluted MSLN mRNA and constant A*02 mRNA and Jurkat cells were transiently transfected to express MSLN CAR3 and A*02 blocker. The functional response (RLU) was assessed after a 6 hour co-culture.

[0076] FIG. 27C shows a transfection of MSLN(-) HeLa target cells with serially diluted A*02 mRNA and constant MSLN mRNA to establish IC50 for the MSLN CAR3 Tmod construct in Jurkat cells.

[0077] FIG. 28A shows plotted levels of MSLN and A*02 mRNA and protein. EC50 and IC50 of construct in relation to MSLN and HLA-A expression levels in normal (GTEx database) and tumor tissues and cell lines (TCGA, CCLE databases). Conversions between protein and mRNA levels were calculated using the standard curves shown in FIG. 25B; Methods). HeLa and MS751 A*02 transgenic cell line variants shown on the graph better mimic activator and blocker target ratios in normal tissues.

[0078] FIG. 28B shows MSLN CARs and CAR3 Tmod cytotoxicity in primary T cells. Primary T cells transduced with CARs or Tmod were co-cultured at an effector:target (E:T) = 1:1 for 48 hours with either tumor or normal target cells as shown. A*02:MSLN (B:A) target

antigen ratios ranged from 2-27:1. M5 was a Gen2 CAR; all others Gen3. Tumor = MSLN(+)A*02(-) target cells; Normal = MSLN(+)A*02(+) target cells.

[0079] FIG. 29A shows a comparison of lead CAR3 receptor paired with A*02 blocker to benchmark CARs in cytotoxicity assays. SS1 CAR is a Gen2 construct; others are Gen3. Primary T cells transduced with various CARs +/- A*02 blocker using 2 separate lentiviral vectors were cultured with endogenous MSLN(+) A*02(-) tumor or MSLN(+)A*02(+) normal HeLa cells to assess cytotoxicity. Transduced primary T cells were normalized to a constant activator or activator-blocker double-positive population percentage [15% A(+) or A(+)B(+)] cells by dilution with untransduced T cells for a final effective effector:target (E:T) ratios of 0.6:1 or 0.3:1. Both E:T ratios resulted in selective killing in the presence of A*02 antigen when T cells also expressed A*02 blocker.

[0080] FIG. 29B shows secreted IFN-g after 48-hours of co-culture with tumor or normal target cells.

[0081] FIG. 30A shows MSLN CAR3 Tmod cells selectively kill RFP(+) tumor cells and spare GFP(+) normal cells in mixed tumor and normal cell co-cultures. Due to the adherent nature of the HeLa cell line, killed targets tend to remain as clusters on the surface. White arrows point to some examples of killed RFP(+) tumor cells. Example of E:T 0.6:1 and normal:tumor = 1:1.

[0082] FIG. 30B shows cytotoxicity in mixed normal and tumor co-cultures with E:T = 1:1 and normal:tumor = 9:1 (see FIG. 31B for other ratios). Primary T cells transduced with CAR3 or CAR3 Tmod construct were co-cultured with HeLa target cells for 48 hours and imaged using GFP and RFP expressed in MSLN(+)A*02(+) normal and MSLN(+)A*02(-) tumor cell lines, respectively.

[0083] FIG. 31A shows MSLN CAR3 Tmod cells selectively kill RFP(+) tumor cells in mixed tumor and normal cell co-cultures. Primary T cells transduced with CAR3 Tmod construct were co-cultured with HeLa cells for 48 hours and imaged using GFP and RFP expressed in MSLN(+)A*02(+) normal and MSLN(+)A*02(-) tumor cell lines, respectively.

[0084] FIG. 31B shows cytotoxicity of CAR3 and CAR3 Tmod in mixed normal and tumor co-cultures with normal:tumor ranging from 9:1 to 1:9; E:T = 0.6:1.

[0085] FIG. 32A shows the MSLN CAR3 Tmod construct mediates selective, persistent and reversible cytotoxicity. CAR3 or CAR3 Tmod transduced primary T cells were co-cultured with E:T = 1.2:1 for 48 hours with either tumor or normal target cells. T cells were then collected, depleted of dead or nonadherent target cells, and re-seeded onto fresh tumor or

normal target cells for an additional 48 hours. RACA, repeat-antigen challenge assay. R1, round 1; R2, round 2.

[0086] FIG. 32B shows MSLN CAR3 Tmod construct selectivity in a Jurkat cell functional assay on a subset of MSLN(+) and MSLN(-) control target cells showed no off-target activity (see Methods for Example 8, *infra*). Bar height corresponds to the average from technical replicates.

[0087] FIG. 33A shows a schematic of RACA (repeat-antigen challenge assay) and reversibility assay. CAR3 or CAR3 Tmod transduced primary T cells were co-cultured with E:T = 1.2:1 for 48 hours with either tumor or normal targets. T cells were then collected, depleted of any dead or lifted target cells, and re-seeded onto fresh tumor or normal targets for an additional 48 hours.

[0088] FIG. 33B shows soluble circulating MSLN (sMSLN) does not affect CAR-T activity. Acute cytotoxicity of tumor or normal target cells by M5 benchmark CAR or CAR3 were not affected by the presence of 500ng/mL sMSLN (Acro Bio).

[0089] FIG. 33C shows the staining of transiently-transfected CAR(+) Jurkat cells with labeled sMSLN monomer or tetramer analyzed by flow cytometry shows that the sMSLN is structurally intact and able to bind the receptors.

[0090] FIG. 34A, FIG. 34B, and FIG. 34C show the Tmod construct mediates selective killing of tumor cells in a xenograft model. FIG. 34A shows a schematic diagram of the dual-flank tumor and normal MS751 xenograft model. FIG. 34B shows bioluminescence values are to the right of the color scale in flux units of photons/sec/cm2/sr. Day 0 = pre T cell injection; days 8 and 15 = post T cell injection. FIG. 34C shows graft sizes assessed by caliper measurement (see Results for Example 8, *infra*).

[0091] FIG. 35A, FIG. 35B, and FIG. 35C show MSLN CAR Tmod selectively kill tumors in xenograft model FIG. 35A shows primary T cells transduced with MSLN CARs or CAR3 Tmod were co-cultured with either HLA-A KO tumor or A*02-transgenic normal MS751 target cells in vitro at an E:T = 1.4:1 for 48 hours. M5 was a Gen2 CAR; all others Gen3. Tumor = MSLN(+)A*02(-) target cells; Normal = MSLN(+)A*02(+) target cells. FIG. 35B shows individual mouse xenograft growth curves for data shown in FIG 34C. FIG. 35C shows BLI quantification of normal and tumor cells post T cell injection.

[0092] FIG. 36 shows cis binding of A*02 blocker in A*02(+) or (-) T cells abrogates function. Binding of the blocker in A*02(+) Jurkat cells and primary T cells by A*02 tetramer was significantly reduced due to cis-binding of autologous A*02. Reduced binding

(due to reduced availability of the blocker) correlated with reduced blocker activity. Cytotoxicity assay shown at an E:T = 0.5:1.

[0093] FIG. 37A, FIG. 37B, and FIG. 37C show the MSLN Tmod system can be extended to autologous T cells. FIG. 37A shows cis-binding of autologous A*02 in an A*02(+) donor eliminates binding to A*02 tetramer B2M knockout (KO) by CRISPR restores blocker availability as demonstrated by binding to A*02 tetramer, similar to observed levels in an A*02(-) donor. FIG. 37B shows a cytotoxicity assay showing activator-only and MSLN SS1 CAR Tmod primary T cells cultured with tumor (solid) or normal (open) target cells. MSLN SS1 CAR Tmod construct kills MSLN(+) A*02(-) tumor HeLa target cells but no longer blocks in the presence of autologous A*02 as a result of cis-binding. For the A*02(+) donor, blocking is only achieved through B2M CRISPR KO. E:T = 1.2:1. FIG. 37C shows representative images at 48h.

[0094] FIG. 38A shows enrichment of anti-HLA-A*11 binders through multiple rounds of cell sorting from scFv library. On-target probe was labeled HLA-A*11 tetramer; off-target proteins were a mixture of unrelated MHC tetramers.

[0095] FIG. 38B shows Jurkat cell activation in an mRNA titration assay: HeLa target cells were transfected with serially diluted HLA-A*11 mRNA and Jurkat cells were transiently transfected to express HLA-A*11 CAR4. The functional response (RLU) was assessed after a 6 hour co-culture. PE, phycoerythrin.

[0096] FIG. 39A shows Jurkat cells expressing MSLN CAR3 and A*03, A*11 or B*07 blocker constructs were blocked in the presence of increasing blocker antigen on endogenous MSLN(+) HeLa target cells.

[0097] FIG. 39B and FIG. 39C show primary T cell cytotoxicity assay of MSLN CAR3 + A*11 blocker. Primary T cells transduced with CAR3 and A*11:01-directed blocker efficiently blocks HeLa target cells with A*11:01 and kills wildtype HeLa cells as effectively as CAR-only cells. Transduced primary T cells were co-cultured with HeLa cells with or without HLA-A*11:01 at an E:T = 0.8:1. Note that both tumor and normal target cells used here expressed GFP. FIG. 39C shows representative co-culture images at 48 hours for FIG. 39B.

DETAILED DESCRIPTION

[0098] Provided herein are compositions and methods for treating cancers using immune cells comprising a two receptor system responsive to differences in gene expression of a

ligand between cancer and normal (*i.e.* healthy or wild type) cells. These differences in expression can be due to loss of heterozygosity in the cancer cells. Alternatively, the differences in expression can be because the gene expression is not expressed in cancer cells, or is expressed in cancer cells at a lower level than normal cells. The two-receptor system is expressed in immune cells, for example immune cells used in adoptive cell therapy, and targets activity of these immune cells to cancer cells exhibiting loss of heterozygosity or expression differences. In this two receptor system, the first receptor (an activator receptor, sometimes referred to herein as an A module) activates, or promotes activation of the immune cells, while the second receptor (an inhibitory receptor, sometimes referred to herein as a blocker, inhibitor receptor, or B module) acts to inhibit activation of the immune cells by the first receptor. Each receptor contains a ligand-binding domain (LBD) that binds a specific ligand. Signals from the two receptors upon ligand binding are integrated by the immune cell. Differential expression of ligands for the first and second receptors in cancer and normal cells, for example through loss of heterozygosity of the locus encoding the inhibitory ligand in cancer cells, or differences in transcription levels, mediates activation of immune cells by target cancer cells that express the first activator ligand but not the second inhibitory ligand.

[0099] Loss of heterozygosity (LOH) from large-scale chromosomal deletions is a source of genetic difference in tumors. LOH is a common event in tumorigenesis which affects nearly every locus in the genome, with approximately 20% of genes displaying LOH in an average tumor. LOH provides the means to discriminate tumor from normal tissue in a definitive way because tumors can be found in which all malignant cells lack certain germline alleles. One locus that undergoes LOH is the human leukocyte antigen (HLA) locus, which encodes polymorphic, abundant, ubiquitous surface antigens. The two-receptor system described herein employs one receptor to activate T cells exposed to tumor-antigen-positive tumor cells (sometimes referred to as an "activator module"), and a second receptor to prevent activation of the immune cells in the presence of a surface blocker antigen such as HLA-A*02 protein. The dual-receptor system described herein (sometimes referred to herein as "Tmod") possesses other advantageous properties as a cell therapy, including but not limited to reversible activation/blockade of immune cells, and selectivity in mixtures of tumor and "normal" cells.

[0100] In particular embodiments of the compositions and methods provided herein, immune cells comprising the two receptor system described herein are used to treat Mesothelin (MSLN) positive cancers. This includes mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine

cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma. In some embodiments, the cancer has relapsed in a subject. In some embodiments, the cancer is refractory to one or more prior administered anticancer therapies. In some embodiments, the cancer is metastatic. In the case of MSLN-positive cancers, the target antigen of the activator receptor is MSLN, or a peptide antigen thereof, in a complex with a major histocompatibility complex class I (MHC-I). MSLN is expressed in normal adipose, fallopian tube, lung and salivary gland tissues, among others (FIG. 2). Because of its expression in certain tumors, MSLN is an attractive tumor-specific antigen that could mediate selective killing of MSLN+ tumors if these cancer cells could be specifically targeted with an appropriate therapeutic. However, normal MSLN expression in non-cancer (non-target) cells has prevented the effective use of MSLN for targeted therapies such as adoptive cell therapies. By pairing an MSLN activator receptor with an inhibitory receptor, the methods provided herein increase the specificity of adoptive cell therapies and decrease harmful effects associated with these therapies, such as dose-limited toxicity.

[0101] In some embodiments, the ligand for the activator is a MSLN peptide complexed with MHC class I. In the methods described herein, this MSLN targeted activator receptor is paired with an inhibitory receptor, which increases the safety window of the activator by blocking its cytolytic effect on normal MSLN-positive tissues. However, the activator receptor still directs the targeted killing of tumor cells by immune cells comprising the two-receptor system, as the tumor cells do not express the ligand for the inhibitor, or blocker, receptor. The target for the second, inhibitory receptor is expressed by MSLN positive tissues such as lung, mesothelium and adipose tissues, but not in cancer cells, and the inhibitory receptor recognizes this “non-target antigen” as an inhibitory stimulus. An exemplary target for the second inhibitory receptor is expressed by lung tissue, and is lost from MSLN positive cancer cells due to loss of heterozygosity (LOH) or other mechanisms, leaving a single allelic form in cancer cells that can be distinguished from other alleles via an allele-specific ligand binding domain on the inhibitory receptor. Exemplary targets of the inhibitory receptor include, but are not limited to, Major Histocompatibility Complex (MHC) proteins such as human leukocyte antigen A (HLA-A). HLA-B, HLA-C, and other HLAs. HLAs are encoding by variant genes, such as HLA-A*01., HLA-A*02, HLA-A*03, HLA-C*07, and others, which can be lost from MSLN positive cancer cells through loss of heterozygosity. Alternatively, further exemplary targets of the inhibitory receptor include, but are not limited to, intercellular adhesion molecule 1 (ICAM1), catechol-O-methyltransferase (COMT) and C-X-C motif chemokine ligand 16 (CXCL16). Each of these has a common nonsynonymous

variant form, with the amino-acid alteration in its extracellular domain accessible to antibodies, which can be used as a inhibitory receptor, or blocker receptor target for a cellular integrator designed to safely treat patients with MSLN positive cancers with engineered T cells activated by an activator receptor such as a MSLN or MSLN pMHC responsive activator receptor.

[0102] The compositions and methods of the disclosure can reduce or eliminate dose-limiting toxicity (DLT) caused by expression of MSLN on normal tissue. The disclosure provides methods of targeting MSLN in cancer cells to treat MSLN positive cancers using adoptive cell therapies by adding a second inhibitory receptor that blocks activation of the adoptive immune cells in the presence of a second ligand (a ligand other than MSLN, termed the non-target antigen or alternatively, blocker antigen). Using the compositions and methods described herein, tumor cells that express MSLN are attacked by the adoptive cells, such as immune cells, expressing the two receptors because these tumor cells express only the activator ligand, MSLN. In contrast, normal cells that express MSLN plus the non-target antigen are protected from the adoptive immune cells. The inhibitory receptor response to the non-target antigen on normal cells prevents activation of immune cells by the MSLN-targeted activator receptor. This dual-targeting approach creates the therapeutic window that will allow a MSLN-directed cell therapy to be dosed safely and effectively in MSLN-positive cancer patients.

[0103] The disclosure provides methods and compositions that allow the use of potent MSLN CAR and TCRs that induce on-target toxicity, and renders these MSLN targeted receptors useful as a therapeutic by mitigating their toxicity.

[0104] In variations, the compositions and methods described herein may be used to kill target cells and/or treat subjects in which expression of the non-target antigen is partially or completely decreased by causes other than loss of heterozygosity, including but not limited to partial gene deletion, epigenetic silencing, and point mutations or truncating mutations in the sequence encoding the non-target antigen.

Definitions

[0105] Prior to setting forth this disclosure in more detail, it may be helpful to an understanding thereof to provide definitions of certain terms to be used herein.

[0106] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of particular embodiments, preferred embodiments of

compositions, methods and materials are described herein. For the purposes of the present disclosure, the following terms are defined below. Additional definitions are set forth throughout this disclosure.

[0107] As used herein, the term "about" or "approximately" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In one embodiment, the term "about" or "approximately" refers a range of quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length ± 15%, ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, or ± 1% about a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

[0108] As used herein, the term "isolated" means material that is substantially or essentially free from components that normally accompany it in its native state. In particular embodiments, the term "obtained" or "derived" is used synonymously with isolated.

[0109] The terms "subject," "patient" and "individual" are used interchangeably herein to refer to a vertebrate, preferably a mammal, more preferably a human. Tissues, cells, and their progeny of a biological entity obtained in vivo or cultured in vitro are also encompassed. A "subject," "patient" or "individual" as used herein, includes any animal that exhibits pain that can be treated with the vectors, compositions, and methods contemplated herein. Suitable subjects (e.g., patients) include laboratory animals (such as mouse, rat, rabbit, or guinea pig), farm animals, and domestic animals or pets (such as a cat or dog). Non-human primates and, preferably, human patients, are included.

[0110] As used herein "treatment" or "treating," includes any beneficial or desirable effect, and may include even minimal improvement in symptoms. "Treatment" does not necessarily indicate complete eradication or cure of the disease or condition, or associated symptoms thereof.

[0111] As used herein, "prevent," and similar words such as "prevented," "preventing" etc., indicate an approach for preventing, inhibiting, or reducing the likelihood of a symptom of disease. It also refers to delaying the onset or recurrence of a disease or condition or delaying the occurrence or recurrence of the symptoms of a disease. As used herein, "prevention" and similar words also includes reducing the intensity, effect, symptoms and/or burden of disease prior to onset or recurrence.

[0112] As used herein, the term "amount" refers to "an amount effective" or "an effective amount" of a virus to achieve a beneficial or desired prophylactic or therapeutic result, including clinical results.

[0113] A "therapeutically effective amount" of a virus or cell may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the virus or cell to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the virus or cell are outweighed by the therapeutically beneficial effects. The term "therapeutically effective amount" includes an amount that is effective to "treat" a subject (e.g., a patient).

[0114] An "increased" or "enhanced" amount of a physiological response, e.g., electrophysiological activity or cellular activity, is typically 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 level of activity in an untreated cell.

[0115] A "decreased" or "reduced" amount of a physiological response, e.g., electrophysiological activity or cellular activity, is typically a "statistically significant" amount, and may include an 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 level of activity in an untreated cell.

[0116] By "maintain," or "preserve," or "maintenance," or "no change," or "no substantial change," or "no substantial decrease" refers generally to a physiological response that is comparable to a response caused by either vehicle, or a control molecule/composition. A comparable response is one that is not significantly different or measurable different from the reference response.

[0117] In general, "sequence identity" or "sequence homology" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Typically, techniques for determining sequence identity include determining the nucleotide sequence of a polynucleotide and/or determining the amino acid sequence encoded thereby, and comparing these sequences to a second nucleotide or amino acid sequence. Two or more sequences (polynucleotide or amino acid) can be compared by determining their "percent identity." The percent identity of two sequences, whether nucleic acid or amino acid sequences, is the number of exact matches between two aligned sequences divided by the length of the shorter sequences and multiplied by 100. Percent identity may also be determined, for example, by comparing sequence information

using the advanced BLAST computer program, including version 2.2.9, available from the National Institutes of Health. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul, et al., J. Mol. Biol. 215:403-410 (1990); Karlin And Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997). Briefly, the BLAST program defines identity as the number of identical aligned symbols (generally nucleotides or amino acids), divided by the total number of symbols in the shorter of the two sequences. The program may be used to determine percent identity over the entire length of the proteins being compared. Default parameters are provided to optimize searches with short query sequences in, for example, with the blastp program. The program also allows use of an SEG filter to mask-off segments of the query sequences as determined by the SEG program of Wootton and Federhen, Computers and Chemistry 17:149-163 (1993). Ranges of desired degrees of sequence identity are approximately 80% to 100% and integer values therebetween. Typically, the percent identities between a disclosed sequence and a claimed sequence are at least 80%, at least 85%, at least 90%, at least 95%, or at least 98%.

[0118] As used herein, a "polynucleotide system" refers to one or more polynucleotides. The one or more polynucleotides may be designed to work in concert for a particular application, or to produce a desired transformed cell.

[0119] The term "exogenous" is used herein to refer to any molecule, including nucleic acids, protein or peptides, small molecular compounds, and the like that originate from outside the organism. In contrast, the term "endogenous" refers to any molecule that originates from inside the organism (i.e., naturally produced by the organism).

[0120] The term "MOI" is used herein to refer to multiplicity of infection, which is the ratio of agents (e.g. viral particles) to infection targets (e.g. cells).

[0121] In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated. The term "about", when immediately preceding a number or numeral, means that the number or numeral ranges plus or minus 10%.

[0122] As used herein, a "target cell" refers to cell that is targeted by an adoptive cell therapy. For example, a target cell can be cancer cell, which can be killed by the transplanted T cells of the adoptive cell therapy. Target cells of the disclosure express a target antigen, as described herein, and do not express a non-target antigen.

[0123] As used herein, a "non-target cell" refers to cell that is not targeted by an adoptive cell therapy. For example, in an adoptive cell targeting cancer cells, normal, healthy, non-cancerous cells are non-target cells. Some, or all, non-target cells in a subject may express both the target antigen and the non-target antigen. Non-target cells in a subject may express the non-target antigen irrespective of whether or not these cells also express the target antigen.

[0124] As used herein, a "non-target allelic variant" refers to an allele of a gene whose product is expressed by non-target cells, but is not expressed by target cells. For example, a non-target allelic variant is an allele of a gene that is expressed by normal, non-cancer cells of subject, but not expressed by cancer cells of the subject. The expression of the non-target allelic variant can be lost in the cancer cells by any mechanism, including, but not limited to, loss of heterozygosity, mutation, or epigenetic modification of the gene encoding the non-target allelic variant.

[0125] As used herein, "specific to" or "specifically binds to" when used with respect to a ligand binding domain, such as an antigen binding domain, refers to a ligand binding domain that has a high specificity for a named target. Antibody specificity can viewed as a measure of the goodness of fit between the ligand binding domain and the corresponding ligand, or the ability of the ligand binding domain to discriminate between similar or even dissimilar ligands. In comparison with specificity, affinity is a measure of the strength of the binding between the ligand binding domain and ligand, such that a low-affinity ligand binding domain binds weakly and high-affinity ligand binding domain binds firmly. A ligand binding domain that is specific to a target allele is one that can discriminate between different alleles of a gene. For example, a ligand binding domain that is specific to HLA-A*02 will not bind, or bind only weakly to, other HLA-A alleles such as HLA-A*01 or HLA-A*03. The person of skill in the art will appreciate that a ligand binding domain can be said to be specific to a particular target, and yet still have low levels of binding to one or more additional targets that do not affect its function in the receptor systems described herein.

[0126] As used herein, a "target antigen," whether referred to using the term antigen or the name of a specific antigen, refers to an antigen expressed by a target cell, such as a cancer cell. Expression of target antigen is not limited to target cells. Target antigens may be expressed by both cancer cells and normal, non-cancer cells in a subject.

[0127] As used herein, a "non-target antigen" (or "blocker antigen") whether referred to using the term antigen or the name of a specific antigen, refers to an antigen that is expressed by normal, non-cancer cells and is not expressed in cancer cells. This difference in expression

allows the inhibitory receptor to inhibit immune cell activation in the presence of non-target cells, but not in the presence of target cells.

[0128] Polymorphism refers to the presence of two or more variants of a nucleotide sequence in a population. A polymorphism may comprise one or more base changes, an insertion, a repeat, or a deletion. A polymorphism includes e.g. a simple sequence repeat (SSR) and a single nucleotide polymorphism (SNP), which is a variation, occurring when a single nucleotide of adenine (A), thymine (T), cytosine (C) or guanine (G) is altered.

[0129] As used herein, "affinity" refers to strength of binding of a ligand to a single ligand binding site on a receptor, for example an antigen for the antigen binding domain of any of the receptors described herein. Ligand binding domains can have a weaker interaction (low affinity) with their ligand, or a stronger interaction (high affinity).

[0130] Kd, or dissociation constant, is a type of equilibrium constant that measures the propensity of a larger object to separate reversibly into smaller components, such as, for example, when a macromolecular complex comprising receptor and its cognate ligand separates into the ligand and the receptor. When the Kd is high, it means that a high concentration of ligand is need to occupy the receptor, and the affinity of the receptor for the ligand is low. Conversely, a low Kd means that the ligand has a high affinity for the receptor.

[0131] As used herein, a receptor that is "responsive" or "responsive to" refers to a receptor comprising an intracellular domain, that when bound by a ligand (*i.e.* antigen) generates a signal corresponding to the known function of the intracellular domain. An activator receptor bound to a target antigen can generate a signal that causes activation of an immune cell expressing the activator receptor. An inhibitory receptor bound to a non-target antigen can generate an inhibitory signal that prevents or reduces an activation of an immune cell expressing the activator receptor. Responsiveness of receptors, and their ability to activate or inhibit immune cells expressing the receptors, can be assayed by any means known in the art and described herein, including, but not limited to, reporter assays and cytotoxicity assays.

[0132] As used herein, "activation" of an immune cell or an immune cell that is "activated" refers to an immune cell that can carry out one or more functions characteristic of an immune response. These functions include proliferation, release of cytokines, and cytotoxicity, i.e. killing of a target cell. Activated immune cells express markers that will be apparent to persons of skill in the art. For example, activated T cells can express one or more of CD69, CD71, CD25 and HLA-DR. An immune cell expressing an activator receptor (*e.g.* a MSLN CAR) can be activated by the activator receptor when it becomes responsive to the binding of the receptor to a target antigen (*e.g.* MSLN) expressed by the target cell. A "target antigen"

can also be referred to an “activator antigen” and may be isolated or expressed by a target cell. Activation of an immune cell expressing an inhibitory receptor can be prevented when the inhibitory receptor becomes responsive to a non-target antigen (*e.g.* HLA-A*02), even when the activator receptor is bound to the target activator ligand. A “non-target antigen” can also be referred to as an “inhibitory ligand” or a “blocker”, and may be isolated or expressed by a target cell.

[0133] Receptor expression on an immune cell can be verified by assays that report the presence of the activator receptors and inhibitory receptors described herein. For example, a population of immune cells can be stained with a labeled molecule (*e.g.* a fluorophore labeled receptor-specific antibody or a fluorophore-labeled receptor-specific ligand), and quantified using fluorescence activated cell sorting (FACS) flow cytometry. This method allows a percentage of immune cells in a population of immune cells to be characterized as expressing an activator receptor, an inhibitory receptor, or both receptors. The ratio of activator receptor and inhibitory receptors expressed by the immune cells described herein can be determined by, for example, digital droplet PCR. These approaches can be used to characterize the population of cells for the production and manufacturing of the immune cells, pharmaceutical compositions, and kits described herein. For the immune cells, pharmaceutical compositions, and kits described herein, it is understood that a suitable percentage of immune cells expressing both an activator receptor and an inhibitory receptor is determined specifically for the methods described herein. For example, a suitable percentage of immune cells expressing both an activator receptor and in inhibitory receptor can be at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%. As a further example, between 50% and 99%, between 60% and 95%, between 65% and 95%, between 65% and 90%, between 70% and 90% , between 75% and 90%, between 75% and 85%, between 80% and 99%, between 85% and 99%, between 90% and 99% or between 95% and 99% of immune cells can express both the activator receptor and the inhibitory receptor. For example, a suitable ratio of activator receptor and inhibitory receptor in an immune cell can be about 5:1, about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, or about 1:5. It is understood that purification, enrichment, and/or depletion steps can be used on populations of immune cells to meet suitable values for the immune cells, pharmaceutical compositions, and kits described herein.

[0134] A responsive receptor expressed by the immune cells described herein can be verified by assays that measure the generation of a signal expected to be generated by the intracellular domain of the receptor. Reporter cell lines, such as Jurkat-Luciferase NFAT cells (Jurkat

cells), can be used to characterize a responsive receptor. Jurkat cells are derived from T cells and comprise a stably integrated nuclear factor of activated T-cells (NFAT)-inducible luciferase reporter system. NFAT is a family of transcription factors required for immune cell activation, whose activation can be used as a signaling marker for T cell activation. Jurkat cells can be transduced or transfected with the activator receptors and/or inhibitory receptors described herein. The activator receptor is responsive to the binding of a ligand if the Jurkat cell expresses a luciferase reporter gene, and the level of responsiveness can be determined by the level of reporter gene expression. The presence of luciferase can be determined using any known luciferase detection reagent, such as luciferin. An inhibitory receptor is responsive to the binding of a ligand if, when co-expressed with an activator receptor in Jurkat cells, it prevents a normally responsive immune cell from expressing luciferase in response to the activator receptor. For example, the responsiveness of an inhibitory receptor can be determined and quantified in a Jurkat cell expressing both an activator and an inhibitor by observing the following: 1) the Jurkat cell expresses luciferase in the presence of activator receptor ligand and absence of inhibitory receptor ligand; and 2) luciferase expression in the Jurkat cell is reduced or eliminated in the presence of both an activator receptor ligand and an inhibitory receptor ligand. This approach can be used to determine the sensitivity, potency, and selectivity of activator receptors and specific pairs of activator receptors and inhibitory receptors. The sensitivity, potency, and selectivity can be quantified by EC50 or IC50 values using dose-response experiments, where an activator receptor ligand and/or inhibitory receptor ligand is titrated into a culture of Jurkat cells expressing an activator receptor or a specific pair of activator and inhibitory receptors. Alternatively, the EC50 and IC50 values can be determined in a co-culture of immune cells (*e.g.* Jurkat cells or primary immune cells) expressing an activator receptor or a specific pair of activator and inhibitory receptors and target cells expressing an increasing amount of an activator ligand or inhibitor ligand. An increasing amount of activator ligand or inhibitor ligand can be accomplished in the target cell by, for example, titration of activator ligand or inhibitor ligand encoding mRNA into target cells, or use of target cells that naturally express different levels of the target ligands. Exemplary suitable EC50 and IC50 values for the activator and inhibitory receptors as determined used target cells expressing varying amounts of the target and non-target ligands include an EC50 of 10 transcripts per million (TPM) or less for the activator receptor, for example an EC50 of between 2-10 TPM, and an IC50 of 25 TPM or less for the inhibitory receptor, for example an IC50 of 5-21 TPM.

[0135] Activation of the immune cells described herein that express an activator receptor or specific pairs of activator and inhibitory receptors can be further determined by assays that measure the viability of a target cell following co-incubation with said immune cells. The immune cells, sometimes referred to as effector cells, are co-incubated with target cells that express an activator receptor ligand, an inhibitory receptor ligand, or both an activator and inhibitory receptor ligand. Following co-incubation, viability of the target cell is measured using any method to measure viability in a cell culture. For example, viability can be determined using a mitochondrial function assay that uses a tetrazolium salt substrate to measure active mitochondrial enzymes. Viability can also be determined using imaging based methods. Target cells can express a fluorescent protein, such as green fluorescent protein or red fluorescent protein. Reduction in total cell fluorescence indicates a reduction in viability of the target cell. A reduction in viability of the target cell following incubation with immune cells expressing an activator receptor or a specific pair of activator and inhibitory receptors is interpreted as target cell-mediated activation of the immune cell. A measure of the selectivity of the immune cells can also be determined using this approach. The immune cell expressing a pair of activator and inhibitory receptors is selective if the following is observed: 1) viability is reduced in target cells expressing the activator receptor ligand but not the inhibitory receptor ligand; 2) viability is not reduced in target cells expressing both an activator receptor ligand and an inhibitory receptor ligand. From these measurements, a "specific killing" value can be derived that quantifies the percentage of immune cell activation based on the reduction in viability of target cell as a percentage of a negative control (immune cells that do not express an activator receptor). Further, from these measurements a "selectivity ratio" value can be derived that represents the ratio of the specific killing observed in target cells expressing an activator receptor ligand in the absence of inhibitory receptor ligand to the specific killing observed in target cells expressing both an activator receptor ligand and an inhibitory receptor ligand. This approach can be used to characterize the population of cells for the production and manufacturing of the immune cells, pharmaceutical compositions, and kits described herein. A suitable specific killing value for the immune cells, pharmaceutical compositions, and kits can be, for example, the following criteria: 1) at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97% or at least 99% specific killing following a 48 hour co-incubation of immune cells and target cells expressing activator receptor ligand in the absence of inhibitory receptor ligand; and 2) less than or equal to 40%, less than or equal to 35%, less than or equal to 30%, less than or equal to 25%, less than or equal to 20%, less than

or equal to 15%, less than or equal to 10%, less than or equal to 5%, less than or equal to 3% or less than or equal to 1% specific killing of target cell expressing both an activator receptor ligand and an inhibitory receptor ligand.

[0136] As a further example, a suitable specific killing value for the immune cells, pharmaceutical compositions and kits can be the following criteria: 1) between 30% and 99%, between 40% and 99%, between 50% and 99%, between 55% and 95%, between 60% and 95%, between 60% and 90%, between 50% and 80%, between 50% and 70% or between 50% and 60% of target cells expressing the activator ligand but not the inhibitor ligand are killed; and 2), between 1% and 40%, between 3% and 40%, between 5% and 40%, between 5% and 30%, between 10% and 30%, between 15% and 30% or between 5% and 20% of target cells expressing the activator ligand and the inhibitor ligand are killed. As a still further example, a suitable specific killing value for the immune cells, pharmaceutical compositions, and kits can be, for example, the following criteria: 1) at least 50% specific killing following a 48 hour co-incubation of immune cells and target cells expressing activator receptor ligand in the absence of inhibitory receptor ligand; and 2) less than or equal to 20% specific killing of target cell expressing both an activator receptor ligand and an inhibitory receptor ligand. As a further example, the immune cells are capable of killing at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97% or at least 99% of target cells expressing the activator ligand and not the inhibitor ligand over a period of 6 hours, 12 hours, 18 hours, 24 hours, 30 hours, 36 hours, 42 hours, 48 hours, 54 hours, or 60 hours, while killing less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, less than 3% or less than 1% of target cells expressing the activator and inhibitor ligands over the same time period.

[0137] A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at least about 50% to at least about 95%. A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%. A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at most about 50%, at most about 55%, at most about 60%, at most about 65%, at most about 70%, at most about 75%, at most about 80%, at

most about 85%, at most about 90%, or at most about 95%. A suitable specific killing value of target cells expressing both an activator receptor ligand and an inhibitory receptor ligand for the immune cells, pharmaceutical compositions, and kits can be can be less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5%. The suitable specific killing value for the immune cells, pharmaceutical compositions, and kits can be can be determined following about 6 hours, about 12 hours, about 18 hours, about 24, about 30 hours, about 36 hours, about 42 hours, about 48 hours, about 54 hours, about 60 hours, about 66 hours, or about 72 hours of co-incubation of immune cells with target cells.

[0138] A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at least about 50% to at least about 95%. A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%. A suitable specific killing value of the target cell expressing an activator ligand in the absence of an inhibitory ligand value for the immune cells, pharmaceutical compositions, and kits can be, for example, at most about 50%, at most about 55%, at most about 60%, at most about 65%, at most about 70%, at most about 75%, at most about 80%, at most about 85%, at most about 90%, or at most about 95%. A suitable specific killing value of target cells expressing both an activator receptor ligand and an inhibitory receptor ligand for the immune cells, pharmaceutical compositions, and kits can be can be less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, or less than about 5%. The suitable specific killing value for the immune cells, pharmaceutical compositions, and kits can be can be determined following about 6 hours, about 12 hours, about 18 hours, about 24, about 30 hours, about 36 hours, about 42 hours, about 48 hours, about 54 hours, about 60 hours, about 66 hours, or about 72 hours of co-incubation of immune cells with target cells.

[0139] As used herein, the term “functional variant” refers to a protein that has one or more amino-acid substitutions, insertions, or deletions as compared to a parental protein, and which retains one or more desired activities of the parental protein. A functional variant may be a

fragment of the protein (*i.e.* a variant having N- and/or C-terminal deletions) that retain the one or more desired activities of the parental protein.

[0140] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

Activator Receptors

[0141] The disclosure provides a first receptor, comprising a first extracellular ligand binding domain specific to a target antigen comprising a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I). The first receptor is an activator receptor, and mediates activation of an immune cell expressing the first receptor upon binding of the target antigen by the extracellular ligand binding domain of the first receptor. The first receptor is responsive to a target antigen (*i.e.* activator ligand). For example, when a target antigen binds to or contacts the first receptor, the first receptor is responsive and activates an immune cell expressing the first receptor upon binding of the target antigen by the extracellular ligand binding domain of the first receptor. In some embodiments, the first receptor is a chimeric antigen receptor (CAR). In some embodiments, the first receptor is a T cell receptor (TCR).

[0142] In some embodiments, the first receptor is humanized. As used herein, "humanized" refers to the replacement of a sequence or a subsequence in a transgene that has been isolated or derived from a non-human species with a homologous, or functionally equivalent, human sequence. For example, a humanized antibody can be created by grafting mouse CDRs into human framework sequences, followed by back substitution of certain human framework residues for the corresponding mouse residues from the source antibody.

<u>Activator Targets</u>

[0143] In some embodiments, the target antigen for the first receptor is a cancer cell specific antigen. Any cell surface molecule expressed by the target cancer cells may be a suitable target antigen for the first receptor ligand binding domain. For example, a cell adhesion molecule, a cell-cell signaling molecule, an extracellular domain, a molecule involved in

chemotaxis, a glycoprotein, a G protein-coupled receptor, a transmembrane, a receptor for a neurotransmitter or a voltage gated ion channel can be used as a target antigen.

[0144] In some embodiments, the target antigen is a peptide antigen of a cancer cell-specific antigen in a complex with a major histocompatibility complex class I (MHC-I). Any molecule expressed by the target cancer cells and presented by the major histocompatibility complex class I (MHC-I) on the cancer cell surface as a peptide antigen (pMHC) may be a suitable target antigen for the first receptor extracellular ligand binding domain.

[0145] In some embodiments, the cancer cell-specific antigen is Mesothelin (MSLN), or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I).

[0146] The major histocompatibility complex class I (MHC-I) is a protein complex that displays antigens to cells of the immune system, triggering an immune response. The Human Leukocyte Antigens (HLAs) corresponding to MHC-I are HLA-A, HLA-B and HLA-C.

[0147] Cancer cell-specific pMHC antigens comprising any of HLA-A, HLA-B, HLA-C, HLA-E, HLA-F or HLA-G are envisaged as within the scope of the disclosure. In some embodiments, the cancer cell-specific antigen comprises HLA-A. HLA-A receptors are heterodimers comprising a heavy α chain and smaller β chain. The α chain is encoded by a variant of HLA-A, while the β chain (β2-microglobulin) is an invariant. There are several thousand variant HLA-A genes, all of which fall within the scope of the instant disclosure. In some embodiments, the MHC-I comprises a human leukocyte antigen A*02 allele (HLA-A*02).

[0148] In some embodiments, the cancer cell-specific antigen comprises HLA-B. Hundreds of versions (alleles) of the HLA-B gene are known, each of which is given a particular number (such as HLA-B*27).

[0149] In some embodiments, the cancer cell-specific antigen comprises HLA-C. HLA-C belongs to the HLA class I heavy chain paralogues. This class I molecule is a heterodimer consisting of a heavy chain and a light chain (beta-2 microglobulin). Over one hundred HLA-C alleles are known in the art.

[0150] In some embodiments, the cancer cell-specific antigen is an ovarian cancer antigen, a pancreatic cancer antigen, a lung cancer antigen, a colorectal cancer antigen or a mesothelioma antigen. In some embodiments, the cancer cell-specific antigen is a colorectal cancer antigen. In some embodiments, the cancer cell-specific antigen is MSLN or a peptide antigen thereof.

[0151] In some embodiments, the cancer cell-specific antigen is MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I). MSLN is a 40 KDa protein that is normally expressed in mesothelial cells, as well as lung, fallopian tube, salivary gland and adipose tissues (FIG. 2). MSLN is expressed in multiple human tumor types, including mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma. In some embodiments, the cancer has relapsed in a subject. In some embodiments, the cancer is refractory to one or more prior administered anticancer therapies. In some embodiments, the cancer is metastatic.

[0152] All isoforms of MSLN are envisaged as cancer cell-specific antigens of the disclosure. MSLN isoform 1 preprotein is described in NCBI record number NP_005814.2, the contents of which are incorporated by reference herein. In some embodiments, MSLN comprises an amino acid sequence of:

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  1 MALPTARPLL GSCGTPALGS LLFLLFSLGW VQPSRTLAGE TGQEAAPLDG VLANPPNISS
 61 LSPRQLLGFP CAEVSGLSTE RVRELAVALA QKNVKLSTEQ LRCLAHRLSE PPEDLDALPL
121 DLLLFLNPDA FSGPQACTRF FSRITKANVD LLPRGAPERQ RLLPAALACW GVRGSLLSEA
181 DVRALGGLAC DLPGRFVAES AEVLLPRLVS CPGPLDQDQQ EAARAALQGG GPPYGPPSTW
241 SVSTMDALRG LLPVLGQPII RSIPQGIVAA WRQRSSRDPS WRQPERTILR PRFRREVEKT
301 ACPSGKKARE IDESLIFYKK WELEACVDAA LLATQMDRVN AIPFTYEQLD VLKHKLDELY
361 PQGYPESVIQ HLGYLFLKMS PEDIRKWNVT SLETLKALLE VNKGHEMSPQ VATLIDRFVK
421 GRGQLDKDTL DTLTAFYPGY LCSLSPEELS SVPPSSIWAV RPQDLDTCDP RQLDVLYPKA
481 RLAFQNMNGS EYFVKIQSFL GGAPTEDLKA LSQQNVSMDL ATFMKLRTDA VLPLTVAEVQ
541 KLLGPHVEGL KAEERHRPVR DWILRQRQDD LDTLGLGLQG GIPNGYLVLD LSMQEALSGT
601 PCLLGPGPVL TVLALLLAST LA
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(SEQ ID NO: 1).

[0153] In some embodiments, MSLN comprises a sequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 1.

[0154] MSLN isoform 2 preprotein is described in NCBI record number NP_037536.2, the contents of which are incorporated by reference herein. In some embodiments, MSLN comprises an amino acid sequence of:

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  1 MALPTARPLL GSCGTPALGS LLFLLFSLGW VQPSRTLAGE TGQEAAPLDG VLANPPNISS
 61 LSPRQLLGFP CAEVSGLSTE RVRELAVALA QKNVKLSTEQ LRCLAHRLSE PPEDLDALPL
121 DLLLFLNPDA FSGPQACTRF FSRITKANVD LLPRGAPERQ RLLPAALACW GVRGSLLSEA
181 DVRALGGLAC DLPGRFVAES AEVLLPRLVS CPGPLDQDQQ EAARAALQGG GPPYGPPSTW
241 SVSTMDALRG LLPVLGQPII RSIPQGIVAA WRQRSSRDPS WRQPERTILR PRFRREVEKT
301 ACPSGKKARE IDESLIFYKK WELEACVDAA LLATQMDRVN AIPFTYEQLD VLKHKLDELY
361 PQGYPESVIQ HLGYLFLKMS PEDIRKWNVT SLETLKALLE VNKGHEMSPQ APRRPLPQVA
421 TLIDRFVKGR GQLDKDTLDT LTAFYPGYLC SLSPEELSSV PPSSIWAVRP QDLDTCDPRQ
481 LDVLYPKARL AFQNMNGSEY FVKIQSFLGG APTEDLKALS QQNVSMDLAT FMKLRTDAVL
541 PLTVAEVQKL LGPHVEGLKA EERHRPVRDW ILRQRQDDLD TLGLGLQGGI PNGYLVLDLS
601 MQEALSGTPC LLGPGPVLTV LALLLASTLA
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(SEQ ID NO: 2).

[0155] In some embodiments, MSLN comprises a sequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 2.

In some embodiments, the cancer cell-specific antigen is a peptide antigen derived from MSLN. In some embodiments, the peptide antigen is comprises a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a subsequence of SEQ ID NO: 1 and/or SEQ ID NO: 2. In some embodiments, the peptide antigen comprises a sequence identical to a subsequence of SEQ ID NO: 1 and/or SEQ ID NO: 2.

Extracellular Ligand Binding Domain

[0156] The disclosure provides a first receptor, comprising a first extracellular ligand binding domain specific to a target antigen. In some embodiments, the target antigen comprises a cancer cell-specific antigen.

[0157] In some embodiments, the cancer cell-specific antigen is MSLN or a MSLN-derived peptide antigen complexed with MHC-I, and the ligand binding domain of the first receptor recognizes and binds to the MSLN antigen.

[0158] Any type of ligand binding domain that can regulate the activity of a receptor in a ligand dependent manner is envisaged as within the scope of the instant disclosure. In some embodiments, the ligand binding domain is an antigen binding domain. Exemplary antigen binding domains include, *inter alia*, scFv, SdAb, Vβ-only domains, and TCR antigen binding domains derived from the TCR α and β chain variable domains.

[0159] Any type of antigen binding domain is envisaged as within the scope of the instant disclosure.

[0160] For example, the first extracellular ligand binding domain may be part of a contiguous polypeptide chain including, for example, a Vβ-only domain, a single domain antibody fragment (sdAb) or heavy chain antibodies HCAb, a single chain antibody (scFv) derived from a murine, humanized or human antibodies (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 some aspects, the first extracellular ligand binding domain comprises an antigen binding domain that comprises an antibody fragment. In further aspects, the first extracellular ligand binding domain comprises an antibody fragment that comprises a scFv or an sdAb.

[0161] The term "antibody," as used herein, refers to a protein, or polypeptide sequences derived from an immunoglobulin molecule, which specifically binds to an antigen. Antibodies can be intact immunoglobulins of polyclonal or monoclonal origin, or fragments thereof and can be derived from natural or from recombinant sources.

[0162] The terms "antibody fragment" or "antibody binding domain" refer to at least one portion of an antibody, or recombinant variants thereof, that contains the antigen binding domain, *i.e.*, an antigenic determining variable region of an intact antibody, that is sufficient to confer recognition and specific binding of the antibody fragment to a target, such as an antigen and its defined epitope. Examples of antibody fragments include, but are not limited to, Fab, Fab′, F(ab′)2, and Fv fragments, single-chain (sc)Fv ("scFv") antibody fragments, linear antibodies, single domain antibodies (abbreviated "sdAb") (either VL or VH), camelid VHH domains, and multi-specific antibodies formed from antibody fragments.

[0163] The term "scFv" refers to a fusion 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, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single polypeptide chain, and wherein the scFv retains the specificity of the intact antibody from which it is derived.

[0164] "Heavy chain variable region" or "VH" (or, in the case of single domain antibodies, *e.g.*, nanobodies, "VHH") with regard to an antibody refers to the fragment of the heavy chain that contains three CDRs interposed between flanking stretches known as framework regions, these framework regions are generally more highly conserved than the CDRs and form a scaffold to support the CDRs.

[0165] Unless specified, as used herein a 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.

[0166] In some embodiments, the antigen binding domain of the activator and/or inhibitory receptor comprises an scFv. In some embodiments, the scFv comprises a VL and VH region joined by a linker. In some embodiments, the linker comprises a glycine serine linker, for example GGGGSGGGGSGGGGSGG (SEQ ID NO: 152). In some embodiments, the scFv further comprises a signal sequence at the N terminus of the scFv. Exemplary signal sequences include MDMRVPAQLLGLLLLWLRGARC (SEQ ID NO: 362), which is encoded by

ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTACTCTGGCTCCGAG GTGCCAGATGT (SEQ ID NO: 153).

[0167] The term "antibody light chain," refers to the smaller of the two types of polypeptide chains present in antibody molecules in their naturally occurring conformations. Kappa ("K") and lambda ("λ") light chains refer to the two major antibody light chain isotypes.

[0168] The term "recombinant antibody" refers to an antibody that 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 well known in the art.

[0169] The term "Vβ domain", "Vβ-only domain", "β chain variable domain" or "single variable domain TCR (svd-TCR)" refers to an antigen binding domain that consists essentially of a single T Cell Receptor (TCR) beta variable domain that specifically binds to an antigen in the absence of a second TCR variable domain. The Vβ-only domain engages antigen using complementarity-determining regions (CDRs). Each Vβ-only domain contains three complement determining regions (CDR1, CDR2, and CDR3). Additional elements may be combined provided that the Vβ domain is configured to bind the epitope in the absence of a second TCR variable domain.

[0170] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an antibody fragment, a single chain Fv antibody fragment (scFv), or a β chain variable domain (Vβ).

[0171] In some embodiments, the extracellular ligand binding domain of the first receptor comprises a TCR α chain variable domain and a TCR β chain variable domain.

[0172] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an scFv antigen binding domain. Exemplary MSLN scFv are shown in Table 1 below.

Table 1: Exemplary MSLN scFv domains

	Protein Sequence	DNA Sequence
M5	QVQLVQSGAEV EKPGASVKVSCK ASGYTFTDYYM HWVRQAPGQGL EWMGWINPNSG	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGGA GAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGG CTTCTGGATACACCTTCACCGACTACTATATGCACT GGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGG ATGGGATGGATCAACCCTAACAGTGGTGGCACAAA

	GTNYAQKFQGR VTMTRDTSISTA YMELSRLRSDDT AVYYCASGWDF DYWGQGTLVTV SSGGGGSGGGGS GGGGSGGDIVM TQSSSLSASVGD RVTITCRASQSIR YYLSWYQQKPG KAPKLLIYTASIL QNGVPSRFSGSG SGTDFTLTISSLQ PEDFATYYCLQT YTTPDFGPGTKV EIK (SEQ ID NO: 3)	CTATGCACAGAAGTTTCAGGGCAGGGTCACCATGA CCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCCGTGTA TTACTGTGCGTCTGGCTGGGACTTTGACTACTGGGG CCAGGGAACCCTGGTCACCGTGTCCTCAGGCGGAG GTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGG AAGCGGAGGCGACATCGTGATGACCCAGTCTTCCT CCCTGTCTGCATCTGTCGGAGACAGAGTCACCATCA CTTGCCGGGCCAGTCAGAGCATTAGGTACTATTTAA GTTGGTATCAGCAGAAACCAGGAAAAGCCCCTAAG CTCCTGATCTATACTGCATCCATTTTACAAAATGGG GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGAC AGATTTCACTCTCACCATCAGCAGCCTGCAACCTGA GGATTTTGCAACTTATTACTGCCTCCAGACTTACAC TACTCCGGACTTTGGCCCAGGGACCAAGGTGGAAA TCAAA (SEQ ID NO: 363)
M1 4	QVQLVQSGAEV RAPGASVKISCK ASGFTFRGYYIH WVRQAPGQGLE WMGIINPSGGSR AYAQKFQGRVT MTRDTSTSTVY MELSSLRSDDTA MYYCARTASCG GDCYYLDYWGQ GTLVTVSSGGGG SGGGGSGGGGS GGDIQMTQSPPT LSASVGDRVTIT CRASENVNIWLA WYQQKPGKAPK LLIYKSSSLASGV PSRFSGSGSGAEF TLTISSLQPDDFA TYYCQQYQSYPL TFGGGTKVEIK (SEQ ID NO 4)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAG GGCACCTGGGGCCTCAGTGAAGATTTCCTGCAAGG CTTCTGGATTCACCTTCAGAGGCTACTATATCCACT GGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGG ATGGGAATCATCAACCCTAGTGGTGGTAGCAGAGC CTACGCACAGAAGTTCCAGGGCAGGGTCACCATGA CCAGGGACACTTCCACGAGCACAGTCTACATGGAG CTGAGCAGCCTGAGATCTGACGACACGGCCATGTA TTACTGTGCGAGAACCGCAAGTTGTGGTGGTGACTG CTACTACCTTGACTACTGGGGCCAGGGAACCCTGGT CACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGG GAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATC CAGATGACCCAGTCTCCTCCCACCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCGGGCCAG TGAGAATGTTAATATCTGGTTGGCCTGGTATCAGCA GAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATA AGTCATCCAGTTTAGCAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGGCAGAATTCACTCTCA CCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTT ATTACTGCCAACAGTATCAAAGTTACCCCCTCACTT TCGGCGGAGGGACCAAGGTGGAAATCAAA (SEQ ID NO: 364)
S5 H	QVQLVQSGAEV KKPGASVKVSC KASGYSFTGYT MNWVRQAPGQR LEWMGLITPYNG ASSYNQKFRGRV TITRDTSASTAY MELSSLRSEDTA	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAA GAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATACTCATTCACCGGCTACACCATGAACT GGGTGAGGCAGGCCCCTGGACAAAGACTTGAGTGG ATGGGACTTATCACCCCTTACAATGGTGCTTCTAGC TACAACCAGAAGTTCAGGGGCAGGGTCACAATCAC TAGAGACACGTCAGCCAGCACAGCCTACATGGAGC TCTCCAGCCTGAGATCTGAAGACACTGCAGTCTATT

	VYYCARGGYDG RGFDYWGQGTT VTVSSGGGGSGG GGSGGGGSGGDI QMTQSPSSLSAS VGDRVTITCSAS SSVSYMHWYQQ KPGKAPKRLIYD TSKLASGVPSRF SGSGSGTEFTLTI SSLQPEDFATYY CQQWSGYPLTF GQGTKLEIK (SEQ ID NO: 5)	ACTGTGCAAGGGGGGGTTACGACGGGAGGGGTTTT GACTACTGGGGCCAGGGAACCACGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGACATCCAGATGACC CAGTCTCCTTCAAGCTTGTCTGCATCTGTAGGAGAC AGGGTCACCATCACTTGCAGTGCCAGCTCAAGTGTA AGTTACATGCACTGGTATCAGCAGAAACCAGGCAA GGCCCCTAAGAGATTGATCTATGACACATCCAAATT AGCAAGTGGGGTCCCAAGTCGCTTCAGTGGCAGTG GATCTGGGACCGAATTCACTCTCACCATCAGCAGCT TGCAGCCTGAGGATTTTGCAACTTATTACTGCCAGC AGTGGAGTGGTTACCCTCTCACGTTCGGTCAGGGGA CAAAGTTGGAAATCAAA (SEQ ID NO: 365)
S5 M	QVQLQQSGPELE KPGASVKISCKA SGYSFTGYTMN WVKQSHGKSLE WIGLITPYNGAS SYNQKFRGKATL TVDKSSSTAYM DLLSLTSEDSAV YFCARGGYDGR GFDYWGQGTTV TVSSGGGGSGGG GSGGGGSGGDIE LTQSPAIMSASP GEKVTMTCSASS SVSYMHWYQQK SGTSPKRWIYDT SKLASGVPGRFS GSGSGNSYSLTIS SVEAEDDATYY CQQWSGYPLTF GAGTKLEIK (SEQ ID NO: 6)	CAGGTGCAGCTGCAGCAGTCTGGGCCTGAGCTGGA GAAGCCTGGGGCCTCAGTGAAGATTTCCTGCAAGG CTTCTGGATACTCATTCACCGGCTACACCATGAACT GGGTGAAGCAGAGCCATGGAAAAAGCCTTGAGTGG ATTGGACTTATCACCCCTTACAATGGTGCTTCTAGC TACAACCAGAAGTTCAGGGGCAAGGCCACATTAAC TGTAGACAAGTCATCCAGCACAGCCTACATGGACC TCCTCAGCCTGACATCTGAAGACTCTGCAGTCTATT TCTGTGCAAGGGGGGGTTACGACGGGAGGGGTTTT GACTACTGGGGCCAGGGAACCACGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGACATCGAGCTCACC CAGTCTCCTGCAATCATGTCTGCATCTCCAGGAGAG AAGGTCACCATGACTTGCAGTGCCAGCTCAAGTGT AAGTTACATGCACTGGTATCAGCAGAAATCAGGCA CCTCCCCTAAGAGATGGATCTATGACACATCCAAAT TGGCAAGTGGGGTCCCAGGTCGCTTCAGTGGCAGT GGATCTGGGAACTCTTACTCTCTCACCATCAGCAGC GTGGAGGCTGAGGATGATGCAACTTATTACTGCCA GCAGTGGAGTGGTTACCCTCTCACGTTCGGTGCTGG GACAAAGTTGGAAATCAAA (SEQ ID NO: 366)
SS1	QVQLQQSGPELE KPGASVKISCKA SGYSFTGYTMN WVKQSHGKSLE WIGLITPYNGAS SYNQKFRGKATL TVDKSSSTAYM DLLSLTSEDSAV YFCARGGYDGR GFDYWGQGTTV	ND

	TVSSGGGGSGGG GSGGGGSDIELT QSPAIMSASPGE KVTMTCSASSSV SYMHWYQQKSG TSPKRWIYDTSK LASGVPGRFSGS GSGNSYSLTISSV EAEDDATYYCQ QWSGYPLTFGA GTKLEI (SEQ ID NO: 80	
1	EVQLVESGGGLVKP GGSLRLSCAASGFTF SNAWMSWVRQAP GKGLEWVGRIKSKT DGGTTDYAAPVKGR FTISRDDSKNTLYLQ MNSLKTEDTAVYYC TTDLPKLRNFHIWG QGTLVTVSSGGGGS GGGGSGGGGSGGDI QMTQSPSSLSASVG DRVTITCRASQSISSY LNWYQQKPGKAPKL LIYAASSLQSGVPSRF SGSGSGTDFTLTISSL QPEDFATYYCQQSYS TPLTFGGGTKVEIK (SEQ ID NO: 154)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCTCGAACGCCTGGATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTCGGACGGATCAAGAGCAAGACCGACGG CGGCACCACCGACTACGCTGCCCCCGTGAAGGGCCGGTTCACC ATCAGCCGGGACGACAGCAAGAACACCCTGTACCTGCAGATGA ACAGCCTGAAAACCGAGGACACCGCCGTGTATTACTGTACCAC AGATCTTCCTAAGCTTAGGAATTTTCATATTTGGGGCCAGGGAA CCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGG GAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGA CCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAA TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAG TGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTAC AGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCA AG (SEQ ID NO: 367)
2	EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYAMHWVRQAPG KGLEYVSAISSNGGS TYYANSVKGRFTISR DNSKNTLYLQMGSL RAEDMAVYYCASLE YHGFRQYGLRYWH WGQGTLVTVSSGG GGSGGGGSGGGGS GGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSGV PSRFSGSGSGTDFTL TISSLQPEDFATYYCQ QSYSTPLTFGGGTKV	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATACGTGTCCGCCATCAGCTCGAACGGCGGCAGC ACCTACTACGCCAACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACAGCAAGAACACCCTGTACCTGCAGATGGGCAGCCT GCGGGCCGAGGATATGGCCGTGTATTACTGTGCGAGCCTAGAA TACCATGGCTTTCGACAATATGGGCTTCGTTATTGGCATTGGGG CCAGGGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGC GGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACAT CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAG CTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAG CTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATC AAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACC ATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCA

	EIK (SEQ ID NO: 155)	ACAGAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAG GTGGAGATCAAG (SEQ ID NO: 368)
3	QLQLQESGSGLVKPS QTLSLTCAVSGGSISS GGYSWSWIRQPPGK GLEWIGYIYHSGSTY YNPSLKSRVTISVDRS KNQFSLKLSSVTAAD TAVYYCASIKFWFAG INYFFPWGQGTLVT VSSGGGGSGGGGSG GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 156)	CAGCTGCAGCTCCAGGAAAGCGGCAGCGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGTGCCGTGTCCGGCGGCAGCA TCAGCAGCGGCGGCTACAGCTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCTACCACAGCGGC TCGACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAG CGTGGACAGAAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAG CGTGACAGCCGCCGACACCGCTGTGTATTACTGTGCCAGCATAA AATTCTGGTTTGCGGGGATTAATTATTTTTTTCCGTGGGGCCAG GGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGA GGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCA GATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTA TTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTC CTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAG GTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCA GCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAG AGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGG AGATCAAG (SEQ ID NO: 369)
4	EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYWMHWVRQAP GKGLVWVSRINSDG SSTSYADSVKGRFTIS RDNAKNTLYLQMNS LRAEDTAVYYCASGF LGMGSNFIWGQGTL VTVSSGGGGSGGGG SGGGGSGGDIQMT QSPSSLSASVGDRVT ITCRASQSISSYLNWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQSYSTPLT FGGGTKVEIK (SEQ ID NO: 157)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACTGGATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGTCTGGGTGTCTCGAATCAACAGCGACGGCAGCAGC ACCAGCTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACACCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCAAGCGGATTT TTGGGAATGGGCTCGAATTTTATTTGGGGCCAGGGAACCCTGG TCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGT CTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATC ACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTA TCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCT GCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCA GTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA CCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTAC CCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 370)
5	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS SGGYYWSWIRQHP GKGLEWIGYIYYSGS TYYNPSLKSLVTISVD TSKNQFSLKLSSVTA ADTAVYYCASGDRA RYFDLWGRGTLVTV SSGGGGSGGGGSG	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCAGCA TCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCACCC CGGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGC AGCACCTACTACAACCCCAGCCTGAAGTCCCTGGTGACAATCTC CGTCGATACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGC GTGACAGCCGCCGACACCGCTGTGTATTACTGTGCAAGCGGGG ACAGGGCACGGTACTTCGATCTCTGGGGCCGTGGCACCCTGGT CACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC

	GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 158)	TGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTC TCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCA CTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTG CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAG TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAAC CTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 371)
6	EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYWMHWVRQAP GKGLVWVSRINSDG SSTSYADSVKGRFTIS RDNAKNTLYLQMNS LRAEDTAVYYCARYP RGYHQMVDAFDIW GQGTMVTVSSGGG GSGGGGSGGGGSG GDIQMTQSPSSLSAS VGDRVTITCRASQSI SSYLNWYQQKPGKA PKLLIYAASSLQSGVP SRFSGSGSGTDFTLTI SSLQPEDFATYYCQQ SYSTPLTFGGGTKVEI K (SEQ ID NO: 159)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACTGGATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGTCTGGGTGTCTCGAATCAACAGCGACGGCAGCAGC ACCAGCTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACACCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCAAGATATCCA CGTGGATATCATCAGATGGTTGATGCTTTTGATATCTGGGGCCA AGGGACAATGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGG AGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCC AGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCT ATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCT CCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAA GGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC AGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACA GAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTG GAGATCAAG (SEQ ID NO: 372)
7	QLQLQESGPGLVKPS ETLSLTCTVSGGSISS SSYYWGWIRQPPGK GLEWIGSIYYSGSTYY NPSLKSRVTISVDTSK NQFSLKLSSVTAADT AVYYCARVRFLAART TIPEANFLWGQGTL VTVSSGGGGSGGGG SGGGGSGGDIQMT QSPSSLSASVGDRVT ITCRASQSISSYLNWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQSYSTPLT FGGGTKVEIK (SEQ ID NO: 160)	CAGCTGCAGCTCCAGGAAAGCGGCCCTGGCCTGGTGAAACCCA GCGAGACACTGAGCCTGACCTGCACCGTGTCCGGCGGCAGCAT CAGCAGCAGCAGCTACTACTGGGGCTGGATCAGACAGCCCCCT GGCAAGGGCCTGGAATGGATCGGCTCGATCTACTACAGCGGCT CCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGC GTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCG TGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGTACG ATTTTTGGCTGCTCGCACTACTATTCCGGAGGCGAATTTTCTTTG GGGCCAGGGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGG AAGCGGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCG ACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAG CAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCT AAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCC ATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGT CAACAGAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAA GGTGGAGATCAAG (SEQ ID NO: 373)
8	EVQLVESGGGLVQP GGSLRLSCAASGFTF	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT

	SSYSMNWVRQAPG KGLEWVSYISSSSSTI YYADSVKGRFTISRD NAKNSLYLQMNSLR AEDTAVYYCARVLSR ARFDYWGQGTLVTV SSGGGGSGGGGSG GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 161)	TCAGCAGCTACAGCATGAACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCAGCTCCACC ATCTACTACGCCGACAGCGTGAAGGGTCGATTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGTACTC TCCAGGGCTAGGTTTGACTACTGGGGCCAGGGAACCCTGGTCA CCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTC CATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACT TGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCA TCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCC TCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 374)
9	EVQLVESGGGLVKP GGSLRLSCAASGFTF SSYSMNWVRQAPG KGLEWVSSISSSSSYI YYADSVKGRFTISRD NAKNSLYLQMNSLR AEDTAVYYCARLRGR VFDPWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSPS SLSASVGDRVTITCR ASQSISSYLNWYQQ KPGKAPKLLIYAASSL QSGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 162)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACAGCATGAACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTCGATCAGCAGCAGCAGCTCCTAC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGATTACGA GGGAGGGTGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACC GTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGC GGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTCCA TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAG CAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATC CAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGA TCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGA AGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCT CACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 375)
10	QLQLQESGPGLVKPS ETLSLTCTVSGGSISS SSYYWGWIRQPPGK GLEWIGSIYYSGSTYY NPSLKSRVTISVDTSK NQFSLKLSSVTAADT AVYYCARIKFTSFLYV HGFLWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSPS SLSASVGDRVTITCR ASQSISSYLNWYQQ KPGKAPKLLIYAASSL	CAGCTGCAGCTCCAGGAAAGCGGCCCTGGCCTGGTGAAACCCA GCGAGACACTGAGCCTGACCTGCACCGTGTCCGGCGGCAGCAT CAGCAGCAGCAGCTACTACTGGGGCTGGATCAGACAGCCCCCT GGCAAGGGCCTGGAATGGATCGGCTCGATCTACTACAGCGGCT CCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGC GTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCG TGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAATAAA ATTTACCAGCTTTTTATATGTTCATGGTTTTCTGTGGGGCCAGG GAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAG GGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAG ATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATT TAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT

	QSGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 163)	GATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAG TTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAG ATCAAG (SEQ ID NO: 376)
11	QVQLVQSGAEVKKP GASVKVSCKASGYTF TSYAMHWVRQAPG QRLEWMGWINAG NGNTKYSQKFQGRV TITRDTSASTAYMEL SSLRSEDTAVYYCAR GQRWLYLGGIRRH WGQGTLVTVSSGG GGSGGGGSGGGGS GGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSGV PSRFSGSGSGTDFTL TISSLQPEDFATYYCQ QSYSTPLTFGGGTKV EIK (SEQ ID NO: 164)	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCT GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCT TCACCAGCTACGCCATGCACTGGGTTCGACAGGCCCCTGGCCA GAGACTGGAATGGATGGGCTGGATCAACGCCGGCAACGGCAA CACCAAGTACAGCCAGAAATTCCAGGGCAGAGTGACCATCACC CGGGACACCAGCGCCAGCACCGCCTACATGGAACTGAGCAGCC TGCGGAGCGAGGACACCGCTGTGTATTACTGTGCGAGAGGCCA GAGATGGCTGTACCTCGGGGGGATTCGTCGGCATTGGGGCCA GGGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGG AGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCC AGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC AGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCT ATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCT CCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAA GGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC AGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACA GAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTG GAGATCAAG (SEQ ID NO: 377)
12	QVQLQESGPGLVKP SETLSLTCTVSGGSIS SYYWSWIRQPPGKG LEWIGYIYYSGSTNY NPSLKSRVTISVDTSK NQFSLKLSSVTAADT AVYYCAREWIPSRPY YFDYWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSPS SLSASVGDRVTITCR ASQSISSYLNWYQQ KPGKAPKLLIYAASSL QSGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 165)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCGAGACACTGAGCCTGACCTGCACCGTGTCCGGCGGCAGCA TCAGCAGCTACTACTGGTCCTGGATCAGACAGCCCCCTGGCAA GGGCCTGGAATGGATCGGCTACATCTACTACAGCGGCAGCACC AACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCTCCGTCGA TACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACA GCCGCCGACACCGCTGTGTATTACTGTGCGAGAGAATGGATTC CCAGCCGTCCGTACTACTTTGACTACTGGGGCCAGGGAACCCTG GTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA TCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAG TCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT CACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTA CCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 378)
13	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS SGGYYWSWIRQPPG KGLEWIGYIYYSGSTY YNPSLKSRVTISVDTS	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCTCGA TCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGC AGCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCA

	KNQFSLKLSSVTAAD TAVYYCARESTGTGA FDIWGQGTMVTVSS GGGGSGGGGSGGG GSGGDIQMTQSPSS LSASVGDRVTITCRA SQSISSYLNWYQQKP GKAPKLLIYAASSLQS GVPSRFSGSGSGTDF TLTISSLQPEDFATYY CQQSYSTPLTFGGGT KVEIK (SEQ ID NO: 166)	GCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAG CGTGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGAA AGTACCGGTACAGGAGCTTTTGATATCTGGGGCCAAGGGACAA TGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCC AGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT GCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTG GCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTG CAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAG TACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 379)
14	EVQLVESGGGVVRP GGSLRLSCAASGFTF DDYGMSWVRQAPG KGLEWVSGINWNG GSTGYADSVKGRFTI SRDNAKNSLYLQMN SLRAEDTALYHCARE RYRRVLHWYFDLW GRGTLVTVSSGGGG SGGGGSGGGGSGG DIQMTQSPSSLSASV GDRVTITCRASQSISS YLNWYQQKPGKAPK LLIYAASSLQSGVPSR FSGSGSGTDFTLTISS LQPEDFATYYCQQSY STPLTFGGGTKVEIK (SEQ ID NO: 167)	GAAGTGCAGCTGGTGGAAAGCGGAGGCGGAGTGGTTCGACCT GGCGGAAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TTGACGACTACGGCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCGGCATCAACTGGAACGGCGGCAG CACCGGCTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCTTGTATCACTGTGCGAGAGAGAG GTACAGGCGGGTACTCCACTGGTACTTCGATCTCTGGGGCCGT GGCACCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGA GGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCA GATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTA TTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTC CTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAG GTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCA GCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAG AGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGG AGATCAAG (SEQ ID NO: 380)
15	QVQLVQSGAEVKKP GASVKVSCKASGYTF TSYDINWVRQATGQ GLEWMGWMNPNS GNTGYAQKFQGRVT MTRNTSISTAYMELS SLRSEDTAVYYCARE PDAFDIWGQGTMV TVSSGGGGSGGGGS GGGGSGGDIQMTQ SPSSLSASVGDRVTIT CRASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCT GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCT TCACCAGCTACGACATCAACTGGGTCCGCCAGGCCACCGGACA GGGCCTGGAATGGATGGGCTGGATGAACCCCAACAGCGGCAA CACCGGCTACGCCCAGAAATTCCAGGGCAGAGTGACCATGACC CGGAACACCTCGATCAGCACCGCCTACATGGAACTGAGCAGCC TGCGGAGCGAGGACACCGCTGTGTATTACTGTGCGAGAGAACC GGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTG TCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGG CGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTCCATCC TCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCG GGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAG TTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGA TTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCTCAC

	GGGTKVEIK (SEQ ID NO: 168)	TTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 381)
16	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS SGGYYWSWIRQPPG KGLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCAREHMGTI PYYFDYWGQGTLVT VSSGGGGSGGGGSG GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 169)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCTCGA TCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGC AGCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCA GCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAG CGTGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGAA CATATGGGGACGATTCCGTACTACTTTGACTACTGGGGCCAGG GAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAG GGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAG ATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAG AGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATT TAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCT GATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAG TTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAG ATCAAG (SEQ ID NO: 382)
17	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS SGGYYWSWIRQPPG KGLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCAREEFGYGD VLYWGQGTLVTVSS GGGGSGGGGSGGG GSGGDIQMTQSPSS LSASVGDRVTITCRA SQSISSYLNWYQQKP GKAPKLLIYAASSLQS GVPSRFSGSGSGTDF TLTISSLQPEDFATYY CQQSYSTPLTFGGGT KVEIK (SEQ ID NO: 170)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCTCGA TCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGC AGCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCA GCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAG CGTGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGAA GAGTTTGGTTATGGGGACGTCCTCTACTGGGGCCAGGGAACCC TGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCC AGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACC ATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTAT GCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTG GCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTG CAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAG TACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 383)
18	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS SGDYYWSWIRQPPG KGLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCAREDVVKG AFDIWGQGTMVTV SSGGGGSGGGGSG	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCAGCA TCAGCAGCGGCGACTACTACTGGTCCTGGATCAGACAGCCCCCT GGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGCA GCACCTACTACAACCCCAGCCTGAAGTCTCGAGTGACCATCAGC GTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCG TGACAGCCGCCGACACCGCTGTGTATTACTGTGCCAGAGAGGA CGTAGTCAAAGGCGCTTTTGATATCTGGGGCCAAGGGACAATG GTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA

	GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 171)	TCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAG TCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT CACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTA CCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 384)
19	EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYSMNWVRQAPG KGLEWVSYISSSSSTI YYADSVKGRFTISRD NAKNSLYLQMNSLR AEDTAVYYCAREDFS HKLGYFQHWGQGT LVTVSSGGGGSGGG GSGGGGSGGDIQM TQSPSSLSASVGDRV TITCRASQSISSYLNW YQQKPGKAPKLLIYA ASSLQSGVPSRFSGS GSGTDFTLTISSLQPE DFATYYCQQSYSTPL TFGGGTKVEIK (SEQ ID NO: 172)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACAGCATGAACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCAGCTCCACC ATCTACTACGCCGACAGCGTGAAGGGTCGATTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGAAGA CTTCTCGCATAAGCTAGGGTACTTCCAGCACTGGGGCCAGGGC ACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGG GGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGAT GACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAG TCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTA AATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA TCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTC AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCA GTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGT TACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGA TCAAG (SEQ ID NO: 385)
20	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARDYDY VWGQGTLVTVSSG GGGSGGGGSGGGG SGGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSGV PSRFSGSGSGTDFTL TISSLQPEDFATYYCQ QSYSTPLTFGGGTKV EIK (SEQ ID NO: 173)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATTAC GATTACGTGTGGGGCCAGGGAACCCTGGTCACCGTGTCCTCAG GCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGGA AGCGGAGGCGACATCCAGATGACCCAGTCTCCATCCTCCCTGTC TGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGT CAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAG GGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAA AGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAG ATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAA CTTACTACTGTCAACAGAGTTACAGTACCCCTCTCACTTTCGGCG GCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 386)
21	QVQLQESGPGLVKP SQTLSLTCTVSGGSIS	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCAGCA

	SGDYYWSWIRQPPG KGLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCARDRRDWD WFDPWGQGTLVTV SSGGGGSGGGGSG GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 174)	TCAGCAGCGGCGACTACTACTGGTCCTGGATCAGACAGCCCCCT GGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGCA GCACCTACTACAACCCCAGCCTGAAGTCTCGAGTGACCATCAGC GTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCG TGACAGCCGCCGACACCGCTGTGTATTACTGTGCCAGAGATCG CCGTGATTGGGACTGGTTCGACCCCTGGGGCCAGGGAACCCTG GTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA TCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAG TCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT CACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTA CCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 387)
22	QVQLQESGPGLVKP SGTLSLTCAVSGGSIS SSNWWSWVRQPP GKGLEWIGEIYHSGS TNYNPSLKSRVTISV DKSKNQFSLKLSSVT AADTAVYYCARDQQ ALKYRVDWGQGTLV TVSSGGGGSGGGGS GGGGSGGDIQMTQ SPSSLSASVGDRVTIT CRASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 175)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCGGCACCCTGAGCCTGACCTGTGCCGTGTCTGGCGGCAGCA TCAGCAGCAGCAACTGGTGGTCCTGGGTCCGCCAGCCTCCCGG CAAGGGCCTCGAATGGATCGGCGAGATCTACCACAGCGGCAGC ACCAACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGCG TGGACAAGAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGT GACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGATCAG CAGGCGTTGAAATACCGTGTGGATTGGGGCCAGGGAACCCTG GTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA TCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAG TCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCAT CACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGT ATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA ACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTA CCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 388)
23	QVQLVQSGAEVKKP GASVKVSCKASGYTF TSYGISWVRQAPGQ GLEWMGWISAYNG NTNYAQKLQGRVT MTTDTSTSTAYMEL RSLRSDDTAVYYCAR DLTLGCFDYWGQGT LVTVSSGGGGSGGG GSGGGGSGGDIQM TQSPSSLSASVGDRV TITCRASQSISSYLNW YQQKPGKAPKLLIYA	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAAGAAACCT GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCT TCACCAGCTACGGCATCAGCTGGGTCCGCCAGGCTCCTGGACA GGGACTGGAATGGATGGGCTGGATCAGCGCCTACAACGGCAA CACCAACTACGCCCAGAAACTGCAGGGCAGAGTGACCATGACC ACCGACACCAGCACCAGCACCGCCTACATGGAACTTCGAAGCC TGAGAAGCGACGACACCGCCGTGTATTACTGTGCGAGAGATCT TACGCTAGGATGCTTTGACTACTGGGGCCAGGGAACCCTGGTC ACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCT CCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCAC TTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATC AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGC

	ASSLQSGVPSRFSGS GSGTDFTLTISSLQPE DFATYYCQQSYSTPL TFGGGTKVEIK (SEQ ID NO: 176)	ATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACC TGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCC CTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 389)
24	EVQLVESGGGLVQP GGSLRLSCAASGFTV SSNYMSWVRQAPG KGLEWVSVIYSGGST YYADSVKGRFTISRD NSKNTLYLQMNSLR AEDTAVYYCARDGS NSWYFDLWGRGTL VTVSSGGGGSGGGG SGGGGSGGDIQMT QSPSSLSASVGDRVT ITCRASQSISSYLNWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQSYSTPLT FGGGTKVEIK (SEQ ID NO: 177)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCG TGTCCAGCAACTACATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCGTGATCTACAGCGGCGGCAGCAC CTACTACGCCGACAGCGTGAAGGGTCGATTCACCATCAGCCGG GACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCCTGC GGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATGGGTC AAACTCTTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGGTCA CTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTC CATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACT TGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCA TCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCC TCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 390)
25	QVQLVESGGGVVQP GRSLRLSCAASGFTF SSYGMHWVRQAPG KGLEWVAVIWYDGS NKYYADSVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCARAF LFLSFSVWGQGTLVT VSSGGGGSGGGGSG GGGSGGDIQMTQS PSSLSASVGDRVTITC RASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 178)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCGTGGTGCAGCCC GGCAGAAGCCTTCGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGGCATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGGCCGTGATTTGGTACGACGGCAGCAA CAAGTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGGGCATT TTTATTCCTGTCTTTTTCGGTTTGGGGCCAGGGAACCCTGGTCA CCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTC CATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACT TGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCA TCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCC TCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 391)
26	EVQLVESGGVVVQP GGSLRLSCAASGFTF DDYTMHWVRQAPG KGLEWVSLISWDGG STYYADSVKGRFTISR DNSKNSLYLQMNSL	GAAGTGCAGCTGGTGGAATCTGGCGGCGTGGTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCGACGACTACACCATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCCTGATCAGCTGGGACGGCGGCTCT ACCTACTACGCCGACTCCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACAGCAAGAACAGCCTGTACCTGCAGATGAACAGCCT

	RTEDTALYYCAKGIFY SSKEDFDYWGQGTL VTVSSGGGGSGGGG SGGGGSGGDIQMT QSPSSLSASVGDRVT ITCRASQSISSYLNWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQSYSTPLT FGGGTKVEIK (SEQ ID NO: 179)	GCGGACCGAGGACACCGCCTTGTATTACTGTGCAAAAGGGATA TTCTACTCGAGTAAAGAGGATTTTGACTACTGGGGCCAGGGAA CCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGG GAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGA CCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAA TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAG TGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTAC AGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCA AG (SEQ ID NO: 392)
27	EVQLVESGGVVVQP GGSLRLSCAASGFTF DDYTMHWVRQAPG KGLEWVSLISWDGG STYYADSVKGRFTISR DNSKNSLYLQMNSL RTEDTALYYCAKDIW IFYSSNPKPTVYWGQ GTLVTVSSGGGGSG GGGSGGGGSGGDI QMTQSPSSLSASVG DRVTITCRASQSISSY LNWYQQKPGKAPKL LIYAASSLQSGVPSRF SGSGSGTDFTLTISSL QPEDFATYYCQQSYS TPLTFGGGTKVEIK (SEQ ID NO: 180)	GAAGTGCAGCTGGTGGAATCTGGCGGCGTGGTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCGACGACTACACCATGCACTGGGTCCGCCAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCCTGATCAGCTGGGACGGCGGCTCT ACCTACTACGCCGACTCCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACAGCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGACCGAGGACACCGCCTTGTATTACTGTGCAAAAGATATA TGGATATTCTACTCGAGTAATCCAAAGCCGACGGTCTACTGGG GCCAGGGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAA GCGGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGAC ATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGC AGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTA AGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCA TCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCAC CATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTC AACAGAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAA GGTGGAGATCAAG (SEQ ID NO: 393)
28	QVQLVQSGSELKKP GASVKVSCKASGYTF TSYAMNWVRQAPG QGLEWMGWINTNT GNPTYAQGFTGRFV FSFDTSVSTAYLQICS LKAEDTAVYYCARKD QTLTYGNWFDPWG QGTLVTVSSGGGGS GGGGSGGGGSGGDI QMTQSPSSLSASVG DRVTITCRASQSISSY LNWYQQKPGKAPKL LIYAASSLQSGVPSRF SGSGSGTDFTLTISSL QPEDFATYYCQQSYS	CAGGTGCAGCTGGTGCAGAGCGGCAGCGAGCTGAAGAAACCT GGCGCCTCCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCT TCACCAGCTACGCCATGAACTGGGTCCGCCAGGCCCCAGGCCA GGGACTGGAATGGATGGGCTGGATCAACACCAACACCGGCAA CCCCACCTACGCCCAGGGCTTCACCGGCAGATTCGTGTTCAGCT TCGACACCAGCGTGTCCACCGCCTACCTGCAGATCTGTAGCCTG AAGGCCGAGGACACCGCCGTGTATTACTGTGCGAGGAAGGATC AGACGCTGACCTACGGAAACTGGTTCGACCCCTGGGGCCAGGG AACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGG GGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGA TGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTT AAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTG ATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCA GTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGT

	TPLTFGGGTKVEIK (SEQ ID NO: 181)	TACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGA TCAAG (SEQ ID NO: 394)
29	QVQLQESGPGLVKP SETLSLTCTVSGGSVS SGSYYWSWIRQPPG KGLEWIGYIYYSGST NYNPSLKSRVTISVD TSKNQFSLKLSSVTA ADTAVYYCARDHYE RGLYWGQGTLVTVS SGGGGSGGGGSGG GGSGGDIQMTQSPS SLSASVGDRVTITCR ASQSISSYLNWYQQ KPGKAPKLLIYAASSL QSGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 182)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCC AGCGAGACACTGAGCCTGACCTGCACCGTGTCCGGCGGCTCTG TGTCCAGCGGCTCCTACTACTGGTCCTGGATCAGACAGCCCCCT GGCAAGGGCCTCGAATGGATCGGCTACATCTACTACAGCGGCA GCACCAACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAG CGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGC GTGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGAGATC ATTACGAGCGGGGGCTCTACTGGGGCCAGGGAACCCTGGTCAC CGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGG CGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTCC ATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTT GCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCA GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCA TCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCC TCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 395)
30	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARYMYN WYFDLWGRGTLVTV SSGGGGSGGGGSG GGGSGGDIQMTQS PSSVSASVGDRVTIT CRASQGISSWLAWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQANSFPLT FGGGTKVEIK (SEQ ID NO: 183)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGATATATG TATAACTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGGTCAC TGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGG CGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGAGCCC CAGCAGCGTGTCCGCCAGCGTGGGCGATCGAGTGACCATCACC TGTCGGGCCTCCCAGGGCATCAGCAGCTGGCTGGCCTGGTATC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGC CAGCAGCCTGCAGAGCGGCGTGCCAAGCAGATTCAGCGGCAG CGGCTCCGGCACCGACTTCACCCTGACCATCAGCTCCCTGCAGC CCGAGGACTTCGCCACCTACTACTGCCAGCAGGCTAACAGTTTC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 396)
31	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARDRRP AFDIWGQGTMVTV SSGGGGSGGGGSG	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATCGA AGGCCTGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCG TGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCG

	GGGSGGDIQMTQS PSSVSASVGDRVTIT CRASQGISSWLAWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQANSFPLT FGGGTKVEIK (SEQ ID NO: 184)	GCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGAGCCCCA GCAGCGTGTCCGCCAGCGTGGGCGATCGAGTGACCATCACCTG TCGGGCCTCCCAGGGCATCAGCAGCTGGCTGGCCTGGTATCAG CAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGCCGCCA GCAGCCTGCAGAGCGGCGTGCCAAGCAGATTCAGCGGCAGCG GCTCCGGCACCGACTTCACCCTGACCATCAGCTCCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGGCTAACAGTTTCCC TCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 397)
32	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCAVHLKRR PYFDYWGQGTLVTV SSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 185)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGGTACATTTG AAACGACGTCCCTACTTTGACTACTGGGGCCAGGGAACCCTGG TCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCAT CACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGG TATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACG ACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGG CAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGT TACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 398)
33	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASVHKKP IFDYWGQGTLVTVSS GGGGSGGGGSGGG GSGGAIQLTQSPSSL SASVGDRVTITCRAS QGISSALAWYQQKP GKAPKLLIYDASSLES GVPSRFSGSGSGTDF TLTISSLQPEDFATYY CQQFNSYPLTFGGG TKVEIK (SEQ ID NO: 186)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGCGTACAT AAGAAACCCATCTTTGACTACTGGGGCCAGGGAACCCTGGTCA CCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCC CCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCAC CTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTAT CAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACG CCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAG CGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGC CCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTAC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 399)
34	QVQLVESGGGLVKP GGSLRLSCAASGFTF	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT

	SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASTSRRC TFQHWGQGTLVTVS SGGGGSGGGGSGG GGSGGAIQLTQSPSS LSASVGDRVTITCRA SQGISSALAWYQQK PGKAPKLLIYDASSLE SGVPSRFSGSGSGTD FTLTISSLQPEDFATY YCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 187)	TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGTACCAGT CGGCGCTGTACCTTCCAGCACTGGGGCCAGGGCACCCTGGTCA CCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCC CCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCAC CTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTAT CAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACG CCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAG CGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGC CCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTAC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 400)
35	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASTSPRP LFQHWGQGTLVTVS SGGGGSGGGGSGG GGSGGAIQLTQSPSS LSASVGDRVTITCRA SQGISSALAWYQQK PGKAPKLLIYDASSLE SGVPSRFSGSGSGTD FTLTISSLQPEDFATY YCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 188)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGTACCAGC CCGCGTCCTCTCTTCCAGCACTGGGGCCAGGGCACCCTGGTCAC CGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGG CGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCCC CAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCACC TGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTATC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACGC CAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAGC GGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCC CGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTACC CTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 401)
36	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASPYQVR GVYFDYWGQGTLVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGCCCTTAC CAAGTCCGAGGAGTCTACTTTGACTACTGGGGCCAGGGAACCC TGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCC AGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGA CCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGC CTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC

	ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 189)	TACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCA GCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAG CCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTA ATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 402)
37	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASPYKKR RTVFDYWGQGTLVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 190)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGCCCCTAT AAGAAACGACGAACGGTCTTTGACTACTGGGGCCAGGGAACCC TGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCC AGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGA CCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGC CTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCA GCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAG CCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTA ATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 403)
38	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASLQRGL ALFQHWGQGTLVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 191)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGTCTTTACAG CGCGGGCTGGCCCTCTTCCAGCACTGGGGCCAGGGCACCCTGG TCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCAT CACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGG TATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACG ACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGG CAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGT TACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 404)
39	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT

	EDTAVYYCASILSVPY FDLWGRGTLVTVSS GGGGSGGGGSGGG GSGGAIQLTQSPSSL SASVGDRVTITCRAS QGISSALAWYQQKP GKAPKLLIYDASSLES GVPSRFSGSGSGTDF TLTISSLQPEDFATYY CQQFNSYPLTFGGG TKVEIK (SEQ ID NO: 192)	GCGGGCCGAGGACACCGCCGTGTATTACTGTGCTAGCATATTG TCAGTTCCGTACTTCGATCTCTGGGGCCGTGGCACCCTGGTCAC TGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGG CGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCCC CAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCACC TGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTATC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACGC CAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAGC GGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCC CGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTACC CTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 405)
40	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCASGWIR VPLRLPLFQHWGQG TLVTVSSGGGGSGG GGSGGGGSGGAIQL TQSPSSLSASVGDRV TITCRASQGISSALA WYQQKPGKAPKLLI YDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNSY PLTFGGGTKVEIK (SEQ ID NO: 193)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGTGGGTG GATTCGTGTACCTTTACGATTGCCCCTCTTCCAGCACTGGGGCC AGGGCACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCG GAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATC CAGCTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGC GATAGAGTGACCATCACCTGTCGCGCCAGCCAGGGCATCAGCA GCGCTCTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAA GCTGCTGATCTACGACGCCAGCTCCCTGGAAAGCGGCGTGCCC AGCAGATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGA CCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGC CAGCAGTTTAATAGTTACCCTCTCACTTTCGGCGGCGGAACAAA GGTGGAGATCAAG (SEQ ID NO: 406)
41	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARVTIFAI FDIWGQGTMVTVSS GGGGSGGGGSGGG GSGGAIQLTQSPSSL SASVGDRVTITCRAS QGISSALAWYQQKP GKAPKLLIYDASSLES GVPSRFSGSGSGTDF TLTISSLQPEDFATYY CQQFNSYPLTFGGG	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGTAACC ATATTTGCGATATTTGATATCTGGGGCCAAGGGACAATGGTCAC CGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGG CGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCCC CAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCACC TGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTATC AGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACGC CAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAGC GGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCC CGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTACC

	TKVEIK (SEQ ID NO: 194)	CTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 407)
42	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARVGRG FVHFDLWGRGTLVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 195)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGTGGG ACGTGGATTCGTTCATTTTGATCTCTGGGGCCGTGGCACCCTGG TCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCAT CACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGG TATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACG ACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGG CAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGT TACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 408)
43	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARTSRGL CVLFDYWGQGTLVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 196)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGGACGTCA AGAGGTTTGTGTGTTTTATTTGACTACTGGGGCCAGGGAACCCT GGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCC AGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGA CCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGC CTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCA GCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAG CCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTA ATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 409)
44	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARSGPSS YWYFDLWGRGTLVT VSSGGGGSGGGGSG	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAAGTGG GCCCAGTAGCTACTGGTACTTCGATCTCTGGGGCCGTGGCACCC TGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG

	GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 197)	GATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCC AGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGA CCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGC CTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCA GCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAG CCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTA ATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 410)
45	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARNIYM GGIWFDPWGQGTL VTVSSGGGGSGGGG SGGGGSGGAIQLTQ SPSSLSASVGDRVTIT CRASQGISSALAWY QQKPGKAPKLLIYDA SSLESGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQFNSYPLT FGGGTKVEIK (SEQ ID NO: 198)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAAACATT TACATGGGCGGGATCTGGTTCGACCCCTGGGGCCAGGGAACCC TGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCC AGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGA CCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGC CTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCA GCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAG CCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTA ATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 411)
46	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARLTVRT GAFDIWGQGTMVT VSSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 199)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGACTTACA GTCCGCACTGGAGCTTTTGATATCTGGGGCCAAGGGACAATGG TCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCAT CACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGG TATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACG ACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGG CAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGC AGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGT TACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 412)
47	QVQLVESGGGLVKP GGSLRLSCAASGFTF	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT

	SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARLRTAH LDFDLWGRGTLVTV SSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 200)	TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGACTAAGA ACTGCCCACCTGGACTTCGATCTCTGGGGCCGTGGCACCCTGGT CACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAG CCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATC ACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGT ATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGA CGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGC AGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCA GCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTT ACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 413)
48	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARDLIFP VVFDYWGQGTLVTV SSGGGGSGGGGSG GGGSGGAIQLTQSP SSLSASVGDRVTITCR ASQGISSALAWYQQ KPGKAPKLLIYDASSL ESGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 201)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATCTC ATATTTCCAGTAGTCTTTGACTACTGGGGCCAGGGAACCCTGGT CACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAG CCCCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATC ACCTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGT ATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGA CGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGC AGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCA GCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTT ACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 414)
49	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARDGYR KYGYVFFDIWGQGT MVTVSSGGGGSGG GGSGGGGSGGAIQL TQSPSSLSASVGDRV TITCRASQGISSALA WYQQKPGKAPKLLI	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATGG ATATCGCAAATATGGTTACGTATTTTTTGATATCTGGGGCCAAG GGACAATGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAG GGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAG CTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGATA GAGTGACCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCGC TCTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG

	YDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNSY PLTFGGGTKVEIK (SEQ ID NO: 202)	CTGATCTACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGCA GATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATC AGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTTTAATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGTG GAGATCAAG (SEQ ID NO: 415)
50	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARDGRY RRFWHAFDIWGQG TMVTVSSGGGGSG GGGSGGGGSGGAI QLTQSPSSLSASVGD RVTITCRASQGISSAL AWYQQKPGKAPKLL IYDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNSY PLTFGGGTKVEIK (SEQ ID NO: 203)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGATGG GAGGTACAGGCGGTTCTGGCATGCTTTTGATATCTGGGGCCAA GGGACAATGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGA GGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCA GCTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGAT AGAGTGACCATCACCTGTCGCGCCAGCCAGGGCATCAGCAGCG CTCTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCT GCTGATCTACGACGCCAGCTCCCTGGAAAGCGGCGTGCCCAGC AGATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCA TCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAG CAGTTTAATAGTTACCCTCTCACTTTCGGCGGCGGAACAAAGGT GGAGATCAAG (SEQ ID NO: 416)
51	QVQLVESGGGLVKP GGSLRLSCAASGFTF SDYYMSWIRQAPGK GLEWVSYISSSGSTIY YADSVKGRFTISRDN AKNSLYLQMNSLRA EDTAVYYCARAHIRG YFDLWGRGTLVTVS SGGGGSGGGGSGG GGSGGAIQLTQSPSS LSASVGDRVTITCRA SQGISSALAWYQQK PGKAPKLLIYDASSLE SGVPSRFSGSGSGTD FTLTISSLQPEDFATY YCQQFNSYPLTFGG GTKVEIK (SEQ ID NO: 204)	CAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTGAAACCT GGCGGCAGCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACCT TCAGCGACTACTACATGAGCTGGATCAGACAGGCCCCTGGCAA GGGACTGGAATGGGTGTCCTACATCAGCAGCAGCGGCTCGACC ATCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGCC GGGACAACGCCAAGAACAGCCTGTACCTGCAGATGAACAGCCT GCGGGCCGAGGACACCGCCGTGTATTACTGTGCGAGAGCCCAT ATACGGGGGTACTTCGATCTCTGGGGCCGTGGCACCCTGGTCA CTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTG GCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGAGCC CCAGCAGCCTGAGCGCCAGCGTGGGCGATAGAGTGACCATCAC CTGTCGCGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTGGTAT CAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTACGACG CCAGCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCGGCAG CGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGC CCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATAGTTAC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 417)
52	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC

	RAEDTAVYYCATW MGGGGRWYFDLW GRGTLVTVSSGGGG SGGGGSGGGGSGG AIQLTQSPSSLSASVG DRVTITCRASQGISS ALAWYQQKPGKAP KLLIYDASSLESGVPS RFSGSGSGTDFTLTIS SLQPEDFATYYCQQF NNYPLTFGGGTKVEI K (SEQ ID NO: 205)	TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGACGTGGAT GGGGGGCGGGGGACGATGGTACTTCGATCTCTGGGGCCGTGG CACCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGG GGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCT GACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG AGTGACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCT CTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGC TGATCTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAG ATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCA GCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCA GTTTAATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGG AGATCAAG (SEQ ID NO: 418)
53	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCARTSR TTWYFDLWGRGTLV TVSSGGGGSGGGGS GGGGSGGAIQLTQS PSSLSASVGDRVTITC RASQGISSALAWYQ QKPGKAPKLLIYDAS SLESGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQFNNYPLTF GGGTKVEIK (SEQ ID NO: 206)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAGAACTAG TCGTACAACCTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGG TCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTGACCA TCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTG GTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCG GCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCT GCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATA ATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAA G (SEQ ID NO: 419)
54	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKW MGGGGRLYFDLWG RGTLVTVSSGGGGS GGGGSGGGGSGGAI QLTQSPSSLSASVGD RVTITCRASQGISSAL AWYQQKPGKAPKLL IYDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNN	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAATGGAT GGGGGGCGGGGGACGATTATACTTCGATCTCTGGGGCCGTGG CACCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGG GGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCT GACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAG AGTGACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCT CTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGC TGATCTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAG ATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCA GCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCA

	YPLTFGGGTKVEIK (SEQ ID NO: 207)	GTTTAATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGG AGATCAAG (SEQ ID NO: 420)
55	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKWG GRLYWYFDLWGRG TLVTVSSGGGGSGG GGSGGGGSGGAIQL TQSPSSLSASVGDRV TITCRASQGISSALA WYQQKPGKAPKLLI YDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNN YPLTFGGGTKVEIK (SEQ ID NO: 208)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAATGGGG GGGGCGGTTGTACTGGTACTTCGATCTCTGGGGCCGTGGCACC CTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGA GGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACC CAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTG ACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGG CCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGAT CTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTC AGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCA GCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTT AATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGA TCAAG (SEQ ID NO: 421)
56	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKVIR QLWYFDLWGRGTL VTVSSGGGGSGGGG SGGGGSGGAIQLTQ SPSSLSASVGDRVTIT CRASQGISSALAWY QQKPGKAPKLLIYDA SSLESGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQFNNYPLT FGGGTKVEIK (SEQ ID NO: 209)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAAGTTAT TCGGCAACTCTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGG TCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTGACCA TCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTG GTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCG GCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCT GCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATA ATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAA G (SEQ ID NO: 422)
57	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKVFA NSWYFDLWGRGTL VTVSSGGGGSGGGG	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAAGTTTT CGCCAACTCCTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGG TCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT

	SGGGGSGGAIQLTQ SPSSLSASVGDRVTIT CRASQGISSALAWY QQKPGKAPKLLIYDA SSLESGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQFNNYPLT FGGGTKVEIK (SEQ ID NO: 210)	CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTGACCA TCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTG GTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCG GCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCT GCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATA ATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAA G (SEQ ID NO: 423)
58	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKVD RTTWYFDLWGRGTL VTVSSGGGGSGGGG SGGGGSGGAIQLTQ SPSSLSASVGDRVTIT CRASQGISSALAWY QQKPGKAPKLLIYDA SSLESGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQFNNYPLT FGGGTKVEIK (SEQ ID NO: 211)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAAGTAGA TAGGACTACCTGGTACTTCGATCTCTGGGGCCGTGGCACCCTGG TCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGAT CTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAGA GCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTGACCA TCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGGCCTG GTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTAC GACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGCG GCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCCT GCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAATA ATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAA G (SEQ ID NO: 424)
59	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKRW GKDGPYWYFDLWG RGTLVTVSSGGGGS GGGGSGGGGSGGAI QLTQSPSSLSASVGD RVTITCRASQGISSAL AWYQQKPGKAPKLL IYDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNN YPLTFGGGTKVEIK (SEQ ID NO: 212)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAACGATG GGGTAAGGATGGTCCTTACTGGTACTTCGATCTCTGGGGCCGT GGCACCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGA GGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCA GCTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGA CAGAGTGACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGC GCTCTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGC TGCTGATCTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAG CAGATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACC ATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCA GCAGTTTAATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGG TGGAGATCAAG (SEQ ID NO: 425)
60	EVQLLESGGGLVQP GGSLRLSCAASGFTF	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT

	SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKRR DSYGPYWYFDLWG RGTLVTVSSGGGGS GGGGSGGGGSGGAI QLTQSPSSLSASVGD RVTITCRASQGISSAL AWYQQKPGKAPKLL IYDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNN YPLTFGGGTKVEIK (SEQ ID NO: 213)	TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAAAGAAG AGACAGTTATGGTCCTTACTGGTACTTCGATCTCTGGGGCCGTG GCACCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAG GGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAG CTGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACA GAGTGACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGC TCTGGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTG CTGATCTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCA GATTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATC AGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTTTAATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTG GAGATCAAG (SEQ ID NO: 426)
61	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKNR PPPGYWYFDLWGR GTLVTVSSGGGGSG GGGSGGGGSGGAI QLTQSPSSLSASVGD RVTITCRASQGISSAL AWYQQKPGKAPKLL IYDASSLESGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQFNN YPLTFGGGTKVEIK (SEQ ID NO: 214)	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAGAATCG TCCCCCGCCCGGGTACTGGTACTTCGATCTCTGGGGCCGTGGCA CCCTGGTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGG GAGGATCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGA CCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAG TGACCATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCT GGCCTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTG ATCTACGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGAT TCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAG CAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGT TTAATAATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAG ATCAAG (SEQ ID NO: 427)
62	EVQLLESGGGLVQP GGSLRLSCAASGFTF SSYAMSWVRQAPG KGLEWVSAISGSGGS TYYADSVKGRFTISR DNSKNTLYLQMNSL RAEDTAVYYCAKGR RFSWYFDLWGRGTL VTVSSGGGGSGGGG SGGGGSGGAIQLTQ SPSSLSASVGDRVTIT CRASQGISSALAWY QQKPGKAPKLLIYDA	GAAGTGCAGCTGCTGGAAAGCGGCGGAGGCCTGGTGCAGCCT GGCGGCAGCCTGAGACTGTCTTGCGCCGCCAGCGGCTTCACCT TCAGCAGCTACGCCATGAGCTGGGTCCGCCAGGCCCCTGGCAA GGGACTCGAATGGGTGTCCGCCATCAGCGGCAGCGGCGGCAG CACCTACTACGCCGACAGCGTGAAGGGCCGGTTCACCATCAGC CGGGACAACAGCAAGAACACCCTGTACCTGCAGATGAACAGCC TGCGGGCCGAGGACACCGCCGTATATTACTGTGCGAAGGGAA GACGATTTAGCTGGTACTTCGATCTCTGGGGCCGTGGCACCCTG GTCACTGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA TCTGGCGGCGGAGGAAGCGGAGGCGCCATCCAGCTGACCCAG AGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGAGTGACC ATCACCTGTCGGGCCAGCCAGGGCATCAGCAGCGCTCTGGCCT GGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATCTA

	SSLESGVPSRFSGSG SGTDFTLTISSLQPED FATYYCQQFNNYPLT FGGGTKVEIK (SEQ ID NO: 215)	CGACGCGTCCTCCCTGGAAAGCGGCGTGCCCAGCAGATTCAGC GGCAGCGGCTCCGGCACCGACTTCACCCTGACCATCAGCAGCC TGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGTTTAAT AATTACCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCA AG (SEQ ID NO: 428)

[0173] In some embodiments, the extracellular ligand binding domain of the first receptor is an scFv. In some embodiments, the scFv domain binds to MSLN. In some embodiments, the scFv is the ligand binding domain of a CAR. Exemplary scFv domains specific to MSLN are shown in Table 1, *supra*. In Table 1, underlining indicates CDR sequences.

[0174] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an antigen binding domain having at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 97% identity or at least 99% identity to a sequence of SEQ ID NOS: 3-6, 80 or 154-215, or a sequence as set forth in Table 1. In some embodiments, the extracellular ligand binding domain of the first receptor comprises an antigen binding domain comprising a sequence of SEQ ID NOS: 3-6, 80 or 154-215, as set forth in Table 1.

[0175] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an binding domain having at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 97% identity or at least 99% identity to a sequence of SEQ ID NO: 171. In some embodiments, the extracellular ligand binding domain of the first receptor comprises an binding domain comprising a sequence of SEQ ID NO: 171.

[0176] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an scFv antigen binding domain having at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 97% identity or at least 99% identity to any one of SEQ ID NOs: 3-6. In some embodiments, the extracellular ligand binding domain of the first receptor comprises an scFv antigen binding domain comprising a sequence of any one of SEQ ID NOs: 3-6 or 80. In some embodiments, the extracellular ligand binding domain of the first receptor consists essentially of a sequence selected from the group consisting of SEQ ID NOs: 3-6 or 80.

Table 2: Sequences of MSLN complementary determining regions (CDRs)

#	HC CDR1	HC CDR2	HC CDR3	LC
1	NAWMS (SEQ ID NO: 429)	RIKSKTDGGTTDYAAP VKG (SEQ ID NO: 450)	DLPKLRNFHI (SEQ ID NO: 471)	A
2	SYAMH (SEQ ID NO: 430)	AISSNGGSTYYANSVK G (SEQ ID NO: 451)	LEYHGFRQYGLRYWH (SEQ ID NO: 472)	A

3	SGGYSWS (SEQ ID NO: 431)	YIYHSGSTYYNPSLKS (SEQ ID NO: 452)	IKFWFAGINYFFP (SEQ ID NO: 473)	A
4	SYWMH (SEQ ID NO: 449)	RINSDGSSTSYADSVKG (SEQ ID NO: 453)	GFLGMGSNFI (SEQ ID NO: 474)	A
5	SGGYYWS (SEQ ID NO: 432)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	GDRARYFDL (SEQ ID NO: 475)	A
6	SYWMH (SEQ ID NO: 449)	RINSDGSSTSYADSVKG (SEQ ID NO: 453)	YPRGYHQMVDAFDI (SEQ ID NO: 476)	A
7	SSSYYWG (SEQ ID NO: 433)	SIYYSGSTYYNPSLKS (SEQ ID NO: 455)	VRFLAARTTIPEANFL (SEQ ID NO: 477)	A
8	SYSMN (SEQ ID NO: 434)	YISSSSSTIYYADSVKG (SEQ ID NO: 456)	VLSRARFDY (SEQ ID NO: 478)	A
9	SYSMN (SEQ ID NO: 434)	SISSSSSYIYYADSVKG (SEQ ID NO: 457)	LRGRVFDP (SEQ ID NO: 479)	A
10	SSSYYWG (SEQ ID NO: 433)	SIYYSGSTYYNPSLKS (SEQ ID NO: 455)	IKFTSFLYVHGFL (SEQ ID NO: 480)	A
11	SYAMH (SEQ ID NO: 430)	WINAGNGNTKYSQKFQG (SEQ ID NO: 458)	GQRWLYLGGIRRH (SEQ ID NO: 481)	A
12	SYYWS (SEQ ID NO: 435)	YIYYSGSTNYNPSLKS (SEQ ID NO: 459)	EWIPSRPYYFDY (SEQ ID NO: 482)	A
13	SGGYYWS (SEQ ID NO: 432)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	ESTGTGAFDI (SEQ ID NO: 483)	A
14	DYGMS (SEQ ID NO: 436)	GINWNGGSTGYADSVKG (SEQ ID NO: 460)	ERYRRVLHWYFDL (SEQ ID NO: 484)	A
15	SYDIN (SEQ ID NO: 437)	WMNPNSGNTGYAQKFQG (SEQ ID NO: 461)	EPDAFDI (SEQ ID NO: 485)	A
16	SGGYYWS (SEQ ID NO: 432)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	EHMGTIPYYFDY (SEQ ID NO: 486)	A
17	SGGYYWS (SEQ ID NO: 432)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	EEFGYGDVLY (SEQ ID NO: 487)	A
18	SGDYYWS (SEQ ID NO: 438)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	EDVVKGAFDI (SEQ ID NO: 488)	A

19	SYSMN (SEQ ID NO: 434)	YISSSSSTIYYADSVKG (SEQ ID NO: 456)	EDFSHKLGYFQH (SEQ ID NO: 489)	A
20	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	DYDYV (SEQ ID NO: 490)	A
21	SGDYYWS (SEQ ID NO: 438)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	DRRDWDWFDP (SEQ ID NO: 491)	A
22	SSNWWS (SEQ ID NO: 440)	EIYHSGSTNYNPSLKS (SEQ ID NO: 463)	DQQALKYRVD (SEQ ID NO: 492)	A
23	SYGIS (SEQ ID NO: 441)	WISAYNGNTNYAQKLQG (SEQ ID NO: 464)	DLTLGCFDY (SEQ ID NO: 493)	A
24	SNYMS (SEQ ID NO: 442)	VIYSGGSTYYADSVKG (SEQ ID NO: 465)	DGSNSWYFDL (SEQ ID NO: 494)	A
25	SYGMH (SEQ ID NO: 443)	VIWYDGSNKYYADSVKG (SEQ ID NO: 466)	AFLFLSFSV (SEQ ID NO: 495)	A
26	DYTMH (SEQ ID NO: 444)	LISWDGGSTYYADSVKG (SEQ ID NO: 467)	GIFYSSKEDFDY (SEQ ID NO: 496)	A
27	DYTMH (SEQ ID NO: 444)	LISWDGGSTYYADSVKG (SEQ ID NO: 467)	DIWIFYSSNPKPTVY (SEQ ID NO: 497)	A
28	SYAMN (SEQ ID NO: 445)	WINTNTGNPTYAQGFTG (SEQ ID NO: 468)	KDQTLTYGNWFDP (SEQ ID NO: 498)	A
29	SGSYYWS (SEQ ID NO: 446)	YIYYSGSTNYNPSLKS (SEQ ID NO: 459)	DHYERGLY (SEQ ID NO: 499)	A
30	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	YMYNWYFDL (SEQ ID NO: 500)	B
31	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	DRRPAFDI (SEQ ID NO: 501)	B
32	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	HLKRRPYFDY (SEQ ID NO: 502)	C
33	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	VHKKPIFDY (SEQ ID NO: 503)	C
34	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	TSRRCTFQH (SEQ ID NO: 504)	C

35	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	TSPRPLFQH (SEQ ID NO: 505)	C
36	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	PYQVRGVYFDY (SEQ ID NO: 506)	C
37	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	PYKKRRTVFDY (SEQ ID NO: 507)	C
38	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	LQRGLALFQH (SEQ ID NO: 508)	C
39	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	ILSVPYFDL (SEQ ID NO: 509)	C
40	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	GWIRVPLRLPLFQH (SEQ ID NO: 510)	C
41	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	VTIFAIFDI (SEQ ID NO: 511)	C
42	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	VGRGFVHFDL (SEQ ID NO: 512)	C
43	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	TSRGLCVLFDY (SEQ ID NO: 513)	C
44	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	SGPSSYWYFDL (SEQ ID NO: 514)	C
45	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	NIYMGGIWFDP (SEQ ID NO: 515)	C
46	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	LTVRTGAFDI (SEQ ID NO: 516)	C
47	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	LRTAHLDFDL (SEQ ID NO: 517)	C
48	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	DLIFPVVFDY (SEQ ID NO: 518)	C
49	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	DGYRKYGYVFFDI (SEQ ID NO: 519)	C
50	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	DGRYRRFWHAFDI (SEQ ID NO: 520)	C

51	DYYMS (SEQ ID NO: 439)	YISSSGSTIYYADSVKG (SEQ ID NO: 462)	AHIRGYFDL (SEQ ID NO: 521)	C
52	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	WMGGGGRWYFDL (SEQ ID NO: 522)	C
53	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	TSRTTWYFDL (SEQ ID NO: 523)	C
54	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	WMGGGGRLYFDL (SEQ ID NO: 524)	C
55	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	WGGRLYWYFDL (SEQ ID NO: 525)	C
56	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	VIRQLWYFDL (SEQ ID NO: 526)	C
57	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	VFANSWYFDL (SEQ ID NO: 527)	C
58	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	VDRTTWYFDL (SEQ ID NO: 528)	C
59	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	RWGKDGPYWYFDL (SEQ ID NO: 529)	C
60	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	RRDSYGPYWYFDL (SEQ ID NO: 530)	C
61	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	NRPPPGYWYFDL (SEQ ID NO: 531)	C
62	SYAMS (SEQ ID NO: 447)	AISGSGGSTYYADSVKG (SEQ ID NO: 469)	GRRFSWYFDL (SEQ ID NO: 532)	C
	SGDYYWS (SEQ ID NO: 438)	YIYYSGSTYYNPSLKS (SEQ ID NO: 454)	CAREDVVKGAFDIW (SEQ ID NO: 533)	A
	GYTMN (SEQ ID NO: 448)	LITPYNGASSYNQKFRG (SEQ ID NO: 470)	GGYDGRGFDY (SEQ ID NO: 534)	D
Light chain CDRs				
	LC CDR1	**LC CDR2**	**LC CDR3**	
A	RASQSISSYLN (SEQ ID NO: 535)	AASSLQS (SEQ ID NO: 539)	QQSYSTPLT (SEQ ID NO: 542)	

B	RASQGISS WLA (SEQ ID NO: 536)	AASSLQS (SEQ ID NO: 539)	QQANSFPLT (SEQ ID NO: 543)	
C	RASQGISS ALA (SEQ ID NO: 537)	DASSLES (SEQ ID NO: 540)	QQFNSYPLT (SEQ ID NO: 544)	
D	SASSSVSY MH (SEQ ID NO: 538)	DTSKLAS (SEQ ID NO: 541)	QQWSGYPLT (SEQ ID NO: 545)	

[0177] In Table 2, the light chain (LC) CDRs paired with the indicated heavy chain (HC) CDRs are indicated in the left column.

[0178] In some embodiments, the extracellular ligand binding domain of the first receptor comprises the HC CDR1, the HC CDR2, and the HC CDR3 set forth in Table 2 (e.g., the HC CDR 1, the HC CDR2, and the HC CDR 3 of line #1, line #2, line #3, etc. of Table 2) or sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of Table 2. In some embodiments, the extracellular ligand binding domain of the first receptor comprises the LC CDR1, the LC CDR2, and the LC CDR3 set forth in Table 2 (e.g., the LC CDR 1, the LC CDR2, and the LC CDR 3 of line A, line B, or line C of Table 2) or sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of Table 2. In some embodiments, the extracellular ligand binding domain of the first receptor comprises the HC CDR1, the HC CDR2, and the HC CDR3 set forth in Table 2 (e.g., the HC CDR 1, the HC CDR2, and the HC CDR 3 of line #1, line #2, line #3, etc. of Table 2). In some embodiments, the extracellular ligand binding domain of the first receptor comprises the LC CDR1, the LC CDR2, and the LC CDR3 set forth in Table 2 (e.g., the LC CDR 1, the LC CDR2, and the LC CDR 3 of line A, line B, or line C of Table 2).

[0179] In some embodiments, the extracellular ligand binding domain of the first receptor comprises the HC CDR1, HC CDR2, HC CDR3, LC CDR1, the LC CDR2, and the LC CDR3 set forth in Table 2 (e.g., the HC CDR1, HC CDR2 and HC CDR3 set forth in line 1, and the LC CDR 1, the LC CDR2, and the LC CDR 3 in line A) In some embodiments, the extracellular ligand binding domain of the first receptor comprises the HC CDR1, the HC CDR2, and the HC CDR3 set forth in Table 2 (e.g., the HC CDR 1, the HC CDR2, and the HC CDR 3 of line #1, line #2, line #3, etc. of Table 2) or sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of Table 2. In some embodiments,

the extracellular ligand binding domain of the first receptor comprises the LC CDR1, the LC CDR2, and the LC CDR3 set forth in Table 2 (e.g., the LC CDR 1, the LC CDR2, and the LC CDR 3 of line A, line B, or line C of Table 2) or sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of Table 2. In some embodiments, an extracellular ligand binding domain of the first receptor comprises one or more HC CDRs set forth in Table 2 and one or more LC CDRs set forth in Table 2. In some embodiments, the extracellular ligand binding domain of the first receptor comprises (i) the HC CDR1, the HC CDR2, and the HC CDR3 set forth in one line of Table 2 (e.g., the HC CDR 1, the HC CDR2, and the HC CDR 3 of line #1, line #2, line #3, etc. of Table 2) and (ii) the LC CDR1, the LC CDR2, and the LC CDR3 set forth in one line of Table 2 (e.g., the LC CDR 1, the LC CDR2, and the LC CDR 3 of line A, line B, or line C of Table 2). In each case, the HC CDRs may be paired with any of the LC CDRs, as the heavy chains and light chains share similarity, with routine testing to confirm desired expression and binding activity; however, preferred pairing between heavy and light chains of some embodiments are indicated in the right hand column of Table 2.

[0180] In some embodiments, the extracellular ligand binding domain of the first receptor comprises a HC CDR1 comprising a sequence of SGDYYWS (SEQ ID NO: 438), a HC CDR2 comprising a sequence of YIYYSGSTYYNPSLKS (SEQ ID NO: 454), and HC CDR3 comprising a sequence of CAREDVVKGAFDIW (SEQ ID NO: 533), or CDR sequences having at most 1, 2 or 3 amino acid substitutions, insertions or deletions relative thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a HC CDR1 comprising a sequence of SGDYYWS (SEQ ID NO: 438), a HC CDR2 comprising a sequence of YIYYSGSTYYNPSLKS (SEQ ID NO: 454), and HC CDR3 comprising a sequence of CAREDVVKGAFDIW (SEQ ID NO: 533). In some embodiments, the extracellular ligand binding domain of the first receptor comprises a LC CDR1 comprising a sequence of RASQSISSYLN (SEQ ID NO: 535), a LC CDR2 comprising a sequence of AASSLQS (SEQ ID NO: 539), and a LC CDR3 comprising a sequence of QQSYSTPLT (SEQ ID NO: 542), or CDR sequences having at most 1, 2 or 3 amino acid substitutions, insertions or deletions relative thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a LC CDR1 comprising a sequence of RASQSISSYLN (SEQ ID NO: 535), a LC CDR2 comprising a sequence of AASSLQS (SEQ ID NO: 539), and a LC CDR3 comprising a sequence of QQSYSTPLT (SEQ ID NO: 542). In some embodiments, the extracellular ligand binding domain of the first receptor comprises a HC CDR1 comprising a sequence of SGDYYWS (SEQ ID NO: 438), a HC CDR2

comprising a sequence of YIYYSGSTYYNPSLKS (SEQ ID NO: 454), HC CDR3 comprising a sequence of CAREDVVKGAFDIW (SEQ ID NO: 533), a LC CDR1 comprising a sequence of RASQSISSYLN (SEQ ID NO: 535), a LC CDR2 comprising a sequence of AASSLQS (SEQ ID NO: 539), and a LC CDR3 comprising a sequence of QQSYSTPLT (SEQ ID NO: 542), or CDR sequences having at most 1, 2 or 3 amino acid substitutions, insertions or deletions relative thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a HC CDR1 comprising a sequence of SGDYYWS (SEQ ID NO: 438), a HC CDR2 comprising a sequence of YIYYSGSTYYNPSLKS (SEQ ID NO: 454), HC CDR3 comprising a sequence of CAREDVVKGAFDIW (SEQ ID NO: 533), a LC CDR1 comprising a sequence of RASQSISSYLN (SEQ ID NO: 535), a LC CDR2 comprising a sequence of AASSLQS (SEQ ID NO: 539), and a LC CDR3 comprising a sequence of QQSYSTPLT (SEQ ID NO: 542).

[0181] In some embodiments, the extracellular ligand binding domain of the first receptor comprises an scFv. In some embodiments, the scFv comprises a heavy chain comprising CDRs selected from the sequences of GYTMN (SEQ ID NO: 448), LITPYNGASSYNQKFRG (SEQ ID NO: 470) and GGYDGRGFDY (SEQ ID NO: 534). In some embodiments, the heavy chain comprises sequences of GYTMN (SEQ ID NO: 448), LITPYNGASSYNQKFRG(SEQ ID NO: 470) and GGYDGRGFDY (SEQ ID NO: 534). In some embodiments, the scFv comprising a light chain comprising CDRs selected from the sequences of SASSSVSYMH (SEQ ID NO: 538), DTSKLAS (SEQ ID NO: 541) and QQWSGYPLT (SEQ ID NO: 545). In some embodiments, the light chain comprises sequences of SASSSVSYMH (SEQ ID NO: 538), DTSKLAS (SEQ ID NO: 541) and QQWSGYPLT (SEQ ID NO: 545).

[0182] Sequences of exemplary heavy and light chains of antigen binding domains that are specific to MSLN are set forth in Tables 3 and 4 below. Light chains paired with heavy chains in preferred embodiments are indicated at right in Table 3.

Table 2: Sequences of heavy chain variable fragments (VH)

#	SEQ ID NO	Heavy Chain (VH)	LC
1	216	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQA PGKGLEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTL YLQMNSLKTEDTAVYYCTTDLPKLRNFHIWGQGTLVTVSS	A
2	217	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAP GKGLEYVSAISSNGGSTYYANSVKGRFTISRDNSKNTLYLQM	A

#	SEQ ID NO	Heavy Chain (VH)	LC
		GSLRAEDMAVYYCASLEYHGFRQYGLRYWHWGQGTLVTVSS	
3	218	QLQLQESGSGLVKPSQTLSLTCAVSGGSISSGGYSWSWIRQPPGKGLEWIGYIYHSGSTYYNPSLKSRVTISVDRSKNQFSLKLSSVTAADTAVYYCASIKFWFAGINYFFPWGQGTLVTVSS	A
4	219	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGFLGMGSNFIWGQGTLVTVSS	A
5	220	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIYYSGSTYYNPSLKSLVTISVDTSKNQFSLKLSSVTAADTAVYYCASGDRARYFDLWGRGTLVTVSS	A
6	221	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLVWVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARYPRGYHQMVDAFDIWGQGTMVTVSS	A
7	222	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVRFLAARTTIPEANFLWGQGTLVTVSS	A
8	223	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARVLSRARFDYWGQGTLVTVSS	A
9	224	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARLRGRVFDPWGQGTLVTVSS	A
10	225	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARIKFTSFLYVHGFLWGQGTLVTVSS	A
11	226	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRLEWMGWINAGNGNTKYSQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARGQRWLYLGGIRRHWGQGTLVTVSS	A
12	227	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAREWIPSRPYYFDYWGQGTLVTVSS	A
13	228	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARESTGTGAFDIWGQGTMVTVSS	A
14	229	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYHCARERYRRVLHWYFDLWGRGTLVTVSS	A
15	230	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCAREPDAFDIWGQGTMVTVSS	A

#	SEQ ID NO	Heavy Chain (VH)	LC
16	231	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQP PGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCAREHMGTIPYYFDYWGQGTLVTVSS	A
17	232	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQP PGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCAREEFGYGDVLYWGQGTLVTVSS	A
18	233	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQP PGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCAREDVVKGAFDIWGQGTMVTVSS	A
19	234	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAP GKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDFSHKLGYFQHWGQGTLVTVSS	A
20	235	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARDYDYVWGQGTLVTVSS	A
21	236	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQP PGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDRRDWDWFDPWGQGTLVTVSS	A
22	237	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQP PGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLS SVTAADTAVYYCARDQQALKYRVDWGQGTLVTVSS	A
23	238	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAP GQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAY MELRSLRSDDTAVYYCARDLTLGCFDYWGQGTLVTVSS	A
24	239	EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAP GKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQM NSLRAEDTAVYYCARDGSNSWYFDLWGRGTLVTVSS	A
25	240	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQA PGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARAFLFLSFSVWGQGTLVTVSS	A
26	241	EVQLVESGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQA PGKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNSLYL QMNSLRTEDTALYYCAKGIFYSSKEDFDYWGQGTLVTVSS	A
27	242	EVQLVESGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQA PGKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNSLYL QMNSLRTEDTALYYCAKDIWIFYSSNPKPTVYWGQGTLVTV SS	A
28	243	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYAMNWVRQA PGQGLEWMGWINTNTGNPTYAQGFTGRFVFSFDTSVSTAYL QICSLKAEDTAVYYCARKDQTLTYGNWFDPWGQGTLVTVS S	A
29	244	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGSYYWSWIRQP PGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCARDHYERGLYWGQGTLVTVSS	A

#	SEQ ID NO	Heavy Chain (VH)	LC
30	245	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARYMYNWYFDLWGRGTLVTVSS	B
31	246	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARDRRPAFDIWGQGTMVTVSS	B
32	247	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAVHLKRRPYFDYWGQGTLVTVSS	C
33	248	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASVHKKPIFDYWGQGTLVTVSS	C
34	249	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASTSRRCTFQHWGQGTLVTVSS	C
35	250	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASTSPRPLFQHWGQGTLVTVSS	C
36	251	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASPYQVRGVYFDYWGQGTLVTVSS	C
37	252	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASPYKKRRTVFDYWGQGTLVTVSS	C
38	253	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASLQRGLALFQHWGQGTLVTVSS	C
39	254	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASILSVPYFDLWGRGTLVTVSS	C
40	255	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCASGWIRVPLRLPLFQHWGQGTLVTVSS	C
41	256	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARVTIFAIFDIWGQGTMVTVSS	C
42	257	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARVGRGFVHFDLWGRGTLVTVSS	C
43	259	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARTSRGLCVLFDYWGQGTLVTVSS	C
44	260	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARSGPSSYWYFDLWGRGTLVTVSS	C

#	SEQ ID NO	Heavy Chain (VH)	LC
45	261	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARNIYMGGIWFDPWGQGTLVTVSS	C
46	262	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARLTVRTGAFDIWGQGTMVTVSS	C
47	263	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARLRTAHLDFDLWGRGTLVTVSS	C
48	264	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARDLIFPVVFDYWGQGTLVTVSS	C
49	265	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARDGYRKYGYVFFDIWGQGTMVTVSS	C
50	266	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARDGRYRRFWHAFDIWGQGTMVTVSS	C
51	267	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARAHIRGYFDLWGRGTLVTVSS	C
52	268	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCATWMGGGGRWYFDLWGRGTLVTVSS	C
53	269	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARTSRTTWYFDLWGRGTLVTVSS	C
54	270	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKWMGGGGRLYFDLWGRGTLVTVSS	C
55	271	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKWGGRLYWYFDLWGRGTLVTVSS	C
56	272	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKVIRQLWYFDLWGRGTLVTVSS	C
57	273	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKVFANSWYFDLWGRGTLVTVSS	C
58	274	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKVDRTTWYFDLWGRGTLVTVSS	C
59	275	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKRWGKDGPYWYFDLWGRGTLVTVS S	C

#	SEQ ID NO	Heavy Chain (VH)	LC
60	276	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKRRDSYGPYWYFDLWGRGTLVTVSS	C
61	277	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKNRPPPGYWYFDLWGRGTLVTVSS	C
62	278	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAP GKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKGRRFSWYFDLWGRGTLVTVSS	C

Table 3: Sequences of light chain variable fragments (VL)

#	SEQ ID NO	Light Chain (VL)
A	279	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLT FGGGTKVEIK
B	280	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPLT FGGGTKVEIK
C	281	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLI YDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLT FGGGTKVEIK
D	282	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLI YDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNNYPLT FGGGTKVEIK

[0183] In some embodiments, the extracellular ligand binding domain of the first receptor comprises a variable heavy region (VH) sequence set forth in Table 3. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VH sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VH set forth in Table 3. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a variable light region (VL) sequence set forth in Table 4. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VL sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VL set forth set forth in Table 4.

[0184] In some embodiments, a the extracellular ligand binding domain of the first receptor comprises a VH that (i) comprises the HC CDR1, the HC CDR2, and the HC CDR3 sequences set forth in Table 2 (e.g., the HC CDR 1, the HC CDR2, and the HC CDR 3 of line #1, line #2, line #3, etc. of Table 2) and (ii) has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VH sequence set forth in Table 3. In some embodiments, extracellular ligand binding domain of the first receptor (i) comprises the LC CDR1, the LC CDR2, and the LC CDR3 sequences set forth in one line Table 2 (e.g., the LC CDR 1, the LC CDR2, and the LC CDR 3 of line A, line B, or line C of Table 2) and a VL sequence set forth in Table 4 and (ii) has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VL set forth set forth in Table 4.

[0185] In some embodiments, the extracellular ligand binding domain of the first receptor comprises (i) a VH sequence set forth in Table 3 or a VH sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VH set forth in Table 3, and (ii) a VL sequence set forth in Table 4 or a VL that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a VL set forth set forth in Table 4. In each case, the VH may be paired with any of the VLs, as the heavy chains and light chains share similarity, with routine testing to confirm desired expression and binding activity; however, the preferred pairing between Table 3 and Table 4 is indicated in the “LC” column of Table 3, corresponding to the # column of Table 4.

[0186] In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VH sequence of SEQ ID NO: 233, or a sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VH sequence of SEQ ID NO: 233.

[0187] In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VL sequence of SEQ ID NO: 279, or a sequence that has at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity thereto. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VL sequence of SEQ

ID NO: 279. In some embodiments, the extracellular ligand binding domain of the first receptor comprises a VH sequence of SEQ ID NO: 233, and a VL sequence of SEQ ID NO: 279, or sequences that have at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity thereto. In some embodiments the VH and VL are separated for a linker, for example a linker comprising a sequence of GGGGSGGGGSGGGGSGG (SEQ ID NO: 152). The VH and VL can be in any orientation, for example VH, linker, VL; or alternatively, VL, linker VH.

[0188] In some embodiments, one or more (e.g., 1, 2, 3, 4, 5, or 6) amino acid residues in a CDR of the antigen binding domains provided herein are substituted with another amino acid. The substitution may be "conservative" in the sense of being a substitution within the same family of amino acids. The naturally occurring amino acids may be divided into the following four families and conservative substitutions will take place within those families: (1) amino acids with basic side chains: lysine, arginine, histidine; (2) amino acids with acidic side chains: aspartic acid, glutamic acid; (3) amino acids with uncharged polar side chains: asparagine, glutamine, serine, threonine, tyrosine; and (4) amino acids with nonpolar side chains: glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, cysteine. By varying the amino acid sequence of the CDRs of an antibody by addition, deletion or substitution of amino acids, various effects such as increased binding affinity for the target antigen may be obtained.

Chimeric Antigen Receptors (CARs)

[0189] The disclosure provides a first, activator receptor and immune cells comprising same. In some embodiments, the first receptor is a chimeric antigen receptor.

[0190] The term "chimeric antigen receptors (CARs)" as used herein, may refer to artificial receptors derived from T-cell receptors and encompasses engineered receptors that graft an artificial specificity onto a particular immune effector cell. CARs may be employed to impart the specificity of a monoclonal antibody onto a T cell, thereby allowing a large number of specific T cells to be generated, for example, for use in adoptive cell therapy. In specific embodiments, CARs direct specificity of the cell to a tumor associated antigen, for example. Exemplary CARs comprise an intracellular activation domain, a transmembrane domain, and an extracellular domain comprising a tumor associated antigen binding region. In some embodiments, CARs further comprise a hinge domain. In particular aspects, CARs comprise fusions of single-chain variable fragments (scFv) derived from monoclonal antibodies, fused to a CD3 transmembrane domain and endodomain. The specificity of other CAR designs may be derived from ligands of receptors (e.g., peptides). In certain cases, CARs comprise

domains for additional co-stimulatory signaling, such as CD3, 4-1BB, FcR, CD27, CD28, CD137, DAP10, and/or OX40. In some cases, molecules can be co-expressed with the CAR, including co-stimulatory molecules, reporter genes for imaging, gene products that conditionally ablate the T cells upon addition of a pro-drug, homing receptors, cytokines, and cytokine receptors.

[0191] In some embodiments, the extracellular ligand binding domain of the first receptor is fused to the extracellular domain of a CAR.

[0192] In some embodiments, the CARs of the present disclosure comprise an extracellular hinge region. Incorporation of a hinge region can affect cytokine production from CAR-T cells and improve expansion of CAR-T cells *in vivo*. Exemplary hinges can be isolated or derived from IgD and CD8 domains, for example IgG1. In some embodiments, the hinge is isolated or derived from CD8α or CD28.

[0193] In some embodiments, the hinge is isolated or derived from CD8α or CD28. In some embodiments, the CD8α hinge comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 7). In some embodiments, the CD8α hinge comprises SEQ ID NO: 7. In some embodiments, the CD8α hinge consists essentially of SEQ ID NO: 7. In some embodiments, the CD8α hinge is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of

ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGCAGCCCCTGTCCCTGCGCCCAGAG
GCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTTCGCCTGTGAT (SEQ ID NO:
8). In some embodiments, the CD8α hinge is encoded by SEQ ID NO: 8.

[0194] In some embodiments, the CD28 hinge comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of CTIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP (SEQ ID NO: 9). In some embodiments, the CD28 hinge comprises or consists essentially of SEQ ID NO: 9. In some embodiments, the CD28 hinge is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of

TGTACCATTGAAGTTATGTATCCTCCTCCTTACCTAGACAATGAGAAGAGCAATGGAACCAT
TATCCATGTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCC

(SEQ ID NO: 10). In some embodiments, the CD28 hinge is encoded by SEQ ID NO: 10.

[0195] The CARs of the present disclosure can be designed to comprise a transmembrane domain that is fused to the extracellular domain of the CAR. In some embodiments, the transmembrane domain that naturally is associated with one of the domains in the CAR is used. For example, a CAR comprising a CD28 co-stimulatory domain might also use a CD28 transmembrane domain. In some instances, 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.

[0196] The transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Transmembrane regions may be isolated or derived from (i.e. comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or from an immunoglobulin such as IgG4. Alternatively the transmembrane domain may be synthetic, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In some embodiments, a triplet of phenylalanine, tryptophan and valine will be found at each end of a synthetic transmembrane domain. Optionally, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the cytoplasmic signaling domain of the CAR. A glycine-serine doublet provides a particularly suitable linker.

[0197] In some embodiments of the CARs of the disclosure, the CARs comprise a CD28 transmembrane domain. In some embodiments, the CD28 transmembrane domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of FWVLVVVGGVLACYSLLVTVAFIIFWV (SEQ ID NO: 11). In some embodiments, the CD28 transmembrane domain comprises or consists essentially of SEQ ID NO: 11. In some embodiments, the CD28 transmembrane domain is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of TTCTGGGTGCTGGTCGTTGTGGGCGGCGTGCTGGCCTGCTACAGCCTGCTGGTGACAGTGGCCTTCATCATCTTTTGGGTG (SEQ ID NO: 12). In some embodiments, the CD28 transmembrane domain is encoded by SEQ ID NO: 12.

[0198] In some embodiments of the CARs of the disclosure, the CARs comprise an IL-2Rbeta transmembrane domain. In some embodiments, the IL-2Rbeta transmembrane domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of IPWLGHLLVGLSGAFGFIILVYLLI (SEQ ID NO: 13). In some embodiments, the IL-2Rbeta transmembrane domain comprises or consists essentially of SEQ ID NO: 13. In some embodiments, the IL-2Rbeta transmembrane domain is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of ATTCCGTGGC TCGGCCACCT CCTCGTGGGC CTCAGCGGGG CTTTTGGCTT CATCATCTTA GTGTACTTGC TGATC (SEQ ID NO: 14). In some embodiments, the IL-2Rbeta transmembrane domain is encoded by SEQ ID NO: 14.

[0199] The cytoplasmic domain or otherwise the intracellular signaling domain of the CARs of the instant disclosure is responsible for activation of at least one of the normal effector functions of the immune cell in which the CAR has been placed. The term "effector function" refers to a specialized function of a cell. Thus the term "intracellular signaling domain" refers to the portion of a protein which transduces the effector function signal and directs the cell to perform a specialized function. While usually the entire intracellular signaling domain can be employed, in many cases it is not necessary to use the entire domain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion may be used in place of the intact chain as long as it transduces the effector function signal. In some cases, multiple intracellular domains can be combined to achieve the desired functions of the CAR-T cells of the instant disclosure. The term intracellular signaling domain is thus meant to include any truncated portion of one or more intracellular signaling domains sufficient to transduce the effector function signal.

[0200] Examples of intracellular signaling domains for use in the CARs of the instant disclosure include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability.

[0201] Accordingly, the intracellular domain of CARs of the instant disclosure comprises at least one cytoplasmic activation domain. In some embodiments, the intracellular activation domain ensures that there is T-cell receptor (TCR) signaling necessary to activate the effector functions of the CAR T-cell. In some embodiments, the at least one cytoplasmic activation is

a CD247 molecule (CD3ζ) activation domain, a stimulatory killer immunoglobulin-like receptor (KIR) KIR2DS2 activation domain, or a DNAX-activating protein of 12 kDa (DAP12) activation domain.

[0202] In some embodiments, the CD3ζ activation domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 15).

[0203] In some embodiments, the CD3ζ activation domain comprises or consists essentially of SEQ ID NO: 15. In some embodiments, the CD3ζ activation domain is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGCGTAGAGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGACTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGC (SEQ ID NO: 16). In some embodiments, the CD3ζ activation domain is encoded by SEQ ID NO: 16).

[0204] It is known that signals generated through the TCR alone are often insufficient for full activation of the T cell and that a secondary or co-stimulatory signal is also required. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequence: those that initiate antigen-dependent primary activation through the TCR (primary cytoplasmic signaling sequences) and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary cytoplasmic signaling sequences).

[0205] Primary cytoplasmic signaling sequences regulate primary activation of the TCR complex either in a stimulatory way, or in an inhibitory way. Primary cytoplasmic signaling sequences that act in a stimulatory manner may contain signaling motifs, which are known as immunoreceptor tyrosine-based activation motifs or ITAMs. In some embodiments, the ITAM contains a tyrosine separated from a leucine or an isoleucine by any two other amino acids (YxxL/I (SEQ ID NO: 546)). In some embodiments, the cytoplasmic domain contains 1, 2, 3, 4 or 5 ITAMs. An exemplary ITAM containing cytoplasmic domain is the CD3ζ activation domain. Further examples of ITAM containing primary cytoplasmic signaling

sequences that can be used in the CARs of the instant disclosure include those derived from TCRζ, FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD5, CD22, CD79a, CD79b, and CD66d.

[0206] In some embodiments, the CD3ζ activation domain comprising a single ITAM comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLHMQALPPR (SEQ ID NO: 17). In some embodiments, the CD3ζ activation domain comprises SEQ ID NO: 17. In some embodiments, the CD3ζ activation domain comprising a single ITAM consists essentially of an amino acid sequence of RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLHMQALPPR (SEQ ID NO: 17). In some embodiments, the CD3ζ activation domain comprising a single ITAM is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of

AGAGTGAAGT TCAGCAGGAG CGCAGACGCC CCCGCGTACC AGCAGGGCCA GAACCAGCTC TATAACGAGC TCAATCTAGG ACGAAGAGAG GAGTACGATG TTTTGCACAT GCAGGCCCTG CCCCCTCGC (SEQ ID NO: 18). In some embodiments, the CD3ζ activation domain is encoded by SEQ ID NO: 18.

[0207] In some embodiments, the cytoplasmic domain of the CAR can be designed to comprise the CD3ζ signaling domain by itself or combined with any other desired cytoplasmic domain(s) useful in the context of the CAR of the instant disclosure. For example, the cytoplasmic domain of the CAR can comprise a CD3ζ chain portion and a co-stimulatory domain. The co-stimulatory domain refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or its ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include the co-stimulatory domain is selected from the group consisting of IL-2Rβ, Fc Receptor gamma (FcRγ), Fc Receptor beta (FcRβ), CD3g molecule gamma (CD3γ), CD3δ, CD3ε, CD5 molecule (CD5), CD22 molecule (CD22), CD79a molecule (CD79a), CD79b molecule (CD79b), carcinoembryonic antigen related cell adhesion molecule 3 (CD66d), CD27 molecule (CD27), CD28 molecule (CD28), TNF receptor superfamily member 9 (4-1BB), TNF receptor superfamily member 4 (OX40), TNF receptor superfamily member 8 (CD30), CD40 molecule (CD40), programmed cell death 1 (PD-1), inducible T cell costimulatory (ICOS), lymphocyte function-associated antigen-1 (LFA-1), CD2 molecule (CD2), CD7 molecule (CD7), TNF superfamily member 14 (LIGHT), killer cell lectin like receptor C2 (NKG2C) and CD276 molecule (B7-H3) c-stimulatory domains, or functional variants

thereof. In some embodiments, the intracellular domains of CARs of the instant disclosure comprise at least one co-stimulatory domain. In some embodiments, the co-stimulatory domain is isolated or derived from CD28.

[0208] In some embodiments, the intracellular domains of CARs of the instant disclosure comprise at least one co-stimulatory domain. In some embodiments, the co-stimulatory domain is isolated or derived from CD28. In some embodiments, the CD28 co-stimulatory domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS (SEQ ID NO: 19). In some embodiments, the CD28 co-stimulatory domain comprises or consists essentially of SEQ ID NO: 19. In some embodiments, the CD28 co-stimulatory domain is encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of AGGAGCAAGCGGAGCAGACTGCTGCACAGCGACTACATGAACATGACCCCCCGG AGGCCTGGCCCCACCCGGAAGCACTACCAGCCCTACGCCCCTCCCAGGGATTTCG CCGCCTACCGGAGC (SEQ ID NO: 20). In some embodiments, the CD28 co-stimulatory domain is encoded by SEQ ID NO: 20.

[0209] In some embodiments, the co-stimulatory domain is isolated or derived from 4-1BB. In some embodiments, the 4-1BB co-stimulatory domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO: 283). In some embodiments, the 4-1BB co-stimulatory domain comprises or consists essentially of KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID NO: 283). In some embodiments, the 4-1BB co-stimulatory domain s encoded by a nucleotide sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity or is identical to a sequence of AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGGCCA GTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAA GAAGGAGGATGTGAACTG (SEQ ID NO: 284).

[0210] In some embodiments, the intracellular domain of the CAR comprises a CD28 co-stimulatory domain, a 4-1BB costimulatory domain, and a CD3ζ activation domain. In some embodiments, the intracellular domain of the CAR comprises a sequence of

RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPF MRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK GHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 285), or a sequence having at least 80% identity, at least 90% identity, at least 95% identity, at least 99% identity thereto.

[0211] The cytoplasmic domains within the cytoplasmic signaling portion of the CARs of the instant disclosure may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example between 2 and 10 amino acids in length may form the linkage. A glycine-serine doublet provides an example of a suitable linker. An exemplary linker comprises a sequence of GGGGSGGGGSGGGGSGG (SEQ ID NO: 152).

[0212] The cytoplasmic domains within the cytoplasmic signaling portion of the CARs of the instant disclosure may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example between 2 and 10 amino acids in length may form the linkage. A glycine-serine doublet provides an example of a suitable linker.

Exemplary full length activator receptors of the disclosure are described in Table 20. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NOS: 286-347, as set forth in Table 20, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NOS: 286-347, as set forth in Table 20. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 288, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 297, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 301, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 302, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 303, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 314, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 335, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 340, or a sequence having at

least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the first activator receptor comprises a sequence of SEQ ID NO: 344, or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0213] The cytoplasmic domains within the cytoplasmic signaling portion of the CARs of the instant disclosure may be linked to each other in a random or specified order. Optionally, a short oligo- or polypeptide linker, for example between 2 and 10 amino acids in length may form the linkage. A glycine-serine doublet provides an example of a suitable linker.

T Cell Receptors (TCRs)

[0214] The disclosure provides a first, activator receptor and immune cells comprising same. In some embodiments, the first receptor is a T cell receptor (TCR).

[0215] As used herein, a "TCR", sometimes also called a "TCR complex" or "TCR/CD3 complex" refers to a protein complex comprising a TCR alpha chain, a TCR beta chain, and one or more of the invariant CD3 chains (zeta, gamma, delta and epsilon), sometimes referred to as subunits. The TCR alpha and beta chains can be disulfide-linked to function as a heterodimer to bind to peptide-MHC complexes. Once the TCR alpha/beta heterodimer engages peptide-MHC, conformational changes in the TCR complex in the associated invariant CD3 subunits are induced, which leads to their phosphorylation and association with downstream proteins, thereby transducing a primary stimulatory signal. In an exemplary TCR complex, the TCR alpha and TCR beta polypeptides form a heterodimer, CD3 epsilon and CD3 delta form a heterodimer, CD3 epsilon and CD3 gamma for a heterodimer, and two CD3 zeta form a homodimer.

[0216] Any suitable ligand binding domain may be fused to an extracellular domain, hinge domain or transmembrane of the TCRs described herein. For example, the ligand binding domain can be an antigen binding domain of an antibody or TCR, or comprise an antibody fragment, a Vβ only domain, a linear antibody, a single-chain variable fragment (scFv), or a single domain antibody (sdAb).

[0217] In some embodiments, the ligand binding domain is fused to one or more extracellular domains or transmembrane domains of one or more TCR subunits. The TCR subunit can be TCR alpha, TCR beta, CD3 delta, CD3 epsilon, CD3 gamma or CD3 zeta. For example, the ligand binding domain can be fused to TCR alpha, or TCR beta, or portions of the ligand binding can be fused to two subunits, for example portions of the ligand binding domain can be fused to both TCR alpha and TCR beta.

[0218] TCR subunits include TCR alpha, TCR beta, CD3 zeta, CD3 delta, CD3 gamma and CD3 epsilon. Any one or more of TCR alpha, TCR beta chain, CD3 gamma, CD3 delta, CD3

epsilon, or CD3 zeta, or fragments or derivative thereof, can be fused to one or more domains capable of providing a stimulatory signal of the disclosure, thereby enhancing TCR function and activity.

[0219] TCR transmembrane domains isolated or derived from any source are envisaged as within the scope of the disclosure. The transmembrane domain may be derived either from a natural or from a recombinant source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein.

[0220] In some embodiments, the transmembrane domain is capable of signaling to the intracellular domain(s) whenever the TCR complex has bound to a target. A transmembrane domain of particular use in this disclosure may include at least the transmembrane region(s) of *e.g.*, the alpha, beta or zeta chain of the TCR, CD3 delta, CD3 epsilon or CD3 gamma, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154.

[0221] In some embodiments, the transmembrane domain can be attached to the extracellular region of a polypeptide of the TCR, *e.g.*, the antigen binding domain of the TCR alpha or beta chain, via a hinge, *e.g.*, a hinge from a human protein. For example, the hinge can be a human immunoglobulin (Ig) hinge, *e.g.*, an IgG4 hinge, or a CD8a hinge. In some embodiments, the hinge is isolated or derived from CD8α or CD28.

[0222] In some embodiments, the extracellular ligand binding domain is attached to one or more transmembrane domains of the TCR. In some embodiments, the transmembrane domain comprises a TCR alpha transmembrane domain, a TCR beta transmembrane domain, or both. In some embodiments, the transmembrane comprises a CD3 zeta transmembrane domain.

[0223] A transmembrane domain can include one or more additional amino acids adjacent to the transmembrane region, e.g., one or more amino acid associated with the extracellular region of the protein from which the transmembrane was derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or up to 15 amino acids of the extracellular region) and/or one or more additional amino acids associated with the intracellular region of the protein from which the transmembrane protein is derived (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or up to 15 amino acids of the intracellular region).

[0224] In some embodiments, 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, e.g., to minimize interactions with other members of the receptor complex.

[0225] When present, the transmembrane domain may be a natural TCR transmembrane domain, a natural transmembrane domain from a heterologous membrane protein, or an artificial transmembrane domain. The transmembrane domain may be a membrane anchor domain. Without limitation, a natural or artificial transmembrane domain may comprise a hydrophobic a-helix of about 20 amino acids, often with positive charges flanking the transmembrane segment. The transmembrane domain may have one transmembrane segment or more than one transmembrane segment. Prediction of transmembrane domains/segments may be made using publicly available prediction tools (e.g. TMHMM, Krogh et al. Journal of Molecular Biology 2001; 305(3):567-580; or TMpred, Hofmann & Stoffel Biol. Chem. Hoppe-Seyler 1993; 347: 166). Non-limiting examples of membrane anchor systems include platelet derived growth factor receptor (PDGFR) transmembrane domain, glycosylphosphatidylinositol (GPI) anchor (added post- translationally to a signal sequence) and the like.

[0226] In some embodiments, the transmembrane domain comprises a TCR alpha transmembrane domain. In some embodiments, the TCR alpha transmembrane domain comprises an amino acid sequence having at least 85% identity, at least 90% identity, at least 95% identity, at least 96% identity, at least 97% identity, at least 98% identity, at least 99% identity or is identical to a sequence of: VIGFRILLLKVAGFNLLMTLRLW (SEQ ID NO: 21). In some embodiments, the TCR alpha transmembrane domain comprises, or consists essentially of, SEQ ID NO: 21. In some embodiments, the TCR alpha transmembrane domain is encoded by a sequence of GTGATTGGGTTCCGAATCCTCCTCCTGAAAGTGGCCGGGTTTAATCTGCTCATGACGCTGCGGCTGTGG (SEQ ID NO: 22).

[0227] In some embodiments, the transmembrane domain comprises a TCR beta transmembrane domain. In some embodiments, the TCR beta transmembrane domain comprises an amino acid sequence having at least 85% identity, at least 90% identity, at least 95% identity, at least 96% identity, at least 97% identity, at least 98% identity, at least 99% identity or is identical to a sequence of: TILYEILLGKATLYAVLVSALVL (SEQ ID NO: 23). In some embodiments, the TCR beta transmembrane domain comprises, or consists essentially of, SEQ ID NO: 23. In some embodiments, the TCR beta transmembrane domain is encoded by a sequence of ACCATCCTCTATGAGATCTTGCTAGGGAAGGCCACCTTGTATGCCGTGCTGGTCAGTGCCCTCGTGCTG (SEQ ID NO: 24).

[0228] TCRs of the disclosure can comprise one or more intracellular domains. Exemplary TCRs comprising intracellular domains for use in the instant disclosure are described in PCT/US2020/045250 filed on September 6, 2020, the contents of which are incorporated herein by reference. In some embodiments, the intracellular domain comprises one or more domains capable of providing a stimulatory signal to a transmembrane domain. In some embodiments, the intracellular domain comprises a first intracellular domain capable of providing a stimulatory signal and a second intracellular domain capable of providing a stimulatory signal. In other embodiments, the intracellular domain comprises a first, second and third intracellular domain capable of providing a stimulatory signal. The intracellular domains capable of providing a stimulatory signal are selected from the group consisting of a CD28 molecule (CD28) domain, a LCK proto-oncogene, Src family tyrosine kinase (Lck) domain, a TNF receptor superfamily member 9 (4-1BB) domain, a TNF receptor superfamily member 18 (GITR) domain, a CD4 molecule (CD4) domain, a CD8a molecule (CD8a) domain, a FYN proto-oncogene, Src family tyrosine kinase (Fyn) domain, a zeta chain of T cell receptor associated protein kinase 70 (ZAP70) domain, a linker for activation of T cells (LAT) domain, lymphocyte cytosolic protein 2 (SLP76) domain, (TCR) alpha, TCR beta, CD3 delta, CD3 gamma and CD3 epsilon intracellular domains.

[0229] In some embodiments, an intracellular domain comprises at least one intracellular signaling domain. An intracellular signaling domain generates a signal that promotes a function a cell, for example an immune effector function of a TCR containing cell, e.g., a TCR-expressing T-cell. In some embodiments, the intracellular domain of the first receptor of the disclosure includes at least one intracellular signaling domain. For example, the intracellular domains of CD3 gamma, delta or epsilon comprise signaling domains.

[0230] In some embodiments, the extracellular domain, transmembrane domain and intracellular domain are isolated or derived from the same protein, for example T-cell receptor (TCR) alpha, TCR beta, CD3 delta, CD3 gamma, CD3 epsilon or CD3 zeta.

[0231] Examples of intracellular domains for use in activator receptors of the disclosure include the cytoplasmic sequences of the TCR alpha, TCR beta, CD3 zeta, and 4-1BB, and the intracellular signaling co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any recombinant sequence that has the same functional capability.

[0232] In some embodiments, the intracellular signaling domain comprises a primary intracellular signaling domain. Exemplary primary intracellular signaling domains include

those derived from the proteins responsible for primary stimulation, or antigen dependent stimulation.

[0233] In some embodiments, the intracellular domain comprises a CD3 delta intracellular domain, a CD3 epsilon intracellular domain, a CD3 gamma intracellular domain, a CD3 zeta intracellular domain, a TCR alpha intracellular domain or a TCR beta intracellular domain.

[0234] In some embodiments, the intracellular domain comprises a TCR alpha intracellular domain. In some embodiments, a TCR alpha intracellular domain comprises Ser-Ser. In some embodiments, a TCR alpha intracellular domain is encoded by a sequence of TCCAGC.

[0235] In some embodiments, the intracellular domain comprises a TCR beta intracellular domain. In some embodiments, the TCR beta intracellular domain comprises an amino acid sequence having at least 80% identity, at least 90% identity, or is identical to a sequence of: MAMVKRKDSR (SEQ ID NO: 25). In some embodiments, the TCR beta intracellular domain comprises, or consists essentially of SEQ ID NO: 25. In some embodiments, the TCR beta intracellular domain is encoded by a sequence of ATGGCCATGGTCAAGAGAAAGGATTCCAGA (SEQ ID NO: 26).

[0236] In some embodiments, the intracellular signaling domain comprises at least one stimulatory intracellular domain. In some embodiments, the intracellular signaling domain comprises a primary intracellular signaling domain, such as a CD3 delta, CD3 gamma and CD3 epsilon intracellular domain, and one additional stimulatory intracellular domain, for example a co-stimulatory domain. In some embodiments, the intracellular signaling domain comprises a primary intracellular signaling domain, such as a CD3 delta, CD3 gamma and CD3 epsilon intracellular domain, and two additional stimulatory intracellular domains.

[0237] Exemplary co-stimulatory intracellular signaling domains include those derived from proteins responsible for co-stimulatory signals, or antigen independent stimulation. Co-stimulatory molecules include, but are not limited to an MHC class I molecule, BTLA, a Toll ligand receptor, as well as DAP10, DAP12, CD30, LIGHT, OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11a/CD18) 4-1BB (CD137, TNF receptor superfamily member 9), and CD28 molecule (CD28). A co-stimulatory protein 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, CD40, ICOS, BAFFR, HVEM, lymphocyte function-associated antigen-1 (LFA-1), CD2, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD160, B7-H3, a ligand that specifically binds with CD83, CD4, and the like. The co-stimulatory 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 variant thereof.

[0238] In some embodiments, the stimulatory domain comprises a co-stimulatory domain. In some embodiments, the co-stimulatory domain comprises a CD28 or 4-1BB co-stimulatory domain. CD28 and 4-1BB are well characterized co-stimulatory molecules required for full T cell activation and known to enhance T cell effector function. For example, CD28 and 4-1BB have been utilized in chimeric antigen receptors (CARs) to boost cytokine release, cytolytic function, and persistence over the first-generation CAR containing only the CD3 zeta signaling domain. Likewise, inclusion of co-stimulatory domains, for example CD28 and 4-1BB domains, in TCRs can increase T cell effector function and specifically allow co-stimulation in the absence of co-stimulatory ligand, which is typically down-regulated on the surface of tumor cells. In some embodiments, the stimulatory domain comprises a CD28 intracellular domain or a 4-1BB intracellular domain.

Inhibitory Receptors

[0239] The disclosure provides a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen that has been lost in a cancer cell, such as an allelic variant of a gene. The non-target allelic variant can be lost in the cancer cell through any mechanism, such as, without limitation, epigenetic changes that effect non-target allelic variant expression, mutations to the gene encoding the non-target allelic variant, disruption of cellular signaling that regulates expression of the non-target allelic variant, chromosome loss, partial or complete deletion of the genomic locus, gene silencing through modification of nucleic acids or heterochromatin, or loss of expression through other mechanisms. In variations of the compositions and methods disclosed herein, the cells or subject treated may exhibit a loss of expression of the non-target allelic variant because of non-genetic changes. Accordingly the disclosure provides compositions and methods for killing cells and/or treating subject lacking expression of the non-target antigen from any cause, including but not limited to, loss of heterozygosity.

[0240] The non-target antigen can be a protein, or an antigen peptide thereof in a complex with a major histocompatibility complex class I (MHC-I), where the non-target antigen comprises a polymorphism. Because the non-target antigen is polymorphic, loss of a single copy of the gene encoding the non-target antigen, which may occur through loss of heterozygosity in a cancer cell, yields a cancer cell that retains the other polymorphic variant of gene, but has lost the non-target antigen. For example, a subject having HLA-A*02 and

HLA-A*01 alleles at the HLA locus may have a cancer in which only the HLA-A*02 allele is lost. In such a subject, the HLA-A*01 protein remains present, but is not recognized by the inhibitory receptor of immune cells encountering the cancer cell, because the inhibitor receptor is designed to be specific to the HLA-A*02 (or other non-target antigen). In normal non-malignant cells, the HLA-A*02 (or other non-target antigen) is present and inhibits activation of the engineered immune cell. In cancer cells having loss of heterozygosity, the HLA-A*02 allelic variant (or other non-target antigen) is lost. Immune cells engineered to express the inhibitory receptor do not receive an inhibitory signal from the inhibitory receptor, as the inhibitory receptor only responds to the HLA-A*02 (or other non-target antigen), which is absent on cancer cells. By this mechanism, the immune cell is selectively activated, and selectively kills, cancer cells expressing MSLN but having lost HLA-A*02 (or another non-target antigen) due to loss-of-heterozygosity. HLA-A is used here as an example. Similar polymorphic variation occurs in the population at other MHC genes and in other non-MHC genes as well. Accordingly, the disclosure provides a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen selected from intercellular adhesion molecule 1 (ICAM1), catechol-O-methyltransferase (COMT), C-X-C motif chemokine ligand 16 (CXCL16), leucine rich repeat neuronal 4 (LRRN4) and uroplakin 3B (UPK3B), or an antigen peptide thereof in a complex with a major histocompatibility complex class I (MHC-I), wherein the non-target antigen may comprise a nonsynonymous, extracellular-domain polymorphism (e.g., in an extracellular domain of ICAM1, COMT, CXCL16), and immune cells comprising same. In some embodiments, the second receptor is an inhibitory chimeric antigen receptor. Alternatively, the non-target antigen may comprise a protein whose expression is lost in tumors, but present in key MSLN-expression normal tissues (e.g., LRRN4, UPK3B).

[0241] Exemplary inhibitory receptors are described in PCT/US2020/045228 filed on September 6, 2020, PCT/US2020/064607, filed on December 11, 2020, PCT/US2021/029907, filed on April 29, 2021 and PCT/US2020/059856 filed on November 10, 2020, the contents of each of which are incorporated herein by reference.

[0242] In some embodiments, the second receptor is humanized.

[0243] The disclosure provides a second receptor, which is an inhibitory receptor, comprising an extracellular ligand binding that can discriminate between single amino-acid variant alleles of a non-target antigen. This ability to discriminate between allelic variants of a non-target antigen allows the second receptor to inhibit activation of immune cells comprising the second receptor in the presence of non-target cells that express that the allele recognized by

the ligand binding domain. However, activation of immune cells is not inhibited in the presence of target cells that have lost the allele, for example cancer cells that have lost one allele of a gene through loss of heterozygosity.

[0244] The disclosure provides a second receptor, which is an inhibitory receptor, comprising an extracellular ligand binding that can discriminate between different levels of expression of a non-target antigen. This allows the second receptor to inhibit activation of immune cells comprising the second receptor in the presence of non-target cells that express the ligand for the second receptor, but to allow activation of immune cells in the presence of cancer cells that express low levels, or have no expression, of the ligand for the second receptor.

Inhibitor Ligands

[0245] In some embodiments, the non-target antigen is not expressed by the target cells, and is expressed by non-target cells. In some embodiments, the non-target antigen is expressed by healthy cells, i.e. cells that are not cancer cells. In some embodiments, the target cells are a plurality of cancer cells that have lost expression of the non-target antigen through loss of heterozygosity (LOH). In some embodiments, the non-target cells are a plurality of healthy cells (*i.e.*, non-cancer cells), that express both the target and the non-target antigen.

[0246] Any cell surface molecule expressed by the non-target cells that is not expressed by target cells may be a suitable non-target antigen for the second receptor extracellular ligand binding domain. For example, a cell adhesion molecule, a cell-cell signaling molecule, an extracellular domain, a molecule involved in chemotaxis, a glycoprotein, a G protein-coupled receptor, a transmembrane, a receptor for a neurotransmitter or a voltage gated ion channel can be used as a non-target antigen.

In some embodiments, the target antigen is a peptide antigen of a cancer cell-specific antigen in a complex with a major histocompatibility complex class I (MHC-I).

[0247] In some embodiments, the non-target antigen is lost in the cancer cells due to loss of heterozygosity. Exemplary non-target antigens lost in cancer cells due to loss of heterozygosity include ICAM1, COMT and CXCL16. In some embodiments, the non-target antigen is selected from the group consisting of a polymorphic variant of ICAM1, COMT and CXCL16. IN some embodiments, the non-target antigen is an antigen peptide comprising a polymorphic residue of ICAM1, COMT or CXCL16 in a complex with a major histocompatibility complex class I (MHC-I).

[0248] Non-target major histocompatibility complex class I MHC-I (or pMHC-I) antigens comprising any of HLA-A, HLA-B, HLA-C or HLA-E are envisaged as within the scope of the disclosure. In some embodiments, the non-target antigen comprises a Major

Histocompatibility Complex (MHC) protein. In some embodiments, the MHC is MHC class I. In some embodiments, the MHC class I protein comprises a human leukocyte antigen (HLA) protein. In some embodiments, the non-target antigen comprises an allele of an HLA Class I protein selected from the group consisting of HLA-A, HLA-B, HLA-C, or HLA-E. In some embodiments, the HLA-A allele comprises HLA-A*01, HLA-A*02, HLA-A*03 or HLA-A*11. In some embodiments, the HLA-B allele comprises HLA-B*07. In some embodiments, the HLA-C allele comprises HLA-C*07.

[0249] In some embodiments, the non-target antigen comprises HLA-A. In some embodiments, the non-target antigen comprises an allele of HLA-A. in some embodiments, the allele of HLA-A comprises HLA-A*01, HLA-A*02, HLA-A*03 or HLA-A*11. In some embodiments, the non-target antigen comprises HLA-A*69. In some embodiments, the non-target antigen comprises a human leukocyte antigen A*02 allele (HLA-A*02).

[0250] In some embodiments, the non-target antigen comprises an allele of HLA-B. In some embodiments, the allele of HLA-B comprises HLA-B*07.

[0251] In some embodiments, the non-target antigen comprises HLA-C. In some embodiments, the HLA-C allele comprises HLA-C*07.

[0252] In some embodiments, the non-target antigen comprises ICAM1 or an antigen peptide thereof in a complex with MHC-I. Human ICAM1 is frequently lost through LOH in cancer cells.

[0253] A wild type Human ICAM1 is described in NCBI record number NP_000192.2the contents of which are incorporated by reference herein in their entirety. In some embodiments, ICAM1 comprises an amino acid sequence of:

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  1 MAPSSPRPAL PALLVLLGAL FPGPGNAQTS VSPSKVILPR GGSVLVTCST SCDQPKLLGI
 61 ETPLPKKELL LPGNNRKVYE LSNVQEDSQP MCYSNCPDGQ STAKTFLTVY WTPERVELAP
121 LPSWQPVGKN LTLRCQVEGG APRANLTVVL LRGEKELKRE PAVGEPAEVT TTVLVRRDHH
181 GANFSCRTEL DLRPQGLELF ENTSAPYQLQ TFVLPATPPQ LVSPRVLEVD TQGTVVCSLD
241 GLFPVSEAQV HLALGDQRLN PTVTYGNDSF SAKASVSVTA EDEGTQRLTC AVILGNQSQE
301 TLQTVTIYSF PAPNVILTKP EVSEGTEVTV KCEAHPRAKV TLNGVPAQPL GPRAQLLLKA
361 TPEDNGRSFS CSATLEVAGQ LIHKNQTREL RVLYGPRLDE RDCPGNWTWP ENSQQTPMCQ
421 AWGNPLPELK CLKDGTFPLP IGESVTVTRD LEGTYLCRAR STQGEVTRKV TVNVLSPRYE
481 IVIITVVAAA VIMGTAGLST YLYNRQRKIK KYRLQQAQKG TPMKPNTQAT PP (SEQ ID NO:
27).
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[0254] In some embodiments, ICAM1 comprises a sequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 27. Polymorphic residues of ICAM1 are marked as bold and underlined in SEQ ID NO: 27. For example, rs5498 is a polymorphism at position 469 of SEQ ID NO: 27, which can be a K or an E.

[0255] In some embodiments, the non-target antigen comprises a polymorphism of ICAM1. For example, the non-target antigen comprises a peptide derived from ICAM1 comprising a polymorphic residue of ICAM1. Polymorphic residues of ICAM1 include amino acid residue 469 of SEQ ID NO: 27. In some embodiments, the non-target antigen comprises a peptide of ICAM1 comprising amino acid 469 of SEQ ID NO: 27. In some embodiments, the non-target antigen comprises a K at position 469 of SEQ ID NO: 27. In some embodiments, the non-target antigen comprises an E at position 469 of SEQ ID NO: 27.

[0256] In some embodiments, the non-target antigen comprises an ICAM1 polymorphism with an K at position 469 of SEQ ID NO: 27, and the second receptor comprises a ligand binding domain with a higher affinity for an ICAM1 ligand with an K at position 469 of SEQ ID NO: 27 than for an ICAM1 ligand with an E at position 469 of SEQ ID NO: 27. In some embodiments, the non-target antigen comprises an ICAM1 polymorphism with an E at position 469 of SEQ ID NO: 27, and the second receptor comprises a ligand binding domain with a higher affinity for an ICAM1 ligand with an E at position 469 of SEQ ID NO: 27 than for an ICAM1 ligand with a K at position 469 of SEQ ID NO: 27..

[0257] In some embodiments, the non-target antigen comprises COMT or an antigen peptide thereof in a complex with MHC-I. Human COMT is frequently lost through LOH in cancer cells.

[0258] A wild type Human COMT is described in NCBI record number NP_000192.2, the contents of which are incorporated by reference herein in their entirety. In some embodiments, COMT comprises an amino acid sequence of:

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  1 MPEAPPLLLA AVLLGLVLLV VLLLLLRHWG WGLCLIGWNE FILQPIHNLL MGDTKEQRIL
 61 NHVLQHAEPG NAQSVLEAID TYCEQKEWAM NVGDKKGKIV DAVIQEHQPS VLLELGAYCG
121 YSAVRMARLL SPGARLITIE INPDCAAITQ RMVDFAGVKD KVTLVVGASQ DIIPQLKKKY
181 DVDTLDMVFL DHWKDRYLPD TLLLEECGLL RKGTVLLADN VICPGAPDFL AHVRGSSCFE
241 CTHYQSFLEY REVVDGLEKA IYKGPGSEAG P (SEQ ID NO: 28).
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[0259] In some embodiments, COMT comprises a sequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 28. Polymorphic residues of COMT are marked as bold and underlined in SEQ ID NO: 28. For example, V158M is a polymorphism at position 158 of SEQ ID NO: 28, which can be a V or an M.

[0260] In some embodiments, the non-target antigen comprises a polymorphism of COMT. For example, the non-target antigen comprises a peptide derived from COMT comprising a polymorphic residue of COMT. Polymorphic residues of COMT 1 include amino acid residue 158 of SEQ ID NO: 28. In some embodiments, the non-target antigen comprises a

peptide of COMT comprising amino acid 158 of SEQ ID NO: 28. In some embodiments, the non-target antigen comprises a V at position 158 of SEQ ID NO: 28. In some embodiments, the non-target antigen comprises an M at position 158 of SEQ ID NO: 28.

[0261] In some embodiments, the non-target antigen comprises a COMT polymorphism with a V at position 158 of SEQ ID NO: 28, and the second receptor comprises a ligand binding domain with a higher affinity for a COMT ligand with an V at position 158 of SEQ ID NO: 28 than for a COMT ligand with an M at position 158 of SEQ ID NO: 28. In some embodiments, the non-target antigen comprises a COMT polymorphism with a M at position 158 of SEQ ID NO: 28, and the second receptor comprises a ligand binding domain with a higher affinity for a COMT ligand with an M at position 158 of SEQ ID NO: 28 than for a COMT ligand with a V at position 158 of SEQ ID NO: 28.

[0262] In some embodiments, the non-target antigen comprises C-X-C motif chemokine ligand 16 (CXCL16) or an antigen peptide thereof in a complex with MHC-I. Human CXCL16 precursor is described in NCBI record number NP_001094282.1, the contents of which are incorporated by reference herein in their entirety. In some embodiments, CXCL16 comprises an amino acid sequence of:

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  1 MSGSQSEVAP SPQSPRSPEM GRDLRPGSRV LLLLLLLLLV YLTQPGNGNE GSVTGSCYCG
 61 KRISSDSPPS VQFMNRLRKH LRAYHRCLYY TRFQLLSWSV CGGNKDPWVQ ELMSCLDLKE
121 CGHAYSGIVA HQKHLLPTSP PISQASEGAS SDIHTPAQML LSTLQSTQRP TLPVGSLSSD
181 KELTRPNETT IHTAGHSLAA GPEAGENQKQ PEKNAGPTAR TSATVPVLCL LAIIFILTAA
241 LSYVLCKRRR GQSPQSSPDL PVHYIPVAPD SNT (SEQ ID NO: 29).
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[0263] In some embodiments, the non-target antigen comprises a polymorphism of CXCL16. For example, the non-target antigen comprises a peptide derived from CXCL16 comprising a polymorphic residue of CXCL16. Polymorphic residues of CXCL16 include positions 142 and 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising amino acid 142 or 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising an A at amino acid 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising a V at amino acid 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising an I at amino acid 142 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising a T at amino acid 142 of SEQ ID NO: 29.

[0264] In some embodiments, the non-target antigen comprises a polymorphism of CXCL16. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising an A at amino acid 200 of SEQ ID NO: 29, and the second receptor comprises a ligand binding domain with a higher affinity for a CXCL16 ligand with an A at position 200

of SEQ ID NO: 29 than for a CXCL16 ligand with a V at position 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising a V at amino acid 200 of SEQ ID NO: 29, and the second receptor comprises a ligand binding domain with a higher affinity for a CXCL16 ligand with a V at position 200 of SEQ ID NO: 29 than for a CXCL16 ligand with an A at position 200 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising an I at amino acid 142 of SEQ ID NO: 29, and the second receptor comprises a ligand binding domain with a higher affinity for a CXCL16 ligand with an I at position 142 of SEQ ID NO: 29 than for a CXCL16 ligand with a T at position 142 of SEQ ID NO: 29. In some embodiments, the non-target antigen comprises a peptide of CXCL16 comprising a T at amino acid 142 of SEQ ID NO: 29, and the second receptor comprises a ligand binding domain with a higher affinity for a CXCL16 ligand with a T at position 142 of SEQ ID NO: 29 than for a CXCL16 ligand with an I at position 142 of SEQ ID NO: 29.

[0265] In some embodiments, the non-target antigen comprises HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11, HLA-B*07 or HLA-C*07. Various single variable domains that bind to or recognize the specified HLA alleles, for use in embodiments described herein, are described in Table 5. (complementarity determining regions underlined):

Table 5: HLA scFv binding domains

HLA-A*02 antigen binding domains	
DVLMTQTPLSLPVSL GDQASISCRSSQSIVH SNGNTYLEWYLQKP GQSPKLLIYKVSNRF SGVPDRFSGSGSGTD FTLKISRVEAEDLGV YYCFQGSHVPRTSGG GTKLEIKGGGGSGGG GSGGGGSGGQVQLQ QSGPELVKPGASVRI SCKASGYTFTSYHIH WVKQRPGQGLEWIG WIYPGNVNTEYNEK FKGKATLTADKSSST AYMHLSSLTSEDSAV YFCAREEITYAMDY WGQGTSVTVSS (SEQ ID NO: 30)	GATGTTTTGATGACCCAAACTCCACTCTCCCTGCCT GTCAGTCTTGGAGATCAAGCCTCCATCTCTTGCAG ATCTAGTCAGAGCATTGTACATAGTAATGGAAACA CCTATTTAGAATGGTACCTGCAGAAACCAGGCCAG TCTCCAAAGCTCCTGATCTACAAAGTTTCCAACCG ATTTTCTGGGGTCCCAGACAGGTTCAGTGGCAGTG GATCAGGGACAGATTTCACACTCAAGATCAGTAGA GTGGAGGCTGAGGATCTGGGAGTTTATTACTGCTT TCAAGGTTCACATGTTCCTCGGACGTCCGGTGGAG GCACCAAGCTGGAAATCAAAGGCGGAGGTGGAAG CGGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGA GGCCAGGTCCAGCTGCAGCAGTCTGGACCTGAGCT GGTGAAGCCTGGGGCTTCAGTGAGGATATCCTGCA AGGCTTCTGGCTACACCTTCACAAGTTACCATATA CATTGGGTGAAGCAGAGGCCTGGACAGGGACTTG AGTGGATTGGATGGATTTATCCTGGAAATGTTAAT ACTGAGTACAATGAGAAGTTCAAGGGCAAGGCCA CACTGACTGCAGACAAATCGTCCAGCACAGCCTAC ATGCACCTCAGCAGCCTGACCTCTGAGGACTCTGC GGTCTATTTCTGTGCCAGAGAGGAGATTACCTATG CTATGGACTACTGGGGTCAAGGAACCTCAGTCACC GTGTCCTCA (SEQ ID NO: 548)

QVQLVQSGAEVKKP GSSVKVSCKASGYTF TSYHIHWVRQAPGQ GLEWMGWIYPGNVN TEYNEKFKGKATITA DKSTSTAYMELSSLR SEDTAVYYCAREEIT YAMDYWGQGTTVT VSSGGGGSGGGGSG GGGSGGEIVLTQSPG TLSLSPGERATLSCRS SQSIVHSNGNTYLEW YQQKPGQAPRLLIYK VSNRFSGIPDRFSGSG SGTDFTLTISRLEPED FAVYYCFQGSHVPRT FGGGTKVEIK (SEQ ID NO: 31)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAA GAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATACACCTTCACTAGCTATCATATACATT GGGTGCGCCAGGCCCCCGGACAAGGGCTTGAGTG GATGGGATGGATCTACCCTGGCAATGTTAACACAG AATATAATGAGAAGTTCAAGGGCAAAGCCACCATT ACCGCGGACAAATCCACGAGCACAGCCTACATGG AGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTG TATTACTGTGCGAGGGAGGAAATTACCTACGCTAT GGACTACTGGGGCCAGGGAACCACAGTCACCGTGT CCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGAGATTGTATTG ACCCAGAGCCCAGGCACCCTGAGCCTCTCTCCAGG AGAGCGGGCCACCCTCAGTTGTAGATCCAGTCAGA GTATTGTACACAGTAATGGGAACACCTATTTGGAA TGGTATCAGCAGAAACCAGGTCAAGCCCCAAGATT GCTCATCTACAAAGTCTCTAACAGATTTAGTGGTA TTCCAGACAGGTTCAGCGGTTCCGGAAGTGGTACT GATTTCACCCTCACGATCTCCAGGCTCGAGCCAGA AGATTTCGCCGTTTATTACTGTTTTCAAGGTTCACA TGTGCCGCGCACATTCGGTGGGGGTACTAAAGTAG AAATCAAA (SEQ ID NO: 549)
QVQLVQSGAEVKKP GSSVKVSCKASGYTF TSYHIHWVRQAPGQ GLEWMGWIYPGNVN TEYNEKFKGKATITA DKSTSTAYMELSSLR SEDTAVYYCAREEIT YAMDYWGQGTTVT VSSGGGGSGGGGSG GGGSGGDIVMTQTPL SLPVTPGEPASISCRS SQSIVHSNGNTYLEW YLQKPGQSPQLLIYK VSNRFSGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCFQGSHV PRTFGGGTKVEIK (SEQ ID NO: 32)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAA GAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATACACCTTCACTAGCTATCATATACATT GGGTGCGCCAGGCCCCCGGACAAGGGCTTGAGTG GATGGGATGGATCTACCCTGGCAATGTTAACACAG AATATAATGAGAAGTTCAAGGGCAAAGCCACCATT ACCGCGGACAAATCCACGAGCACAGCCTACATGG AGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTG TATTACTGTGCGAGGGAGGAAATTACCTACGCTAT GGACTACTGGGGCCAGGGAACCACAGTCACCGTGT CCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGACATTGTAATG ACCCAGACCCCACTCAGCCTGCCCGTCACTCCAGG AGAGCCGGCCAGCATCAGTTGTAGATCCAGTCAGA GTATTGTACACAGTAATGGGAACACCTATTTGGAA TGGTATCTGCAGAAACCAGGTCAATCCCCACAATT GCTCATCTACAAAGTCTCTAACAGATTTAGTGGTG TACCAGACAGGTTCAGCGGTTCCGGAAGTGGTACT GATTTCACCCTCAAGATCTCCAGGGTCGAGGCAGA AGATGTCGGCGTTTATTACTGTTTTCAAGGTTCACA TGTGCCGCGCACATTCGGTGGGGGTACTAAAGTAG AAATCAAA (SEQ ID NO: 550)
EVQLVESGGGLVKP GGSLRLSCAASGYTF TSYHIHWVRQAPGK GLEWVGWIYPGNVN TEYNEKFKGRFTISR DDSKNTLYLQMNSL	GAGGTGCAGCTGGTGGAGTCTGGGGGTGGGCTGGT GAAGCCTGGGGGCTCACTGAGGCTTTCCTGCGCGG CTTCTGGATACACCTTCACTAGCTATCATATACATT GGGTGCGCCAGGCCCCCGGAAAAGGGCTTGAGTG GGTGGGATGGATCTACCCTGGCAATGTTAACACAG AATATAATGAGAAGTTCAAGGGCAGATTCACCATT

KTEDTAVYYCAREEI TYAMDYWGQGTTV TVSSGGGGSGGGGS GGGGSGGDIQMTQS PSSLSASVGDRVTITC RSSQSIVHSNGNTYL EWYQQKPGKAPKLL IYKVSNRFSGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCFQGSHV PRTFGGGTKVEIK (SEQ ID NO: 33)	AGCAGGGACGATTCCAAGAACACACTCTACCTGCA GATGAACAGCCTGAAAACTGAAGACACGGCTGTGT ATTACTGTGCGAGGGAGGAAATTACCTACGCTATG GACTACTGGGGCCAGGGAACCACAGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGACATTCAAATGA CCCAGAGCCCATCCAGCCTGAGCGCATCTGTAGGT GACCGGGTCACCATCACTTGTAGATCCAGTCAGAG TATTGTACACAGTAATGGGAACACCTATTTGGAAT GGTATCAGCAGAAACCAGGTAAAGCCCCAAAATT GCTCATCTACAAAGTCTCTAACAGATTTAGTGGTG TACCAAGCAGGTTCAGCGGTTCCGGAAGTGGTACT GATTTCACCCTCACGATCTCCTCTCTCCAGCCAGAA GATTTCGCCACTTATTACTGTTTTCAAGGTTCACAT GTGCCGCGCACATTCGGTGGGGGTACTAAAGTAGA AATCAAA (SEQ ID NO: 551)
QVQLVQSGAEVKKP GSSVKVSCKASGYTF TSYHIHWVRQAPGQ GLEWIGWIYPGNVN TEYNEKFKGKATITA DESTNTAYMELSSLR SEDTAVYYCAREEIT YAMDYWGQGTLVT VSSGGGGSGGGGSG GGGSGGDIQMTQSPS TLSASVGDRVTITCR SSQSIVHSNGNTYLE WYQQKPGKAPKLLI YKVSNRFSGVPARFS GSGSGTEFTLTISSLQ PDDFATYYCFQGSH VPRTFGQGTKVEVK (SEQ ID NO: 34)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAA GAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATACACCTTCACTAGCTATCATATACATT GGGTGCGCCAGGCCCCCGGACAAGGGCTTGAGTG GATCGGATGGATCTACCCTGGCAATGTTAACACAG AATATAATGAGAAGTTCAAGGGCAAAGCCACCATT ACCGCGGACGAATCCACGAACACAGCCTACATGG AGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTG TATTACTGTGCGAGGGAGGAAATTACCTACGCTAT GGACTACTGGGGCCAGGGAACCCTGGTCACCGTGT CCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGACATTCAAATG ACCCAGAGCCCATCCACCCTGAGCGCATCTGTAGG TGACCGGGTCACCATCACTTGTAGATCCAGTCAGA GTATTGTACACAGTAATGGGAACACCTATTTGGAA TGGTATCAGCAGAAACCAGGTAAAGCCCCAAAATT GCTCATCTACAAAGTCTCTAACAGATTTAGTGGTG TACCAGCCAGGTTCAGCGGTTCCGGAAGTGGTACT GAATTCACCCTCACGATCTCCTCTCTCCAGCCAGAT GATTTCGCCACTTATTACTGTTTTCAAGGTTCACAT GTGCCGCGCACATTCGGTCAGGGTACTAAAGTAGA AGTCAAA (SEQ ID NO: 552)
QVQLVQSGAEVKKP GSSVKVSCKASGYTF TSYHMHWVRQAPG QGLEWIGYIYPGNVN TEYNEKFKGKATLT ADKSTNTAYMELSSL RSEDTAVYFCAREEI TYAMDYWGQGTLV TVSSGGGGSGGGGS GGGGSGGDVQMTQS PSTLSASVGDRVTITC SSSQSIVHSNGNTYM	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAA GAAGCCTGGGTCCTCAGTGAAGGTTTCCTGCAAGG CTTCTGGATACACCTTCACTAGCTATCATATGCATT GGGTGCGCCAGGCCCCCGGACAAGGGCTTGAGTG GATCGGATACATCTACCCTGGCAATGTTAACACAG AATATAATGAGAAGTTCAAGGGCAAAGCCACCCTT ACCGCGGACAAATCCACGAACACAGCCTACATGG AGCTGAGCAGCCTGAGATCTGAAGACACGGCTGTG TATTTCTGTGCGAGGGAGGAAATTACCTACGCTAT GGACTACTGGGGCCAGGGAACCCTGGTCACCGTGT CCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGACGTTCAAATG

EWYQQKPGKAPKLL IYKVSNRFSGVPDRF SGSGSGTEFTLTISSL QPDDFATYYCHQGS HVPRTFGQGTKVEV K (SEQ ID NO: 35)	ACCCAGAGCCCATCCACCCTGAGCGCATCTGTAGG TGACCGGGTCACCATCACTTGTAGCTCCAGTCAGA GTATTGTACACAGTAATGGGAACACCTATATGGAA TGGTATCAGCAGAAACCAGGTAAAGCCCCAAAATT GCTCATCTACAAAGTCTCTAACAGATTTAGTGGTG TACCAGACAGGTTCAGCGGTTCCGGAAGTGGTACT GAATTCACCCTCACGATCTCCTCTCTCCAGCCAGAT GATTTCGCCACTTATTACTGTCATCAAGGTTCACAT GTGCCGCGCACATTCGGTCAGGGTACTAAAGTAGA AGTCAAA (SEQ ID NO: 553)
QVQLQQSGPELVKP GASVKMSCKASGYT FTSYHIQWVKQRPG QGLEWIGWIYPGDGS TQYNEKFKGKTTLT ADKSSSTAYMLLSSL TSEDSAIYFCAREGT YYAMDYWGQGTSV TVSSGGGGSGGGGS GGGGSGGDVLMTQT PLSLPVSLGDQVSISC RSSQSIVHSNGNTYL EWYLQKPGQSPKLLI YKVSNRFSGVPDRFS GSGSGTDFTLKISRV EAEDLGVYYCFQGS HVPRTFGGGTKLEIK (SEQ ID NO: 36)	CAGGTGCAGCTGCAGCAGTCTGGGCCTGAGCTGGT GAAGCCTGGGGCCTCAGTGAAGATGTCCTGCAAGG CTTCTGGATACACCTTCACTAGCTATCATATCCAGT GGGTGAAGCAGAGGCCTGGACAAGGGCTTGAGTG GATCGGATGGATCTACCCTGGCGATGGTAGTACAC AGTATAATGAGAAGTTCAAGGGCAAAACCACCCTT ACCGCGGACAAATCCTCCAGCACAGCCTACATGTT GCTGAGCAGCCTGACCTCTGAAGACTCTGCTATCT ATTTCTGTGCGAGGGAGGGGACCTACTACGCTATG GACTACTGGGGCCAGGGAACCTCAGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGATGTTTTGATGA CCCAGACTCCACTCTCCCTGCCTGTCTCTCTTGGAG ACCAAGTCTCCATCTCTTGTAGATCCAGTCAGAGT ATTGTACACAGTAATGGGAACACCTATTTAGAATG GTATCTGCAGAAACCAGGTCAGTCTCCAAAGTTGC TCATCTACAAAGTCTCTAACAGATTTAGTGGTGTA CCAGACAGGTTCAGCGGTTCCGGAAGTGGTACTGA TTTCACCCTCAAGATCTCGAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGTTTTCAAGGTTCACATG TGCCGCGCACATTCGGTGGAGGTACTAAACTGGAA ATCAAA (SEQ ID NO: 554)
QLQLQESGPGLVKPS ETLSLTCTVSGYTFTS YHIQWIRQPPGKGLE WIGWIYPGDGSTQY NEKFKGRATISVDTS KNQFSLNLDSVSAAD TAIYYCAREGTYYA MDYWGKGSTVTVSS GGGGSGGGGSGGGG SGGDIQMTQSPSSLS ASVGDRVTITCRSSQ SIVHSNGNTYLEWY QQKPGKAPKLLIYKV SNRFSGVPSRFSGSGS GTDFTFTISSLQPEDI ATYYCFQGSHVPRTF GPGTKVDIK (SEQ ID NO: 37)	CAGCTGCAGCTGCAGGAGTCTGGGCCCGGGCTGGT GAAGCCTTCGGAAACGCTGAGCCTCACCTGCACGG TTTCTGGATACACCTTCACCAGCTATCATATCCAGT GGATCCGACAGCCCCCTGGAAAAGGGCTTGAGTGG ATCGGATGGATCTACCCTGGCGATGGTTCAACACA GTACAATGAGAAGTTCAAGGGCAGAGCCACGATT AGCGTGGACACATCCAAGAACCAATTCTCCCTGAA CCTGGACAGCGTGAGTGCTGCGGACACGGCCATTT ATTACTGTGCGAGAGAGGGAACTTACTACGCTATG GACTACTGGGGCAAAGGGAGCACGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGACATCCAGATGA CCCAGAGCCCAAGCTCCCTGAGTGCGTCCGTGGGC GACCGCGTGACCATCACTTGCAGATCCTCTCAGTC CATCGTGCACTCCAACGGCAACACGTACCTCGAGT GGTACCAGCAGAAGCCCGGGAAGGCCCCGAAACT GCTCATCTACAAGGTGAGCAACCGGTTCTCCGGCG TCCCCAGCCGCTTCTCAGGGTCCGGCTCGGGGACG

	GATTTCACCTTCACGATTAGCAGCTTGCAGCCCGA AGACATCGCCACGTACTACTGCTTTCAGGGAAGTC ACGTGCCGCGTACCTTCGGGCCGGGCACGAAAGTG GATATTAAG (SEQ ID NO: 555)
EVQLVQSGAELKKP GSSVKVSCKASGYTF TSYHIQWVKQAPGQ GLEWIGWIYPGDGST QYNEKFKGKATLTV DKSTNTAYMELSSLR SEDTAVYYCAREGT YYAMDYWGQGTLV TVSSGGGGSGGGGS GGGGSGGDIQMTQS PSTLSASVGDRVTITC RSSQSIVHSNGNTYL EWYQQKPGKAPKLL IYKVSNRFSGVPSRFS GSGSGTDFTLTISSLQ PDDFATYYCFQGSH VPRTFGQGTKVEVK (SEQ ID NO: 38)	GAGGTGCAGCTGGTGCAGTCTGGGGCCGAGCTGAA GAAGCCTGGGTCCTCGGTGAAGGTGTCCTGCAAGG CTTCTGGATACACCTTCACCAGCTATCATATCCAGT GGGTAAAACAGGCCCCTGGACAAGGGCTTGAGTG GATCGGATGGATCTACCCTGGCGATGGTTCAACAC AGTACAATGAGAAGTTCAAGGGCAAAGCCACGCTT ACCGTGGACAAATCCACGAACACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCCGTAT ATTACTGTGCGAGAGAGGGAACTTACTACGCTATG GACTACTGGGGCCAAGGGACCCTGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGACATCCAGATGA CCCAGAGCCCATCCACCCTGAGTGCGTCCGTGGGC GACCGCGTGACCATCACTTGCAGATCCTCTCAGTC CATCGTGCACTCCAACGGCAACACGTACCTCGAGT GGTACCAGCAGAAGCCCGGGAAGGCCCCGAAACT GCTCATCTACAAGGTGAGCAACCGGTTCTCCGGCG TCCCCAGCCGCTTCTCAGGGTCCGGCTCGGGGACG GATTTCACCCTCACGATTAGCAGCTTGCAGCCCGA TGACTTCGCCACGTACTACTGCTTTCAGGGAAGTC ACGTGCCGCGTACCTTCGGGCAGGGCACGAAAGTG GAAGTTAAG (SEQ ID NO: 556)
QVQLVQSGAEVKKP GSSVKVSCKASGYTF TSYHIQWVRQAPGQ GLEWMGWIYPGDGS TQYNEKFKGRVTITA DKSTSTAYMELSSLR SEDTAVYYCAREGT YYAMDYWGQGTTV TVSSGGGGSGGGGS GGGGSGGEIVLTQSP GTLSLSPGERATLSC RSSQSIVHSNGNTYL EWYQQKPGQAPRLLI YKVSNRFSGIPDRFS GSGSGTDFTLTISRLE PEDFAVYYCFQGSH VPRTFGGGTKVEIK (SEQ ID NO: 39)	CAGGTGCAGCTGGTGCAGTCTGGGGCCGAGGTGAA GAAGCCTGGGTCCTCGGTGAAGGTGTCCTGCAAGG CTTCTGGATACACCTTCACCAGCTATCATATCCAGT GGGTACGACAGGCCCCTGGACAAGGGCTTGAGTG GATGGGATGGATCTACCCTGGCGATGGTTCAACAC AGTACAATGAGAAGTTCAAGGGCAGAGTCACGATT ACCGCGGACAAATCCACGAGCACAGCCTACATGG AGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTA TATTACTGTGCGAGAGAGGGAACTTACTACGCTAT GGACTACTGGGGCCAAGGGACCACGGTCACCGTGT CCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATC TGGCGGCGGAGGAAGCGGAGGCGAGATCGTCCTG ACCCAGAGCCCAGGGACCCTGAGTTTGTCCCCGGG CGAGCGCGCGACCCTCAGTTGCAGATCCTCTCAGT CCATCGTGCACTCCAACGGCAACACGTACCTCGAG TGGTACCAGCAGAAGCCCGGGCAGGCCCCGCGACT GCTCATCTACAAGGTGAGCAACCGGTTCTCCGGCA TCCCCGACCGCTTCTCAGGGTCCGGCTCGGGGACG GATTTCACCCTCACGATTAGCCGCTTGGAGCCCGA AGACTTCGCCGTGTACTACTGCTTTCAGGGAAGTC ACGTGCCGCGTACCTTCGGGGGGGGCACGAAAGTG GAAATTAAG (SEQ ID NO: 557)
QVTLKQSGAEVKKP GSSVKVSCTASGYTF	CAGGTGACCCTGAAGCAGTCTGGGGCCGAGGTGA AGAAGCCTGGGTCCTCGGTGAAGGTGTCCTGCACG

TSYHVSWVRQAPGQ GLEWLGRIYPGDGST QYNEKFKGKVTITAD KSMDTSFMELTSLTS EDTAVYYCAREGTY YAMDLWGQGTLVT VSSGGGGSGGGGSG GGGSGGEIVLTQSPG TLSLSPGERATLSCRS SQSIVHSNGNTYLAW YQQKPGQAPRLLISK VSNRFSGVPDRFSGS GSGTDFTLTISRLEPE DFAVYYCQQGSHVP RTFGGGTKVEIK (SEQ ID NO: 40)	GCTTCTGGATACACCTTCACCAGCTATCATGTCAGC TGGGTACGACAGGCCCCTGGACAAGGGCTTGAGTG GTTGGGAAGGATCTACCCTGGCGATGGTTCAACAC AGTACAATGAGAAGTTCAAGGGCAAAGTCACGATT ACCGCGGACAAATCCATGGACACATCCTTCATGGA GCTGACCAGCCTGACATCTGAGGACACGGCCGTAT ATTACTGTGCGAGAGAGGGAACTTACTACGCTATG GACCTCTGGGGCCAAGGGACCCTGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGAGATCGTCCTGA CCCAGAGCCCAGGGACCCTGAGTTTGTCCCCGGGC GAGCGCGCGACCCTCAGTTGCAGATCCTCTCAGTC CATCGTGCACTCCAACGGCAACACGTACCTCGCGT GGTACCAGCAGAAGCCCGGGCAGGCCCCGCGACT GCTCATCTCCAAGGTGAGCAACCGGTTCTCCGGCG TCCCCGACCGCTTCTCAGGGTCCGGCTCGGGGACG GATTTCACCCTCACGATTAGCCGCTTGGAGCCCGA AGACTTCGCCGTGTACTACTGCCAACAGGGAAGTC ACGTGCCGCGTACCTTCGGGGGGGGCACGAAAGTG GAAATTAAG (SEQ ID NO: 558)
QVQLVQSGAEVKKP GASVKVSCKASGYT FTSYHMHWVRQAPG QRLEWMGWIYPGDG STQYNEKFKGKVTIT RDTSASTAYMELSSL RSEDTAVYYCAREG TYYAMDYWGQGTL VTVSSGGGGSGGGG SGGGGSGGDIVMTQ TPLSLPVTPGEPASIS CRSSQSIVHSNGNTY LDWYLQKPGQSPQL LIYKVSNRFSGVPDR FSGSGSGTDFTLKISR VEAEDVGVYYCMQ GSHVPRTFGGGTKVE IK (SEQ ID NO: 41)	CAGGTGCAGCTGGTGCAGTCTGGGGCCGAGGTGAA GAAGCCTGGGGCCTCGGTGAAGGTGTCCTGCAAGG CTTCTGGATACACCTTCACCAGCTATCATATGCACT GGGTACGACAGGCCCCTGGACAAAGGCTTGAGTG GATGGGATGGATCTACCCTGGCGATGGTTCAACAC AGTACAATGAGAAGTTCAAGGGCAAAGTCACGATT ACCCGGGACACATCCGCGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCCGTAT ATTACTGTGCGAGAGAGGGAACTTACTACGCTATG GACTACTGGGGCCAAGGGACCCTGGTCACCGTGTC CTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCT GGCGGCGGAGGAAGCGGAGGCGACATCGTCATGA CCCAGACCCCACTGTCCCTGCCTGTGACCCCGGGC GAGCCCGCGAGCATCAGTTGCAGATCCTCTCAGTC CATCGTGCACTCCAACGGCAACACGTACCTCGACT GGTACCTGCAGAAGCCCGGGCAGTCCCCGCAACTG CTCATCTACAAGGTGAGCAACCGGTTCTCCGGCGT CCCCGACCGCTTCTCAGGGTCCGGCTCGGGGACGG ATTTCACCCTCAAGATTAGCCGCGTGGAGGCCGAA GACGTCGGCGTGTACTACTGCATGCAGGGAAGTCA CGTGCCGCGTACCTTCGGGGGGGGCACGAAAGTGG AAATTAAG (SEQ ID NO: 559)
HLA-B*07 antigen binding domains	
1.10_scFv	QVQLQESGPGLVKPSQTLSLTCTVSGYSITSGYSWHW IRQPPGKGLEWIGYIHFSGSTHYHPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARGGVVSHYAMDCW GQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS SLSASVGDRVTITCRASENIYSNLAWYQQKPGKAPKL LIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 560)

1.9_scFv	EVQLVESGGGLVKPGGSLRLSCAASGYSITSGYSWH WVRQAPGKGLEWVSYIHFSGSTHYHPSLKSRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARGGVVSHYAM DCWGQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSVSASVGDRVTITCRASENIYSNLAWYQQKPGK APKLLIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 561)
1.8_scFv	EVQLVESGGGLVKPGGSLRLSCAASGYSITSGYSWH WVRQAPGKGLEWVGYIHFSGSTHYHPSLKSRFTISRD DSKNTLYLQMNSLKTEDTAVYYCARGGVVSHYAMD CWGQGTTVTVSSGGGGSGGGGSGGGGSGGEIVLTQS PATLSLSPGERATLSCRASENIYSNLAWYQQKPGQAP RLLIYAATYLPDGIPARFSGSGSGTDFTLTISSLEPEDF AVYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 562)
1.7_scFv	QVQLQQSGPGLVKPSQTLSLTCAISGYSITSGYSWHW IRQSPSRGLEWLGYIHFSGSTHYHPSLKSRITINPDTSK NQFSLQLNSVTPEDTAVYYCARGGVVSHYAMDCWG QGTTVTVSSGGGGSGGGGSGGGGSGGEIVLTQSPAT LSLSPGERATLSCRASENIYSNLAWYQQKPGQAPRLL IYAATYLPDGIPARFSGSGSGTDFTLTISRLEPEDFAVY YCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 563)
1.6_scFv	EVQLVESGGGLVKPGGSLRLSCAASGYSITSGYSWH WVRQAPGKGLEWVGYIHFSGSTHYHPSLKSRFTISRD DSKNTLYLQMNSLKTEDTAVYYCARGGVVSHYAMD CWGQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQ SPSSVSASVGDRVTITCRASENIYSNLAWYQQKPGKA PKLLIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 564)
1.5_scFv	EVQLVESGGGLVQPGGSLRLSCAASGYSITSGYSWH WVRQAPGKGLEWVSYIHFSGSTHYHPSLKSRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARGGVVSHYAM DCWGQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASENIYSNLAWYQQKPGK APKLLIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 565)
1.4_scFv	EVQLVESGGGLVKPGGSLRLSCAASGYSITSGYSWH WVRQAPGKGLEWVGYIHFSGSTHYHPSLKSRFTISRD DSKNTLYLQMNSLKTEDTAVYYCARGGVVSHYAMD CWGQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQ SPSSLSASVGDRVTITCRASENIYSNLAWYQQKPGKA PKLLIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 566)
1.3_scFv	QVQLQQWGAGLLKPSETLSLTCAVYGYSITSGYSWH WIRQPPGKGLEWIGYIHFSGSTHYHPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARGGVVSHYAMDC WGQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQS

	PSSLSASVGDRVTITCRASENIYSNLAWYQQKPGKAP KLLIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 567)
1.2_scFv	QVQLQESGPGLVKPSQTLSLTCTVSGYSITSGYSWHW IRQHPGKGLEWIGYIHFSGSTHYHPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARGGVVSHYAMDCW GQGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS SLSASVGDRVTITCRASENIYSNLAWYQQKPGKAPKL LIYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 568)
1.1_scFv	QVQLQQSGPGLVKPSQTLSLTCAISGYSITSGYSWHW IRQSPSRGLEWLGYIHFSGSTHYHPSLKSRITINPDTSK NQFSLQLNSVTPEDTAVYYCARGGVVSHYAMDCWG QGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSS LSASVGDRVTITCRASENIYSNLAWYQQKPGKAPKLL IYAATYLPDGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYCQHFWVTPYTFGGGTKVEIK (SEQ ID NO: 569)
HLA-A*11 antigen binding domains	
QVQLQESGPGLVKPS QTLSLTCTVSGGSISS GGYYWSWIRQPPGK GLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCARHYYYYS MDVWGKGTTVTVSS GGGGSGGGGSGGGG SGGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGGGTK VEIK (SEQ ID NO: 114)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGT GAAACCCAGCCAGACCCTGAGCCTGACCTGCACAG TGTCCGGCGGCTCGATCAGCAGCGGCGGCTACTAC TGGTCCTGGATCAGACAGCCCCCTGGCAAGGGCCT GGAATGGATCGGCTACATCTACTACAGCGGCAGCA CCTACTACAACCCCAGCCTGAAGTCCAGAGTGACC ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCT GAAGCTGAGCAGCGTGACAGCCGCCGACACCGCT GTGTATTACTGTGCGAGACACTACTACTACTACTCC ATGGACGTCTGGGGCAAAGGGACCACGGTCACCGT GTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGA TCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGA TGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGCCGGGCAAGTCAG AGCATTAGCAGCTATTTAAATTGGTATCAGCAGAA ACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTG CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTC AGTGGCAGTGGATCTGGGACAGATTTCACTCTCAC CATCAGCAGTCTGCAACCTGAAGATTTTGCAACTT ACTACTGTCAACAGAGTTACAGTACCCCTCTCACTT TCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 123)
QITLKESGPTLVKPT QTLTLTCTFSGFSLST SGVGVGWIRQPPGK ALEWLALIYWNDDK RYSPSLKSRLTITKDT SKNQVVLTMTNMDP VDTATYYCAHRHMR LSCFDYWGQGTLVT VSSGGGGSGGGGSG	CAGATCACCCTGAAAGAGTCCGGCCCCACCCTGGT GAAACCCACCCAGACCCTGACCCTGACATGCACCT TCAGCGGCTTCAGCCTGAGCACCTCTGGCGTGGGC GTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCT GGAATGGCTGGCCCTGATCTACTGGAACGACGACA AGCGGTACAGCCCCAGCCTGAAGTCCCGGCTGACC ATCACCAAGGACACCTCGAAGAACCAGGTGGTGCT GACCATGACAAACATGGACCCCGTGGACACCGCCA CATATTACTGTGCACACAGACACATGCGTTTAAGC

GGGSGGDIQMTQSPS SLSASVGDRVTITCR ASQSISSYLNWYQQK PGKAPKLLIYAASSL QSGVPSRFSGSGSGT DFTLTISSLQPEDFAT YYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 115)	TGTTTTGACTACTGGGGCCAGGGAACCCTGGTCAC CGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGA GGATCTGGCGGCGGAGGAAGCGGAGGCGACATCC AGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTG TAGGAGACAGAGTCACCATCACTTGCCGGGCAAGT CAGAGCATTAGCAGCTATTTAAATTGGTATCAGCA GAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATG CTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGG TTCAGTGGCAGTGGATCTGGGACAGATTTCACTCT CACCATCAGCAGTCTGCAACCTGAAGATTTTGCAA CTTACTACTGTCAACAGAGTTACAGTACCCCTCTCA CTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 124)
QVQLVQSGAEVKKP GASVKVSCKASGYT FTSYAMHWVRQAPG QRLEWMGWINAGN GNTKYSQKFQGRVTI TRDTSASTAYMELSS LRSEDTAVYYCARE GNGANPDAFDIWGQ GTMVTVSSGGGGSG GGGSGGGGSGGDIQ MTQSPSSLSASVGDR VTITCRASQSISSYLN WYQQKPGKAPKLLI YAASSLQSGVPSRFS GSGSGTDFTLTISSLQ PEDFATYYCQQSYST PLTFGGGTKVEIK (SEQ ID NO: 116)	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGTGAA GAAACCTGGCGCCTCCGTGAAGGTGTCCTGCAAGG CCAGCGGCTACACCTTCACCAGCTACGCCATGCAC TGGGTTCGACAGGCCCCTGGCCAGAGACTGGAATG GATGGGCTGGATCAACGCCGGCAACGGCAACACC AAGTACAGCCAGAAATTCCAGGGCAGAGTGACCA TCACCCGGGACACCAGCGCCAGCACCGCCTACATG GAACTGAGCAGCCTGCGGAGCGAGGACACCGCTG TGTATTACTGTGCGAGAGAAGGAAATGGTGCCAAC CCTGATGCTTTTGATATCTGGGGCCAAGGGACAAT GGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGA GGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCG ACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTG CATCTGTAGGAGACAGAGTCACCATCACTTGCCGG GCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTA TCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA TCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCA TCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTT CACTCTCACCATCAGCAGTCTGCAACCTGAAGATT TTGCAACTTACTACTGTCAACAGAGTTACAGTACC CCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGAT CAAG (SEQ ID NO: 125)
EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYDMHWVRQATG KGLEWVSAIGTAGD TYYPGSVKGRFTISR ENAKNSLYLQMNSL RAGDTAVYYCARDL PGSYWYFDLWGRGT LVTVSSGGGGSGGG GSGGGGSGGDIQMT QSPSSLSASVGDRVTI TCRASQSISSYLNWY QQKPGKAPKLLIYAA SSLQSGVPSRFSGSGS GTDFTLTISSLQPEDF	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGG TGCAGCCTGGCGGCAGCCTGAGACTGTCTTGCGCC GCCAGCGGCTTCACCTTCAGCAGCTACGACATGCA CTGGGTCCGCCAGGCCACCGGCAAGGGACTGGAAT GGGTGTCCGCCATCGGCACAGCCGGCGACACTTAC TACCCCGGCAGCGTGAAGGGCCGGTTCACCATCAG CAGAGAGAACGCCAAGAACAGCCTGTACCTGCAG ATGAACAGCCTTCGAGCCGGCGATACCGCCGTGTA TTACTGTGCAAGAGATCTCCCTGGTAGCTACTGGT ACTTCGATCTCTGGGGCCGTGGCACCCTGGTCACT GTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGACATCCA GATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCGGGCAAGTC AGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG

ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 117)	AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAC TTACTACTGTCAACAGAGTTACAGTACCCCTCTCAC TTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 126)
QVQLQESGPGLVKPS QTLSLTCTVSGGSISS GGYYWSWIRQPPGK GLEWIGYIYYSGSTY YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCARHYYYYY LDVWGKGTTVTVSS GGGGSGGGGSGGGG SGGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGGGTK VEIK (SEQ ID NO: 118)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGT GAAACCCAGCCAGACCCTGAGCCTGACCTGCACAG TGTCCGGCGGCTCGATCAGCAGCGGCGGCTACTAC TGGTCCTGGATCAGACAGCCCCCTGGCAAGGGCCT GGAATGGATCGGCTACATCTACTACAGCGGCAGCA CCTACTACAACCCCAGCCTGAAGTCCAGAGTGACC ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCT GAAGCTGAGCAGCGTGACAGCCGCCGACACCGCT GTGTATTACTGTGCGAGACACTACTACTACTACTA CCTGGACGTCTGGGGCAAAGGGACCACGGTCACCG TGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGG ATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAG ATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTA GGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGA AACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCT GCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACT TACTACTGTCAACAGAGTTACAGTACCCCTCTCACT TTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 127)
EVQLVESGGGLVQP GGSLRLSCAASGFTF SSYWMHWVRQAPG KGLVWVSRINSDGSS TSYADSVKGRFTISR DNAKNTLYLQMNSL RAEDTAVYYCCLGV LLYNWFDPWGQGTL VTVSSGGGGSGGGG SGGGGSGGDIQMTQ SPSSLSASVGDRVTIT CRASQSISSYLNWYQ QKPGKAPKLLIYAAS SLQSGVPSRFSGSGS GTDFTLTISSLQPEDF ATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 119)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGG TGCAGCCTGGCGGCAGCCTGAGACTGTCTTGCGCC GCCAGCGGCTTCACCTTCAGCAGCTACTGGATGCA CTGGGTCCGCCAGGCCCCTGGCAAGGGACTGGTCT GGGTGTCTCGAATCAACAGCGACGGCAGCAGCACC AGCTACGCCGACAGCGTGAAGGGCCGGTTCACCAT CAGCCGGGACAACGCCAAGAACACCCTGTACCTGC AGATGAACAGCCTGCGGGCCGAGGACACCGCCGT GTATTACTGTTGTTTGGGTGTTTTATTATACAACTG GTTCGACCCCTGGGGCCAGGGAACCCTGGTCACCG TGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGG ATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAG ATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTA GGAGACAGAGTCACCATCACTTGCCGGGCAAGTCA GAGCATTAGCAGCTATTTAAATTGGTATCAGCAGA AACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCT GCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTT CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA CCATCAGCAGTCTGCAACCTGAAGATTTTGCAACT TACTACTGTCAACAGAGTTACAGTACCCCTCTCACT

	TTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 128)
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARHYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 120)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCCAGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCTCGATCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCCCCCTGGCAAGGGCCTGGAATGGATCGGCTACATCTACTACAGCGGCAGCACCTACTACAACCCCAGCCTGAAGTCCAGAGTGACCATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACAGCCGCCGACACCGCTGTGTATTACTGTGCGAGACACTACTACTACTACATGGACGTCTGGGGCAAAGGGACCACGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 129)
QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKALEWLALIYWNDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHKTTSFYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 121)	CAGATCACCCTGAAAGAGTCCGGCCCCACCCTGGTGAAACCCACCCAGACCCTGACCCTGACATGCACCTTCAGCGGCTTCAGCCTGAGCACCTCTGGCGTGGGCGTGGGCTGGATCAGACAGCCTCCCGGCAAGGCCCTGGAATGGCTGGCCCTGATCTACTGGAACGACGACAAGCGGTACAGCCCCAGCCTGAAGTCCCGGCTGACCATCACCAAGGACACCTCGAAGAACCAGGTGGTGCTGACCATGACAAACATGGACCCCGTGGACACCGCCACATATTACTGTGCACACAAAACGACGTCGTTTTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAGGATCTGGCGGCGGAGGAAGCGGAGGCGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCTCACTTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 130)
QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTY	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCTGGTGAAACCCAGCCAGACCCTGAGCCTGACCTGCACAGTGTCCGGCGGCTCGATCAGCAGCGGCGGCTACTACTGGTCCTGGATCAGACAGCCCCCTGGCAAGGGCCT

YNPSLKSRVTISVDTS KNQFSLKLSSVTAAD TAVYYCARHYYYYY MDVWGKGTTVTVSS GGGGSGGGGSGGGG SGGDIQMTQSPSSLS ASVGDRVTITCRASQ SISSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGGGTK VEIK (SEQ ID NO: 122)	GGAATGGATCGGCTACATCTACTACAGCGGCAGCA CCTACTACAACCCCAGCCTGAAGTCCAGAGTGACC ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCT GAAGCTGAGCAGCGTGACAGCCGCCGACACCGCT GTGTATTACTGTGCGAGACACTACTACTACTACTA CATGGACGTCTGGGGCAAAGGGACCACGGTCACC GTGTCCTCAGGCGGAGGTGGAAGCGGAGGGGGAG GATCTGGCGGCGGAGGAAGCGGAGGCGACATCCA GATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGT AGGAGACAGAGTCACCATCACTTGCCGGGCAAGTC AGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGC TGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCATCAGCAGTCTGCAACCTGAAGATTTTGCAAC TTACTACTGTCAACAGAGTTACAGTACCCCTCTCAC TTTCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 131)
HLA-C*07 antigen binding domains	
C7-45	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA VSFDWFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS SLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 570)
C7-44	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR ERSISPYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 571)
C7-43	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWI GSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDS VIWYWFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGQSVLTQPPS ASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSG VPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTK LTVL (SEQ ID NO: 572)
C7-42	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EEILPRLSYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 573)
C7-41	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYAMNWVRQAPGQGLE WMGWINTNTGNPTYAQGFTGRFVFSFDTSVSTAYLQICSLKAEDTAVY YCARGGRAHSSWYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 574)
C7-40	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR

	DRIKILPRLGYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 575)
C7-39	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DTVIHYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 576)
C7-38	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DVIVEVFLSYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 577)
C7-37	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DIFIHYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQ SPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 578)
C7-36	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEW VSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR DGTFYSYSPYYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 579)
C7-35	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EWIKILPRLGYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 580)
C7-34	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DRSLYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 581)
C7-33	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DKILAPNYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 582)
C7-32	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EKSWKYFYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS

	SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 583)
C7-31	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR ENTSTIPYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 584)
C7-30	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EDVDKNTSTIYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSG GDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 585)
C7-29	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEW VSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR DGGDIVSSSAIYWYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGAI QLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDAS SLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPLTFGGGTK VEIK (SEQ ID NO: 586)
C7-28	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DLILPPYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 587)
C7-27	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR ETWIKILPRYYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGG DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGG TKVEIK (SEQ ID NO: 588)
C7-26	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DLSRYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 589)
C7-25	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEW VSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR EHIVLCFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSS LSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKVEIK (SEQ ID NO: 590)
C7-24	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DKILPRPYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASS LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 591)

C7-23	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEW MGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVY YCARGSNEYFQHWGQGTLVTVSSGGGGSGGGGSGGGGSGGQSALTQ PPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVS KRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNWVFG GGTKLTVL (SEQ ID NO: 592)
C7-22	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYAMNWVRQAPGQGLE WMGWINTNTGNPTYAQGFTGRFVFSFDTSVSTAYLQICSLKAEDTAVY YCARGTSYWYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 593)
C7-21	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EEIVEVFYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 594)
C7-20	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA KVDDYYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS SLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 595)
C7-19	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAPGKGLV WVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYY CAWSTNILLSYTKAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 596)
C7-18	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DKTYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 597)
C7-17	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EKYFHDKYFHDYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSG GDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGG GTKVEIK (SEQ ID NO: 598)
C7-16	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DTSVYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQS GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 599)
C7-15	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EKILPYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM

	TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 600)
C7-14	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAIQWIYIYINPRGFIFLHDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGQSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGWVFGGGTKLTVL (SEQ ID NO: 601)
C7-13	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCAKEDVDFHHDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 602)
C7-12	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAREGVDKNTSTIYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 603)
C7-11	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRRGYFDLWGRGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKVEIK (SEQ ID NO: 604)
C7-10	EVQLVQSGAEVKKPGATVKISCKVSGYTFTDYYMHWVQQAPGKGLEWMGLVDPEDGETIYAEKFQGRVTITADTSTDTAYMELSSLRSEDTAVYYCATGIHVDIRSMEDWFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 605)
C7-9	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDIGTSYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 606)
C7-8	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAREVVEVFLYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 607)
C7-7	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDLYYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 608)

C7-6	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR ESWKYFYPRGSIFIHYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGG SGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTF GGGTKVEIK (SEQ ID NO: 609
C7-5	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DRIVEVFYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQ SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEI K (SEQ ID NO: 610)
C7-4	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR EKYFHDWLYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 611)
C7-3	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPPGKGLE WIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAR DLVDKNTSYYYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAAS SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTK VEIK (SEQ ID NO: 612)
C7-2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEW MGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVY YCARVQNEYFQHWGQGTLVTVSSGGGGSGGGGSGGGGSGGQSALT QPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEV SKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNWVF GGGTKLTVL (SEQ ID NO: 613)
C7-1	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEW VSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAT ANWFDPWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSSV SASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 614)
HLA-A*03 scFv Sequences	
15	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARERVSQRGA FDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGDIQM TQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 615)
16	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNW VRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARGNPDKDPFDY WGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQS PSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP

	KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 616)
17	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGSYYWS WIRQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDFYCTNWYFDL WGRGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQS PSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 617)
18	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWI RQPPGKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSK NQFSLKLSSVTAADTAVYYCARESSSGSYWYFDLWG RGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSS LSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 618)
19	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGW VRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARDSGYKYNLYY YYYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSG GDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 619)
20	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARGGDLSHYY YYYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGQ TVVTQEPSLTVSPGGTVTLTCASSTGAVTSGYYPNWF QQKPGQAPRALIYSTSNKHSWTPARFSGSLLGGKAA LTLSGVQPEDEAEYYCLLYYGGAQWVFGGGTKLTV L (SEQ ID NO: 620)
21	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARENRRYNSC YYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 621)
22	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARGGDLSHYY YYLDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGQT VVTQEPSLTVSPGGTVTLTCASSTGAVTSGYYPNWF QQKPGQAPRALIYSTSNKHSWTPARFSGSLLGGKAA LTLSGVQPEDEAEYYCLLYYGGAQWVFGGGTKLTV L (SEQ ID NO: 622)
23	EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSW VRQAPGKGLEWVSVIYSGGSTYYADSVKGRFTISRD

	NSKNTLYLQMNSLRAEDTAVYYCARATLLSLSYDAF DIWGQGTMVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGK APKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 623)
24	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARGGDLSHYY YMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGQT VVTQEPSLTVSPGGTVTLTCASSTGAVTSGYYPNWF QQKPGQAPRALIYSTSNKHSWTPARFSGSLLGGKAA LTLSGVQPEDEAEYYCLLYYGGAQWVFGGGTKLTV L (SEQ ID NO: 624)
25	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGW VRQMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARERDRWFDPWG QGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPSS LSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 625)
26	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARETPPSLGAF DIWGQGTMVTVSSGGGGSGGGGSGGGGSGGQSALT QPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHP GKAPKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSG LQAEDEADYYCSSYAGSNNWVFGGGTKLTVL (SEQ ID NO: 626)
27	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWG WIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCAREAYCLSDSYWYF DLWGRGTLVTVSSGGGGSGGGGSGGGGSGGQSVLT QPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPG TAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQ SEDEADYYCAAWDDSLNGWVFGGGTKLTVL (SEQ ID NO: 627)
28	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARESWKYFYPRGY MDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKP GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 628)
HLA-A*01 scFv Sequences	
A1-9	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISW VRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTM TTDTSTSTAYMELRSLRSDDTAVYYCARGGWTAWY YYMDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGQ

	TVVTQEPSLTVSPGGTVTLTCASSTGAVTSGYYPNWF QQKPGQAPRALIYSTSNKHSWTPARFSGSLLGGKAA LTLSGVQPEDEAEYYCLLYYGGAQWVFGGGTKLTV L (SEQ ID NO: 629)
A1-8	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNW VRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYCARAKYYYMDVW GKGTTVTVSSGGGGSGGGGSGGGGSGGQSVLTQPPS ASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPK LLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDE ADYYCAAWDDSLNGWVFGGGTKLTVL (SEQ ID NO: 630)
A1-7	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDQVDKNTYYYY MDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKP GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 631)
A1-6	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSW IRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARACQLAEYFQHW GQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS SVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQANSFPLTFGGGTKVEIK (SEQ ID NO: 632)
A1-5	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWS WIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTISVDT SKNQFSLKLSSVTAADTAVYYCARDRVDKNTSYYY MDVWGKGTTVTVSSGGGGSGGGGSGGGGSGGDIQ MTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKP GKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 633)
A1-4	QVQLQESGPGLVKPSDTLSLTCAVSGYSISSSNWWG WIRQPPGKGLEWIGYIYYSGSTYYNPSLKSRVTMSVD TSKNQFSLKLSSVTAVDTAVYYCARRVQLKLVHWF DPWGQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMT QSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGK APKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 634)
A1-3	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINW VRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVT MTRNTSISTAYMELSSLRSEDTAVYYCATYYDYVTV FYFQHWGQGTLVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL

	QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 635)
A1-2	QLQLQESGSGLVKPSQTLSLTCAVSGGSISSGGYSWS WIRQPPGKGLEWIGYIYHSGSTYYNPSLKSRVTISVD RSKNQFSLKLSSVTAADTAVYYCARESYPSFYAFDIW GQGTMVTVSSGGGGSGGGGSGGGGSGGDIQMTQSP SSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPK LLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 636)
A1-1	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGW IRQPPGKALEWLALIYWNDDKRYSPSLKSRLTITKDT SKNQVVLTMTNMDPVDTATYYCAHSNMWSYSLND YYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGDI QMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQK PGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIK (SEQ ID NO: 637)

[0266] In some embodiments, the ligand binding domain of the second, inhibitory receptor comprises an scFv. In some embodiments, the scFv binds to HLA-A*01, HLA-A*02, HLA-A*3, HLA-A*11, HLA-B*07 or HLA-C*07, and comprises a sequence selected from the group of sequences set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the scFv binds to HLA-A*01, HLA-A*02, HLA-A*3, HLA-A*11, HLA-B*07 or HLA-C*07, and comprises a sequence selected from the group of sequences set forth in Table 5. In some embodiments, the non-target antigen comprises HLA-A*01, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-A*01 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-A*02, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-A*02 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-A*03, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-A*03 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-A*11, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-A*11 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at

least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-B*07, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-B*07 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-C*07, and the non-target extracellular ligand binding domain of the second receptor comprises an HLA-C*07 scFv sequence set forth in Table 5, or a sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0267] Exemplary heavy chain and light chain CDRs (CDR-H1, CDR-H2 and CDR-H3, or CDR-L1, CDR-L2 and CDR-L3, respectively) for HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11, HLA-B*07 and HLA-C*07 ligand binding domains are shown in Table 6 below.

Table 6: CDRs corresponding to HLA antigen binding domains

CDR-L1	**CDR-L2**	**CDR-L3**	**CDR-H1**	**CDR-H2**	**CDR-H3**
RSSQSIVHSNGNTYLE (SEQ ID NO: 42)	KVSNRFSGVPDR (SEQ ID NO: 43)	FQGSHVPRT (SEQ ID NO: 44)	ASGYTFTSYHIH (SEQ ID NO: 45)	WIYPGNVNTEYNEKFKGK (SEQ ID NO: 46)	EEITYAMDY (SEQ ID NO: 47)
RSSQSIVHSNGNTYLD (SEQ ID NO: 48)	KVSNRFSGVPDR (SEQ ID NO: 49)	MQGSHVPRT (SEQ ID NO: 50)	SGYTFTSYHMH (SEQ ID NO: 51)	WIYPGDGSTQYNEKFKG (SEQ ID NO: 52)	EGTYYAMDY (SEQ ID NO: 53)
HLA-A*03 CDRs					
RASQSISSYLN (SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYGIS (SEQ ID NO: 657)	WISAYNGNTNYAQKLQG (SEQ ID NO: 676)	ERVSQRGAFDI (SEQ ID NO: 693)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYYADSVKG (SEQ ID NO: 677)	GNPDKDPFDY (SEQ ID NO: 694)

RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGSYYWS (SEQ ID NO: 659)	YIYYSGSTNY NPSLKS (SEQ ID NO: 678)	DFYCTNWYF DL (SEQ ID NO: 695)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYYWS (SEQ ID NO: 660)	YIYYSGSTNY NPSLKS (SEQ ID NO: 678)	ESSSGSYWY FDL (SEQ ID NO: 696)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYWIG (SEQ ID NO: 661)	IIYPGDSDTR YSPSFQG (SEQ ID NO: 679)	DSGYKYNLY YYYYYMDV (SEQ ID NO: 697)
ASSTGAVTS GYYPN (SEQ ID NO: 639)	STSNKHS (SEQ ID NO: 646)	LLYYGGAQ WV (SEQ ID NO: 651)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	GGDLSHYYY YMDV (SEQ ID NO: 698)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	ENRRYNSCY YFDY (SEQ ID NO: 699)
ASSTGAVTS GYYPN (SEQ ID NO: 639)	STSNKHS (SEQ ID NO: 646)	LLYYGGAQ WV (SEQ ID NO: 651)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	GGDLSHYYY YLDV (SEQ ID NO: 700)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SNYMS (SEQ ID NO: 662)	VIYSGGSTYY ADSVKG (SEQ ID NO: 680)	ATLLSLSYDA FDI (SEQ ID NO: 701)
ASSTGAVTS GYYPN (SEQ ID NO: 639)	STSNKHS (SEQ ID NO: 646)	LLYYGGAQ WV (SEQ ID NO: 651)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG	GGDLSHYYY MDV (SEQ ID NO: 702)

				(SEQ ID NO: 676)	
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYWIG (SEQ ID NO: 661)	IIYPGDSDTR YSPSFQG (SEQ ID NO: 679)	ERDRWFDP (SEQ ID NO: 703)
TGTSSDVGG YNYVS (SEQ ID NO: 640)	EVSKRPS (SEQ ID NO: 647)	SSYAGSNN WV (SEQ ID NO: 652)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	ETPPSLGAF DI (SEQ ID NO: 704)
SGSSSNIGS NTVN (SEQ ID NO: 641)	SNNQRPS (SEQ ID NO: 648)	AAWDDSLN GWV (SEQ ID NO: 653)	SSSYYWG (SEQ ID NO: 663)	SIYYSGSTYY NPSLKS (SEQ ID NO: 681)	EAYCLSDSY WYFDL (SEQ ID NO: 705)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	ESWKYFYPR GYMDV (SEQ ID NO: 706)
HLA-B*07 CDRs					
RASENIYSNL A (SEQ ID NO: 642)	AATYLPD (SEQ ID NO: 649)	QHFWVTPY T (SEQ ID NO: 654)	SGYSWH (SEQ ID NO: 665)	YIHFSGSTHY HPSLKS (SEQ ID NO: 683)	GGVVSHYA MDC (SEQ ID NO: 707)
HLA-C*07 CDRs					
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYAMS (SEQ ID NO: 668)	AISGSGGSTY YADSVKG (SEQ ID NO: 686)	SFDWFDP (SEQ ID NO: 708)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS	ERSISPYYYY YMDV (SEQ ID NO: 709)

				(SEQ ID NO: 682)	
SGSSSNIGS NTVN (SEQ ID NO: 641)	SNNQRPS (SEQ ID NO: 648)	AAWDDSLN GWV (SEQ ID NO: 653)	SSSYYWG (SEQ ID NO: 663)	SIYYSGSTYY NPSLKS (SEQ ID NO: 681)	DSVIWYWF DP (SEQ ID NO: 710)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EEILPRLSYYY YMDV (SEQ ID NO: 711)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYAMN (SEQ ID NO: 669)	WINTNTGN PTYAQGFTG (SEQ ID NO: 687)	GGRAHSSW YFDL (SEQ ID NO: 712)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DRIKILPRLG YYYYMDV (SEQ ID NO: 713)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DTVIHYYYY MDV (SEQ ID NO: 714)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DVIVEVFLSY YYYMDV (SEQ ID NO: 715)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DIFIHYYYYM DV (SEQ ID NO: 716)

RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYY ADSVKG (SEQ ID NO: 677)	DGTFYSYSPY YFDY (SEQ ID NO: 717)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EWIKILPRLG YYYYMDV (SEQ ID NO: 718)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DRSLYYYYY MDV (SEQ ID NO: 719)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DKILAPNYYY YMDV (SEQ ID NO: 720)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EKSWKYFYY YYYYMDV (SEQ ID NO: 721)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	ENTSTIPYYY YYMDV (SEQ ID NO: 722)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EDVDKNTST IYYYYYYMD V (SEQ ID NO: 723)
RASQGISSAL A (SEQ ID NO: 643)	DASSLES (SEQ ID NO: 55)	QQFNSYPLT (SEQ ID NO: 60)	DYYMS (SEQ ID NO: 670)	YISSSGSTIYY ADSVKG	DGGDIVSSS AIYWYFDL

				(SEQ ID NO: 688)	(SEQ ID NO: 724)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DLILPPYYYY YMDV (SEQ ID NO: 725)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	ETWIKILPRY YYYYYYMDV (SEQ ID NO: 726)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DLSRYYYYY MDV (SEQ ID NO: 727)
RASQGISSW LA (SEQ ID NO: 644)	AASSLQS (SEQ ID NO: 645)	QQYNSYPLT (SEQ ID NO: 655)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYY ADSVKG (SEQ ID NO: 677)	EHIVLCFDY (SEQ ID NO: 728)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DKILPRPYYY YYMDV (SEQ ID NO: 729)
TGTSSDVGG YNYVS (SEQ ID NO: 640)	EVSKRPS (SEQ ID NO: 647)	SSYAGSNN WV (SEQ ID NO: 652)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	GSNEYFQH (SEQ ID NO: 730)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYAMN (SEQ ID NO: 669)	WINTNTGN PTYAQGFTG (SEQ ID NO: 687)	GTSYWYFDL (SEQ ID NO: 731)

RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EEIVEVFYYY YMDV (SEQ ID NO: 732)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYAMS (SEQ ID NO: 668)	AISGSGGSTY YADSVKG (SEQ ID NO: 686)	VDDYYFDY (SEQ ID NO: 733)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYWMH (SEQ ID NO: 667)	RINSDGSSTS YADSVKG (SEQ ID NO: 685)	STNILLSYTK AFDI (SEQ ID NO: 734)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DKTYYYYYY MDV (SEQ ID NO: 735)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EKYFHDKYF HDYYYYYM DV (SEQ ID NO: 736)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DTSVYYYYY MDV (SEQ ID NO: 737)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EKILPYYYYY YMDV (SEQ ID NO: 738)
SGSSSNIGS NTVN (SEQ ID NO: 641)	SNNQRPS (SEQ ID NO: 648)	AAWDDSLN GWV (SEQ ID NO: 653)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYY ADSVKG	QWIYIYINPR GFIFLHDAF

				(SEQ ID NO: 677)	DI (SEQ ID NO: 739)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SNSAAWN (SEQ ID NO: 671)	RTYYRSKWY NDYAVSVKS (SEQ ID NO: 689)	EDVDFHHD AFDI (SEQ ID NO: 740)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EGVDKNTST IYYYYYYMD V (SEQ ID NO: 741)
RASQGISSW LA (SEQ ID NO: 644)	AASSLQS (SEQ ID NO: 645)	QQYNSYPLT (SEQ ID NO: 655)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYY ADSVKG (SEQ ID NO: 677)	DRRGYFDL (SEQ ID NO: 742)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	DYYMH (SEQ ID NO: 672)	LVDPEDGETI YAEKFQG (SEQ ID NO: 690)	GIHVDIRSM EDWFDP (SEQ ID NO: 743)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DIGTSYYYY MDV (SEQ ID NO: 744)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EVVEVFLYYY YYMDV (SEQ ID NO: 745)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DLYYYYYYY MDV (SEQ ID NO: 746)

RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	ESWKYFYPR GSIFIHYYYY MDV (SEQ ID NO: 747)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DRIVEVFYYY YMDV (SEQ ID NO: 748)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	EKYFHDWLY YYYYMDV (SEQ ID NO: 749)
RASQSISSYL N(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYY NPSLKS (SEQ ID NO: 682)	DLVDKNTSY YYYYMDV (SEQ ID NO: 750)
TGTSSDVGG YNYVS (SEQ ID NO: 640)	EVSKRPS (SEQ ID NO: 647)	SSYAGSNN WV (SEQ ID NO: 652)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	VQNEYFQH (SEQ ID NO: 751)
RASQGISSW LA (SEQ ID NO: 644)	AASSLQS (SEQ ID NO: 645)	QQANSFPLT (SEQ ID NO: 656)	DYYMS (SEQ ID NO: 670)	YISSSGSTIYY ADSVKG (SEQ ID NO: 688)	ANWFDP (SEQ ID NO: 752)
HLA-A*01 CDRs					
ASSTGAVTS GYYPN (SEQ ID NO: 639)	STSNKHS (SEQ ID NO: 646)	LLYYGGAQ WV (SEQ ID NO: 651)	SYGIS (SEQ ID NO: 657)	WISAYNGNT NYAQKLQG (SEQ ID NO: 676)	GGWTAWYY YMDV (SEQ ID NO: 753)

SGSSSNIGSNTVN (SEQ ID NO: 641)	SNNQRPS (SEQ ID NO: 648)	AAWDDSLNGWV (SEQ ID NO: 653)	SYSMN (SEQ ID NO: 658)	YISSSSSTIYYADSVKG (SEQ ID NO: 677)	AKYYYMDV (SEQ ID NO: 754)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYYNPSLKS (SEQ ID NO: 682)	DQVDKNTYYYYMDV (SEQ ID NO: 755)
RASQGISSWLA (SEQ ID NO: 644)	AASSLQS (SEQ ID NO: 645)	QQANSFPLT (SEQ ID NO: 656)	DYYMS (SEQ ID NO: 670)	YISSSGSTIYYADSVKG (SEQ ID NO: 688)	ACQLAEYFQH (SEQ ID NO: 756)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYYWS (SEQ ID NO: 664)	YIYYSGSTYYNPSLKS (SEQ ID NO: 682)	DRVDKNTSYYYMDV (SEQ ID NO: 757)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SSNWWG (SEQ ID NO: 673)	YIYYSGSTYYNPSLKS (SEQ ID NO: 682)	RVQLKLVHWFDP (SEQ ID NO: 758)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SYDIN (SEQ ID NO: 674)	WMNPNSGNTGYAQKFQG (SEQ ID NO: 691)	YYDYVTVFYFQH (SEQ ID NO: 759)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	SGGYSWS (SEQ ID NO: 675)	YIYHSGSTYYNPSLKS (SEQ ID NO: 692)	ESYPSFYAFDI (SEQ ID NO: 760)
RASQSISSYLN(SEQ ID NO: 638)	AASSLQS (SEQ ID NO: 645)	QQSYSTPLT (SEQ ID NO: 650)	TSGVGVG (SEQ ID NO: 666)	LIYWNDDKRYSPSLKS	SNMWSYSLNDYYFDY

				(SEQ ID NO: 684)	(SEQ ID NO: 761)

[0268] In some embodiments, the non-target antigen comprises HLA-A. In some embodiments, the ligand binding domain of the second, inhibitory receptor comprises an HLA-A*01, HLA-A*02, HLA-A*03 or HLA-A*11 ligand binding domain comprising CDR sequences as set forth in Table 6 or Table 7.

[0269] In some embodiments, the non-target antigen comprises HLA-B. In some embodiments, the ligand binding domain of the second, inhibitory receptors comprises an HLA-B*07 ligand binding domain comprising CDR sequences as set forth in Table 6.

[0270] In some embodiments, the non-target antigen comprises HLA-C. In some embodiments, the ligand binding domain of the second, inhibitory receptors comprises an HLA-C*07 ligand binding domain comprising CDR sequences as set forth in Table 6.

[0271] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds an allelic variant of an HLA-A, HLA-B, or HLA-C protein. In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11, HLA-B*07, or HLA-C*07.

[0272] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*01. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-A*01 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-A*01 CDRs of Table 6.

[0273] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*02. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-A*02 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-A*02 CDRs of Table 6.

[0274] In some embodiments, the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOS: 103-108 or of SEQ ID NOS: 109-114; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertion relative to the CDRs of SEQ ID NOS: 103-108 or SEQ ID NOS: 109-114.

[0275] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*03. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-A*03 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-A*03 CDRs of Table 6.

[0276] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-A*11. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-A*11 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 7; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-A*11 CDRs of Table 7.

[0277] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-B*07. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-B*07 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-B*07 CDRs of Table 6.

[0278] In some embodiments, the extracellular ligand binding domain of the second receptor specifically binds to HLA-C*07. In some embodiments, the extracellular ligand binding domain of the second receptor comprises HLA-C*07 complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 as disclosed Table 6; or CDR sequences having at most 1, 2, or 3 substitutions, deletions, or insertions relative to the HLA-C*07 CDRs of Table 6.

[0279] In further embodiments of any of the ligand binding domains, each CDR sequence may have 1, 2, 3 or more substitutions, insertions, or deletions. CDR sequences may tolerate substitutions, deletions, or insertions. Using sequence alignment tools, routine experimentation, and known assays, those of skill in the art may generate and test variant sequences having 1, 2, 3, or more substitutions, insertions, or deletions in CDR sequences without undue experimentation.

[0280] In some embodiments, the non-target antigen comprising HLA-A*02, and the ligand binding domain of the second receptor comprises an HLA-A*02 ligand binding domain. In some embodiments, the ligand binding domain binds HLA-A*02 independent of the peptide in a pMHC complex comprising HLA-A*02. In some embodiments, the HLA-A*02 ligand

binding domain comprises an scFv domain. In some embodiments, the HLA-A*02 ligand binding domain comprises a sequence of any one of SEQ ID NOs: 30-41. In some embodiments, the HLA-A*02 ligand binding domain comprises a sequence at least 90%, at least 95%, at least 97% or at least 99% identical to a sequence of any one of SEQ ID NOs: 30-41.

[0281] In some embodiments, the non-target antigen comprises HLA-A*02, and the extracellular ligand binding domain of the second receptor comprises a sequence of SEQ ID NO: 30, or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-A*02, and the extracellular ligand binding domain of the second receptor comprises a sequence of SEQ ID NO: 30.

[0282] In some embodiments, the non-target antigen comprises HLA-A*02, and the extracellular ligand binding domain of the second receptor comprises a VL comprising a sequence of DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPRTSGGGTKLEIK (SEQ ID NO: 762), or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto. In some embodiments, the extracellular ligand binding domain of the second receptor comprises a VH comprising a sequence of QVQLQQSGPELVKPGASVRISCKASGYTFTSYHIHWVKQRPGQGLEWIGWIYPGNVNTEYNEKFKGKATLTADKSSSTAYMHLSSLTSEDSAVYFCAREEITYAMDYWGQGTSVTVSS (SEQ ID NO: 763), or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto. In some embodiments, the VH and VL are separated by a linker, for example GGGGSGGGGSGGGGSGG (SEQ ID NO: 152). In some embodiments, the VH and VL are ordered, from N to C terminal, VH, linker and VL. In some embodiments, the VH and VL are ordered, from N to C terminal, VL, linker and VH.

[0283] In some embodiments, the HLA-A*02 scFv comprises the complementarity determined regions (CDRs) of any one of SEQ ID NOS: 42-53. In some embodiments, the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 42-53. In some embodiments, the scFv comprises a sequence identical to any one of SEQ ID NOS: 42-53. In some embodiments, the heavy chain of the antigen binding domain comprises the heavy chain CDRs of any one of SEQ ID NOS: 42-53, and wherein the light chain of the antigen binding domain comprises the light chain CDRs of any one of SEQ ID NOS: 42-53. In some embodiments, the HLA-A*02 antigen binding domain comprises a heavy chain and a light

chain, and the heavy chain comprises CDRs selected from SEQ ID NOs: 45-47 and 51-53 and the light chain comprises CDRs selected from SEQ ID NOs: 42-44 and 48-50.

[0284] In some embodiments, the HLA-A*02 antigen binding domain comprises a heavy chain and a light chain, and the heavy chain comprises a sequence at least 95% identical to the heavy chain portion of any one of SEQ ID NOS: 30-41, and the light chain comprises a sequence at least 95% identical to the light chain portion of any one of SEQ ID NOS: 30-41.

[0285] In some embodiments, the heavy chain comprises a sequence identical to the heavy chain portion of any one of SEQ ID NOS: 30-41, and wherein the light chain of comprises a sequence identical to the light chain portion of any one of SEQ ID NOS: 30-41.

[0286] In some embodiments, the non-target antigen comprises HLA-A*01, and the extracellular ligand binding domain of the second receptor comprises an HLA-A*01 ligand binding domain. In some embodiments, the HLA-A*01 ligand binding domain comprises an scFv domain comprising a sequence selected from the group of sequences set forth in Table 5, or a sequence at least 90%, at least 95% or at least 99% identical to thereto. In some embodiments, the HLA-A*01 scFv comprises HLA-A*1 CDR sequences as set forth in Table 6.

[0287] In some embodiments, the non-target antigen comprises HLA-A*03, and the extracellular ligand binding domain of the second receptor comprises an HLA-A*03 ligand binding domain. In some embodiments, the HLA-A*03 ligand binding domain comprises an scFv domain comprising a sequence selected from the group of sequences set forth in Table 5, or a sequence at least 90%, at least 95% or at least 99% identical to thereto. In some embodiments, the HLA-A*03 scFv comprises HLA-A*03 CDR sequences as set forth in Table 6.

[0288] In some embodiments, the non-target antigen comprises HLA-A*11, and the extracellular ligand binding domain of the second receptor comprises an HLA-A*11 ligand binding domain. In some embodiments, the HLA-A*11 ligand binding domain comprises an scFv domain comprising a sequence selected from the group of sequences set forth in Table 5, or a sequence at least 90%, at least 95% or at least 99% identical to thereto. In some embodiments, the HLA-A*11 scFv comprises HLA-A*11 CDR sequences as set forth in Table 7.

[0289] In some embodiments, the non-target antigen comprises HLA-B*07, and the extracellular ligand binding domain of the second receptor comprises an HLA-B*07 ligand binding domain. In some embodiments, the HLA-B*07 ligand binding domain comprises an scFv domain comprising a sequence selected from the group of sequences set forth in Table

5, or a sequence at least 90%, at least 95% or at least 99% identical to thereto. In some embodiments, the HLA-B*07 scFv comprises HLA-B*07 CDR sequences as set forth in Table 6.

[0290] In some embodiments, the non-target antigen comprises HLA-C*07, and the extracellular ligand binding domain of the second receptor comprises an HLA-C*07 ligand binding domain. In some embodiments, the HLA-C*07 ligand binding domain comprises an scFv domain comprising a sequence selected from the group of sequences set forth in Table 5, or a sequence at least 90%, at least 95% or at least 99% identical to thereto. In some embodiments, the HLA-C*07 scFv comprises HLA-C*07 CDR sequences as set forth in Table 6.

[0291] In some embodiments, the non-target antigen comprises HLA-A*11. Various single variable domains known in the art or disclosed herein that bind to and recognize HLA-A*11 are suitable for use in embodiments. Such scFvs include, for example and without limitation, the following mouse and humanized scFv antibodies that bind HLA-A*11 in a peptide-independent way shown in Table 5 supra.

[0292] Exemplary heavy chain and light chain CDRs (CDR-H1, CDR-H2 and CDR-H3, or CDR-L1, CDR-L2 and CDR-L3, respectively) for HLA-A*11 ligand binding domains are shown in Table 7 below. Any of the VH CDRs in Table 7 and may be combined with the VL CDRs disclosed in Table 7.

Table 7: Exemplary anti-HLA-A*11 CDR Sequences

CDR H1	**CDR H2**	**CDR H3**
SGGYYWS (SEQ ID NO: 92)	YIYYSGSTYYNPSLKS (SEQ ID NO: 97)	HYYYYYMDV (SEQ ID NO: 105)
TSGVGVG (SEQ ID NO: 93)	LIYWNDDKRYSPSLKS (SEQ ID NO: 98)	KTTSFYFDY (SEQ ID NO: 106)
SGGYYWS (SEQ ID NO: 92)	YIYYSGSTYYNPSLKS (SEQ ID NO: 97)	HYYYYMDV (SEQ ID NO: 104)
SYWMH (SEQ ID NO: 96)	RINSDGSSTSYADSVKG (SEQ ID NO: 101)	GVLLYNWFDP (SEQ ID NO: 110)
SGGYYWS (SEQ ID NO: 92)	YIYYSGSTYYNPSLKS (SEQ ID NO: 97)	HYYYYYLDV (SEQ ID NO: 103)
SYDMH (SEQ ID NO: 95)	AIGTAGDTYYPGSVKG (SEQ ID NO: 100)	DLPGSYWYFDL (SEQ ID NO: 109)
SYAMH (SEQ ID NO: 94)	WINAGNGNTKYSQKFQG (SEQ ID NO: 99)	EGNGANPDAFDI (SEQ ID NO: 108)

TSGVGVG (SEQ ID NO: 93)	LIYWNDDKRYSPSLKS (SEQ ID NO: 98)	RHMRLSCFDY (SEQ ID NO: 107)
SGGYYWS (SEQ ID NO: 92)	YIYYSGSTYYNPSLKS (SEQ ID NO: 97)	HYYYYSMDV (SEQ ID NO: 102)
CDR1 LC	**CDR2 LC**	**CDR3 LC**
RASQSISSYLN (SEQ ID NO: 111)	AASSLQS (SEQ ID NO: 112)	QQSYSTPLT (SEQ ID NO: 113)

[0293] In some embodiments, the non-target antigen comprising HLA-A*11, and the ligand binding domain of the second receptor comprises an HLA-A*11 ligand binding domain. In some embodiments, the ligand binding domain binds HLA-A*11 independent of the peptide in a pMHC complex comprising HLA-A*11. In some embodiments, the HLA-A*11 ligand binding domain comprises an scFv domain. In some embodiments, the HLA-A*11 ligand binding domain comprises a sequence of any one of SEQ ID NOs: 114-122. In some embodiments, the HLA-A*11 ligand binding domain comprises a sequence at least 90%, at least 95% or at least 99% identical to a sequence of any one of SEQ ID NOs: 114-122.

[0294] In some embodiments, the HLA-A*11 scFv comprises the complementarity determined regions (CDRs) of any one of SEQ ID NOS: 114-122. In some embodiments, the scFv comprises a sequence at least 95% identical to any one of SEQ ID NOS: 114-122. In some embodiments, the scFv comprises a sequence identical to any one of SEQ ID NOS: 114-122. In some embodiments, the heavy chain of the antigen binding domain comprises the heavy chain CDRs of any one of SEQ ID NOS: 132-140, and wherein the light chain of the antigen binding domain comprises the light chain CDRs of SEQ ID NO: 141. In some embodiments, the HLA-A*11 antigen binding domain comprises a heavy chain and a light chain, and the heavy chain comprises one, two, or three CDRs selected from SEQ ID NOs: 92-110 and the light chain comprises one, two or three CDRs selected from SEQ ID NOs: 111-113.

[0295] Exemplary heavy and light chain sequences for HLA-A*11 antigen binding domains are provided in Table 8, below. In some embodiments, the HLA-A*11 antigen binding domain comprises a heavy chain and a light chain, and the heavy chain comprises a sequence at least 95% identical to the heavy chain portion of any one of SEQ ID NOS: 132-140, and the light chain comprises a sequence at least 95% identical to the light chain portion of SEQ ID NO: 141.

[0296] In some embodiments, the heavy chain comprises a sequence identical to the heavy chain portion of any one of SEQ ID NOS: 114-122, and wherein the light chain of comprises a sequence identical to the light chain portion of any one of SEQ ID NOS: 114-122.

Table 8: Exemplary anti-HLA-A*11 heavy and light chain sequences

scFv	Protein Sequence	DNA Sequence
Heavy Chain Sequences		
9	QVQLQESGPGL VKPSQTLSLTCT VSGGSISSGGYY WSWIRQPPGKG LEWIGYIYYSGS TYYNPSLKSRV TISVDTSKNQFS LKLSSVTAADT AVYYCARHYY YYSMDVWGKG TTVTVSS (SEQ ID NO: 132)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCT GGTGAAACCCAGCCAGACCCTGAGCCTGACCT GCACAGTGTCCGGCGGCTCGATCAGCAGCGGC GGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCT ACTACAGCGGCAGCACCTACTACAACCCCAGC CTGAAGTCCAGAGTGACCATCAGCGTGGACAC CAGCAAGAACCAGTTCAGCCTGAAGCTGAGCA GCGTGACAGCCGCCGACACCGCTGTGTATTAC TGTGCGAGACACTACTACTACTACTCCATGGA CGTCTGGGGCAAAGGGACCACGGTCACCGTGT CCTCA (SEQ ID NO: 142)
8	QITLKESGPTLV KPTQTLTLTCTF SGFSLSTSGVGV GWIRQPPGKAL EWLALIYWNDD KRYSPSLKSRLT ITKDTSKNQVV LTMTNMDPVDT ATYYCAHRHM RLSCFDYWGQG TLVTVSS (SEQ ID NO: 133)	CAGATCACCCTGAAAGAGTCCGGCCCCACCCT GGTGAAACCCACCCAGACCCTGACCCTGACAT GCACCTTCAGCGGCTTCAGCCTGAGCACCTCT GGCGTGGGCGTGGGCTGGATCAGACAGCCTCC CGGCAAGGCCCTGGAATGGCTGGCCCTGATCT ACTGGAACGACGACAAGCGGTACAGCCCCAGC CTGAAGTCCCGGCTGACCATCACCAAGGACAC CTCGAAGAACCAGGTGGTGCTGACCATGACAA ACATGGACCCCGTGGACACCGCCACATATTAC TGTGCACACAGACACATGCGTTTAAGCTGTTTT GACTACTGGGGCCAGGGAACCCTGGTCACCGT GTCCTCA (SEQ ID NO: 143)
7	QVQLVQSGAEV KKPGASVKVSC KASGYTFTSYA MHWVRQAPGQ RLEWMGWINA GNGNTKYSQKF QGRVTITRDTSA STAYMELSSLRS EDTAVYYCARE GNGANPDAFDI WGQGTMVTVS S (SEQ ID NO: 134)	CAGGTGCAGCTGGTGCAGTCTGGCGCCGAAGT GAAGAAACCTGGCGCCTCCGTGAAGGTGTCCT GCAAGGCCAGCGGCTACACCTTCACCAGCTAC GCCATGCACTGGGTTCGACAGGCCCCTGGCCA GAGACTGGAATGGATGGGCTGGATCAACGCCG GCAACGGCAACACCAAGTACAGCCAGAAATTC CAGGGCAGAGTGACCATCACCCGGGACACCAG CGCCAGCACCGCCTACATGGAACTGAGCAGCC TGCGGAGCGAGGACACCGCTGTGTATTACTGT GCGAGAGAAGGAAATGGTGCCAACCCTGATGC TTTTGATATCTGGGGCCAAGGGACAATGGTCA CCGTGTCCTCA (SEQ ID NO: 144)
6	EVQLVESGGGL VQPGGSLRLSC AASGFTFSSYD MHWVRQATGK GLEWVSAIGTA	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCC TGGTGCAGCCTGGCGGCAGCCTGAGACTGTCT TGCGCCGCCAGCGGCTTCACCTTCAGCAGCTA CGACATGCACTGGGTCCGCCAGGCCACCGGCA AGGGACTGGAATGGGTGTCCGCCATCGGCACA

scFv	Protein Sequence	DNA Sequence
5	GDTYYPGSVKG RFTISRENAKNS LYLQMNSLRAG DTAVYYCARDL PGSYWYFDLW GRGTLVTVSS (SEQ ID NO: 135)	GCCGGCGACACTTACTACCCCGGCAGCGTGAA GGGCCGGTTCACCATCAGCAGAGAGAACGCCA AGAACAGCCTGTACCTGCAGATGAACAGCCTT CGAGCCGGCGATACCGCCGTGTATTACTGTGC AAGAGATCTCCCTGGTAGCTACTGGTACTTCG ATCTCTGGGGCCGTGGCACCCTGGTCACTGTGT CCTCA (SEQ ID NO: 145)
5	QVQLQESGPGL VKPSQTLSLTCT VSGGSISSGGYY WSWIRQPPGKG LEWIGYIYYSGS TYYNPSLKSRV TISVDTSKNQFS LKLSSVTAADT AVYYCARHYY YYYLDVWGKG TTVTVSS (SEQ ID NO: 136)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCT GGTGAAACCCAGCCAGACCCTGAGCCTGACCT GCACAGTGTCCGGCGGCTCGATCAGCAGCGGC GGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCT ACTACAGCGGCAGCACCTACTACAACCCCAGC CTGAAGTCCAGAGTGACCATCAGCGTGGACAC CAGCAAGAACCAGTTCAGCCTGAAGCTGAGCA GCGTGACAGCCGCCGACACCGCTGTGTATTAC TGTGCGAGACACTACTACTACTACCTGGA CGTCTGGGGCAAAGGGACCACGGTCACCGTGT CCTCA (SEQ ID NO: 146)
4	EVQLVESGGGL VQPGGSLRLSC AASGFTFSSYW MHWVRQAPGK GLVWVSRINSD GSSTSYADSVK GRFTISRDNAKN TLYLQMNSLRA EDTAVYYCCLG VLLYNWFDPW GQGTLVTVSS (SEQ ID NO: 137)	GAAGTGCAGCTGGTGGAAAGCGGCGGAGGCC TGGTGCAGCCTGGCGGCAGCCTGAGACTGTCT TGCGCCGCCAGCGGCTTCACCTTCAGCAGCTA CTGGATGCACTGGGTCCGCCAGGCCCCTGGCA AGGGACTGGTCTGGGTGTCTCGAATCAACAGC GACGGCAGCAGCACCAGCTACGCCGACAGCGT GAAGGGCCGGTTCACCATCAGCCGGGACAACG CCAAGAACACCCTGTACCTGCAGATGAACAGC CTGCGGGCCGAGGACACCGCCGTGTATTACTG TTGTTTGGGTGTTTTATTATACAACTGGTTCGA CCCCTGGGGCCAGGGAACCCTGGTCACCGTGT CCTCA (SEQ ID NO: 147)
3	QVQLQESGPGL VKPSQTLSLTCT VSGGSISSGGYY WSWIRQPPGKG LEWIGYIYYSGS TYYNPSLKSRV TISVDTSKNQFS LKLSSVTAADT AVYYCARHYY YYMDVWGKGT TVTVSS (SEQ ID NO: 138)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCT GGTGAAACCCAGCCAGACCCTGAGCCTGACCT GCACAGTGTCCGGCGGCTCGATCAGCAGCGGC GGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCT ACTACAGCGGCAGCACCTACTACAACCCCAGC CTGAAGTCCAGAGTGACCATCAGCGTGGACAC CAGCAAGAACCAGTTCAGCCTGAAGCTGAGCA GCGTGACAGCCGCCGACACCGCTGTGTATTAC TGTGCGAGACACTACTACTACTACATGGACGT CTGGGGCAAAGGGACCACGGTCACCGTGTCCT CA (SEQ ID NO: 148)
2	QITLKESGPTLV KPTQTLTLTCTF SGFSLSTSGVGV GWIRQPPGKAL EWLALIYWNDD KRYSPSLKSRLT	CAGATCACCCTGAAAGAGTCCGGCCCCACCCT GGTGAAACCCACCCAGACCCTGACCCTGACAT GCACCTTCAGCGGCTTCAGCCTGAGCACCTCT GGCGTGGGCGTGGGCTGGATCAGACAGCCTCC CGGCAAGGCCCTGGAATGGCTGGCCCTGATCT ACTGGAACGACGACAAGCGGTACAGCCCCAGC

scFv	Protein Sequence	DNA Sequence
	ITKDTSKNQVV LTMTNMDPVDT ATYYCAHKTTS FYFDYWGQGTL VTVSS (SEQ ID NO: 139)	CTGAAGTCCCGGCTGACCATCACCAAGGACAC CTCGAAGAACCAGGTGGTGCTGACCATGACAA ACATGGACCCCGTGGACACCGCCACATATTAC TGTGCACACAAAACGACGTCGTTTTACTTTGAC TACTGGGGCCAGGGAACCCTGGTCACCGTGTC CTCA (SEQ ID NO: 149)
1	QVQLQESGPGL VKPSQTLSLTCT VSGGSISSGGYY WSWIRQPPGKG LEWIGYIYYSGS TYYNPSLKSRV TISVDTSKNQFS LKLSSVTAADT AVYYCARHYY YYYMDVWGKG TTVTVSS (SEQ ID NO: 140)	CAGGTGCAGCTGCAGGAAAGCGGCCCTGGCCT GGTGAAACCCAGCCAGACCCTGAGCCTGACCT GCACAGTGTCCGGCGGCTCGATCAGCAGCGGC GGCTACTACTGGTCCTGGATCAGACAGCCCCC TGGCAAGGGCCTGGAATGGATCGGCTACATCT ACTACAGCGGCAGCACCTACTACAACCCCAGC CTGAAGTCCAGAGTGACCATCAGCGTGGACAC CAGCAAGAACCAGTTCAGCCTGAAGCTGAGCA GCGTGACAGCCGCCGACACCGCTGTGTATTAC TGTGCGAGACACTACTACTACTACTACATGGA CGTCTGGGGCAAAGGGACCACGGTCACCGTGT CCTCA (SEQ ID NO: 150)
Light Chain Sequence		
1-9	DIQMTQSPSSLS ASVGDRVTITCR ASQSISSYLNWY QQKPGKAPKLLI YAASSLQSGVPS RFSGSGSGTDFT LTISSLQPEDFA TYYCQQSYSTP LTFGGGTKVEIK (SEQ ID NO: 141)	GACATCCAGATGACCCAGTCTCCATCCTCCCTG TCTGCATCTGTAGGAGACAGAGTCACCATCAC TTGCCGGGCAAGTCAGAGCATTAGCAGCTATT TAAATTGGTATCAGCAGAAACCAGGGAAAGCC CCTAAGCTCCTGATCTATGCTGCATCCAGTTTG CAAAGTGGGGTCCCATCAAGGTTCAGTGGCAG TGGATCTGGGACAGATTTCACTCTCACCATCA GCAGTCTGCAACCTGAAGATTTTGCAACTTACT ACTGTCAACAGAGTTACAGTACCCCTCTCACTT TCGGCGGCGGAACAAAGGTGGAGATCAAG (SEQ ID NO: 151)

Differentially Expressed Inhibitor Ligands

[0297] The disclosure provides inhibitor ligands (non-target antigens) that are differentially expressed between cancer cells and normal cells.

[0298] Activation of the inhibitory receptor is mediated by the presence of the non-target antigen on the surface of a cell. A cell that expresses the non-target antigen will activate the inhibitory receptor based on the level of expression of the non-target antigen. In some embodiments, the non-target antigen is expressed by both target and non-target cells. However, in these embodiments, the non-target antigen is expressed by non-target cells at a higher level than the target cells. The higher levels of non-target antigen expressed by the non-target cells activate the inhibitory receptor, thereby preventing activation of the immune cell. In contrast, the lower levels of non-target antigen expressed by the target are not sufficient to activate the inhibitory receptor, leading to activation of the immune cell.

[0299] In alternative embodiments, the non-target antigen is expressed by non-target cells but not by target cells. In the absence of expression of the non-target antigen, the target cells activate the target receptor, thereby activating the immune cells.

[0300] Differential expression can be determined by any techniques known in the art used to measure expression. These include, *inter alia*, techniques for measuring mRNA and/or protein levels of a target gene in a cell. Methods of measuring protein levels in samples include immunohistochemistry, enzyme-linked immunosorbent assays (ELISA), and analytical methods such as liquid chromatography-mass spectrometry (LC-MS). Methods of measuring mRNA levels include real time quantitative reverse transcription PCR (qRT-PCR), as well as high throughput sequencing. Expression differences can be observed between, for example, a normal cell and a diseased cell, for example a cancer cell.

[0301] Activation of the inhibitory receptor by a non-target antigen can occur according to various modalities known in the art. Activation of the inhibitory receptor by a non-target antigen can be determined by methods known in the art. For example, the level of downstream intracellular signaling in a cell expressing the inhibitory receptor can be measured through the use of a reporter gene.

[0302] Without wishing to be bound by theory, whether or not expression of a non-target antigen inhibits activation of an immune cell via activation of the inhibitory receptor can occur according to the ratio of the non-target antigen to the inhibitor receptor. The expression levels of the non-target antigen and the inhibitory receptor, and the ratio thereof, can be determined by methods known in the art, including, *inter alia*, immunohistochemistry and fluorescence activated cell sorting (FACS). Analysis of the expression levels of the non-target antigen on target and non-target cells can be used to predict selective targeting of the immune cells expressing the inhibitory receptor. Low or no expression of the non-target antigen on a target or non-target cell can indicate, for example, that the inhibitory receptor will not be activated in an immune cell of the disclosure.

[0303] Alternatively, or in addition, and without wishing to be bound by theory, inhibition of immune cell activation by a non-target antigen via activation of the inhibitory receptor can depend on the affinity of the non-target antigen for the inhibitory receptor. Methods of measuring affinity are known in the art, and include, inter alia, enzyme-linked immunosorbent assay or radioimmunoassay methods.

[0304] Alternatively, or in addition, and without wishing to be bound by theory, inhibition of immune cell activation by a non-target antigen via activation of the inhibitory receptor can occur according to cross talk between the inhibitory receptor and the activator receptor,

leading to down-regulation of the activity of the activator receptor. For example, activation of the inhibitory receptor by the non-target antigen can lead to reduced expression of the activator receptor on the surface of the immune cell.

[0305] In some embodiments, the non-target antigen is expressed at a lower level in a target cell than a normal cell. In some embodiments, the non-target antigen is expressed by healthy cells, *i.e.* cells that are not cancer cells. In some embodiments, the non-target antigen expression level is at least about 10 times less, at least about 30 times less, at least about 50 times less, at least about 70 times less, at least about 90 times less, at least about 100 times less, at least about 110 times less, at least about 150 times less, at least about 200 times less, at least about 250 times less, at least about 300 times less, at least about 350 times less, at least about 400 times less, at least about 450 times less, at least about 500 times less, at least about 600 times less, at least about 700 times less, at least about 800 times less, at least about 900 times less or at least about 1000 times less in the target cell than in the non-target cell. In some embodiments, the non-target antigen expression level is about 10 times less, about 30 times less, about 50 times less, about 70 times less, about 90 times less, about 100 times less, or about 110 times less than the plurality of healthy cells. In some embodiments, the non-target antigen expression level is at least about 5 times less in the plurality of cancer cells than in the plurality of healthy cells. In some embodiments, the non-target antigen expression level is at least about 5 times less in a target cell than a non-target cell. In some embodiments, the target cells are a plurality of cancer cells that have low or no expression of the non-target antigen.

[0306] Any cell surface molecule expressed by the non-target cells that is not expressed by target cells (or expressed at a low level) may be a suitable non-target antigen for the second receptor extracellular ligand binding domain. For example, a cell adhesion molecule, a cell-cell signaling molecule, an extracellular domain, a molecule involved in chemotaxis, a glycoprotein, a G protein-coupled receptor, a transmembrane protein, a receptor for a neurotransmitter or a voltage gated ion channel can be used as a non-target antigen.

[0307] In some embodiments, the non-target antigen is selected from the group consisting of leucine rich repeat neuronal 4 (LRRN4) and uroplakin B3 (UPKB3), or a peptide antigen of any of these in a complex with a major histocompatibility complex class I (MHC-I). In some embodiments, the non-target antigen is LRRN4 or a peptide antigen thereof in a complex with MHC-I. In some embodiments, the non-target antigen is UPKB3 or a peptide antigen thereof in a complex with MHC-I.

[0308] In some embodiments, the target antigen is a peptide antigen of a cancer cell-specific antigen in a complex with a major histocompatibility complex class I (MHC-I).

[0309] Non-target MHC-I (pMHC) antigens comprising any of HLA-A, HLA-B or HLA-C are envisaged as within the scope of the disclosure. In some embodiments, the non-target antigen comprises HLA-A. In some embodiments, the non-target antigen comprises HLA-B. In some embodiments, the non-target antigen comprises HLA-C.

[0310] Non-target antigens comprise proteins that have low or no expression in cancer cells, for example lung cancer cells, but are expressed in normal tissues, such as normal lung tissue.

[0311] In some embodiments, the non-target antigen comprises LRRN4 or an antigen peptide thereof in a complex with MHC-I. A human LRRN4 is described in NCBI record number NP_689824.2, the contents of which are incorporated by reference herein in their entirety. In some embodiments, LRRN4 comprises an amino acid sequence of:

```
  1 MRQTLPLLLL TVLRPSWADP PQEKVPLFRV TQQGPWGSSG SNATDSPCEG LPAADATALT
 61 LANRNLERLP GCLPRTLRSL DASHNLLRAL STSELGHLEQ LQVLTLRHNR IAALRWGPGG
121 PAGLHTLDLS YNQLAALPPC TGPALSSLRA LALAGNPLRA LQPRAFACFP ALQLLNLSCT
181 ALGRGAQGGI AEAAFAGEDG APLVTLEVLD LSGTFLERVE SGWIRDLPKL TSLYLRKMPR
241 LTTLEGDIFK MTPNLQQLDC QDSPALASVA THIFQDTPHL QVLLFQNCNL SSFPPWTLDS
301 SQVLSINLFG NPLTCSCDLS WLLTDAKRTV LSRAADTMCA PAAGSSGPFS ASLSLSQLPG
361 VCQSDQSTTL GASHPPCFNR STYAQGTTVA PSAAPATRPA GDQQSVSKAP NVGSRTIAAW
421 PHSDAREGTA PSTTNSVAGH SNSSVFPRAA STTRTQHRGE HAPELVLEPD ISAASTPLAS
481 KLLGPFFPTSW DRSISSPQPG QRTHATPQAP NPSLSEGEIP VLLLDDYSEE EEGRKEEVGT
541 PHQDVPCDYH PCKHLQTPCA ELQRRWRCRC PGLSGEDTIP DPPRLQGVTE TTDTSALVHW
601 CAPNSVVHGY QIRYSAEGWA GNQSVVGVIY ATARQHPLYG LSPGTTYRVC VLAANRAGLS
661 QPRSSGWRSP CAAFTTKPSF ALLLSGLCAA SGLLLASTVV LSACLCRRGQ TLGLQRCDTH
721 LVAYKNPAFD DYPLGLQTVS (SEQ ID NO: 75).
```

[0312] In some embodiments, LRRN4 comprises a sequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO: 75. In some embodiments, LRRN4 comprises a sequence identical to SEQ ID NO: 75.

[0313] In some embodiments, the non-target antigen comprises UPK3B or an antigen peptide thereof in a complex with MHC-I. All isoforms of UPK3B are envisaged as within the scope of the instant disclosure. A human UPK3B isoform a precursor is described in NCBI record number NP_085047.1, the contents of which are incorporated by reference herein in their entirety. In some embodiments, UPK3B isoform a precursor comprises an amino acid sequence of:

```
  1 MGLPWGQPHL GLQMLLLALN CLRPSLSLGE WGSWMDASSQ TQGAGGPAGV IGPWAPAPLR
 61 LGEAAPGTPT PVSVAHLLSP VATELVPYTP QITAWDLEGK VTATTFSLEQ PRCVFDGLAS
121 ASDTVWLVVA FSNASRGFQN PETLADIPAS PQLLTDGHYM TLPLSPDQLP CGDPMAGSGG
181 APVLRVGHDH GCHQQPFCNA PLPGPGPYRE DPRIHRHLAR AAKWQHDRHY LHPLFSGRPP
241 TLGLLGSLYH ALLQPVVAGG GPGAAADRLL HGQALHDPPH PTQRGRHTAG GLQAWPGPPP
301 QPQPLAWPLC MGLGEMGRRE (SEQ ID NO: 76).
```

[0314] A human UPK3B isoform b precursor is described in NCBI record number NP_872625.1, the contents of which are incorporated by reference herein in their entirety. In some embodiments, UPK3B isoform b precursor comprises an amino acid sequence of:

```
  1 MGLPWGQPHL GLQMLLLALN CLRPSLSLEL VPYTPQITAW DLEGKVTATT FSLEQPRCVF
 61 DGLASASDTV WLVVAFSNAS RGFQNPETLA DIPASPQLLT DGHYMTLPLS PDQLPCGDPM
121 AGSGGAPVLR VGHDHGCHQQ PFCNAPLPGP GPYRVKFLLM DTRGSPRAET KWSDPITLHQ
181 GKTPGSIDTW PGRRSGSMIV ITSILSSLAG LLLLAFLAAS TMRFSSLWWP EEAPEQLRIG
241 SFMGKRYMTH HIPPSEAATL PVGCKPGLDP LPSLSP (SEQ ID NO: 77).
```

[0315] A human UPK3B isoform c precursor is described in NCBI record number NP_872624.1, the contents of which are incorporated by reference herein in their entirety. In some embodiments, UPK3B isoform c precursor comprises an amino acid sequence of:

```
  1 MGLPWGQPHL GLQMLLLALN CLRPSLSLEL VPYTPQITAW DLEGKVTATT FSLEQPRCVF
 61 DGLASASDTV WLVVAFSNAS RGFQNPETLA DIPASPQLLT DGHYMTLPLS PDQLPCGDPM
121 AGSGGAPVLR VGHDHGCHQQ PFCNAPLPGP GPYREDPRIH RHLARAAKWQ HDRHYLHPLF
181 SGRPPTLGLL GSLYHALLQP VVAGGGPGAA ADRLLHGQAL HDPPHPTQRG RHTAGGLQAW
241 PGPPPQPQPL AWPLCMGLGE MGRRE (SEQ ID NO: 78).
```

[0316] A human UPK3B isoform d precursor is described in NCBI record number NP_001334613.1, the contents of which are incorporated by reference herein in their entirety. In some embodiments, UPK3B isoform c precursor comprises an amino acid sequence of:

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  1 MGLPWGQPHL GLQMLLLALN CLRPSLSLEL VPYTPQITAW DLEGKVTATT FSLEQPRCVF
 61 DGLASASDTV WLVVAFSNAS RGFQNPETLA DIPASPQLLT DGHYMTLPLS PDQLPCGDPM
121 AGSGGAPVLR VGHDHGCHQQ PFCNAPLPGP GPYRVKFLLM DTRGSPRAET KWSDPITLHQ
181 GKTPGSIDTW PGRRSGSMIV ITSILSSLAG LLLLAFLAAS TMRFSSLWWP EEAPEQLRIG
241 SFMGKRYMTH HIPPREAATL PVGCKPGLDP LPSLSP (SEQ ID NO: 79).
```

[0317] In some embodiments, UPKB3 comprises a sequence or subsequence that shares at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to any one of SEQ ID NOs: 76-79. In some embodiments, UPKB3 comprises a sequence or subsequence identical to SEQ ID NOs: 76-79.

Inhibitory Chimeric Antigen Receptors

[0318] The disclosure provides a second receptor that is an inhibitory chimeric antigen receptor. The inhibitory receptor may comprise an extracellular ligand binding domain that binds to and recognizes the non-target antigen or a peptide derivative thereof in a MHC-I complex.

[0319] The term “inhibitory receptor” as used herein refers to a ligand-binding domain that is fused to an intracellular signaling domain capable of transducing an inhibitory signal that inhibits or suppresses the immune activity of an immune cell. Inhibitory receptors have immune cell inhibitory potential, and are distinct and distinguishable from CARs, which are

receptors with immune cell activating potential. For example, CARs are activating receptors as they include intracellular stimulatory and/or co-stimulatory domains. Inhibitory receptors are inhibiting receptors that contain intracellular inhibitory domains.

[0320] As used herein "inhibitory signal" refers to signal transduction or changes in protein expression in an immune cell resulting in suppression of an immune response (e.g., decrease in cytokine production or reduction of immune cell activation). Inhibition or suppression of an immune cell can selective and/or reversible, or not selective and/or reversible.

[0321] Inhibitory receptors of the disclosure may comprise an extracellular ligand binding domain. Any type of ligand binding domain that can regulate the activity of a receptor in a ligand dependent manner is envisaged as within the scope of the instant disclosure. Inhibitory receptors are responsive to non-target antigens (*e.g.* HLA-A*02). For example, when a non-target antigen (*e.g.* HLA-A*02) binds to or contacts the inhibitory receptor, the inhibitory receptor is responsive and activates an inhibitory signal in the immune cell expressing the inhibitory receptor upon binding of the non-target antigen by the extracellular ligand binding domain of the inhibitory receptor.

[0322] Inhibitory receptors of the disclosure may comprise an extracellular ligand binding domain. Any type of ligand binding domain that can regulate the activity of a receptor in a ligand dependent manner is envisaged as within the scope of the instant disclosure.

[0323] In some embodiments, the ligand binding domain is an antigen binding domain. Exemplary antigen binding domains include, *inter alia*, scFv, SdAb, Vβ-only domains, and TCR antigen binding domains derived from the TCR α and β chain variable domains.

[0324] Any type of antigen binding domain is envisaged as within the scope of the instant disclosure.

[0325] In some embodiments, the extracellular ligand binding domain of the second receptor is an scFv.

[0326] In some embodiments, the extracellular ligand binding domain of the second receptor binds to and recognizes a polymorphic variant of intercellular adhesion molecule 1 (ICAM1), catechol-O-methyltransferase (COMT), C-X-C motif chemokine ligand 16 (CXCL16), leucine rich repeat neuronal 4 (LRRN4) and uroplakin 3B UPK3B, or an antigen peptide thereof in a complex with a major histocompatibility complex class I (MHC-I), or HLA-A*02. In some embodiments, the extracellular ligand binding domain of the second receptor is an scFv.

[0327] In some embodiments, the extracellular ligand binding domain of the second receptor is fused to the extracellular domain of an inhibitory receptor.

[0328] In some embodiments, the inhibitory receptors of the present disclosure comprise an extracellular hinge region. Exemplary hinges can be isolated or derived from IgD and CD8 domains, for example IgG1. In some embodiments, the hinge is isolated or derived from CD8α or CD28.

[0329] The inhibitory receptors of the present disclosure can be designed to comprise a transmembrane domain that is fused to the extracellular domain of the inhibitory receptor. In some instances, 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.

[0330] The transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Transmembrane regions may be isolated or derived from (i.e. comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, or from an immunoglobulin such as IgG4. Alternatively the transmembrane domain may be synthetic, in which case it will comprise predominantly hydrophobic residues such as leucine and valine. In some embodiments, a triplet of phenylalanine, tryptophan and valine will be found at each end of a synthetic transmembrane domain. Optionally, a short oligo- or polypeptide linker, preferably between 2 and 10 amino acids in length may form the linkage between the transmembrane domain and the intracellular domain of the inhibitory receptor. A glycine-serine doublet provides a particularly suitable linker.

[0331] The disclosure provides an inhibitory receptor comprising an intracellular domain. The intracellular domain of the inhibitory receptors of the instant disclosure is responsible for inhibiting activation of the immune cells comprising the inhibitory receptor, which would otherwise be activated in response to activation signals by the first receptor. In some embodiments, the inhibitory intracellular domain comprises an immunoreceptor tyrosine-based inhibitory motif (ITIM). In some embodiments, the inhibitory intracellular domain comprising an ITIM can be isolated or derived from an immune checkpoint inhibitor such as CTLA-4 and PD-1. CTLA-4 and PD-1 are immune inhibitory receptors expressed on the surface of T cells, and play a pivotal role in attenuating or terminating T cell responses.

[0332] In some embodiments, an inhibitory intracellular domain is isolated from human tumor necrosis factor related apoptosis inducing ligand (TRAIL) receptor and CD200 receptor 1. In some embodiments, the TRAIL receptor comprises TR10A, TR10B or TR10D.

[0333] In some embodiments, an inhibitory intracellular domain is isolated from phosphoprotein membrane anchor with glycosphingolipid microdomains 1 (PAG1). In some embodiments, an inhibitory intracellular domain is isolated from leukocyte immunoglobulin like receptor B1 (LILRB1).

[0334] In some embodiments, the inhibitory domain is isolated or derived from a human protein, for example a human TRAIL receptor, CTLA-4, PD-1, PAG1 or LILRB1 protein.

[0335] In some embodiments, the inhibitory domain comprises an intracellular domain, a transmembrane or a combination thereof. In some embodiments, the inhibitory domain comprises an intracellular domain, a transmembrane domain, a hinge region or a combination thereof.

[0336] In some embodiments, the inhibitory domain is isolated or derived from killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2 (KIR3DL2), killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 3 (KIR3DL3), leukocyte immunoglobulin like receptor B1 (LIR1, also called LIR-1 and LILRB1), programmed cell death 1 (PD-1), Fc gamma receptor IIB (FcgRIIB), killer cell lectin like receptor K1 (NKG2D), CTLA-4, a domain containing a synthetic consensus ITIM, a ZAP70 SH2 domain (e.g., one or both of the N and C terminal SH2 domains), or ZAP70 KI_K369A (kinase inactive ZAP70).

[0337] In some embodiments, the inhibitory domain is isolated or derived from a human protein.

[0338] In some embodiments, the second, inhibitory receptor comprises an inhibitory domain. In some embodiments, the second, inhibitory receptor comprises an inhibitory intracellular domain and/or an inhibitory transmembrane domain. In some embodiments, the inhibitory intracellular domain is fused to an intracellular domain of an inhibitory receptor. In some embodiments, the inhibitory intracellular domain is fused to the transmembrane domain of an inhibitory receptor.

[0339] In some embodiments, the second, inhibitory receptor comprises a cytoplasmic domain, a transmembrane domain, and an extracellular domain or a portion thereof isolated or derived isolated or derived from the same protein, for example an ITIM containing protein. In some embodiments, the second, inhibitory receptor comprises a hinge region isolated or

derived from isolated or derived from the same protein as the intracellular domain and/or transmembrane domain, for example an ITIM containing protein.

[0340] In some embodiments, the second receptor is a TCR comprising an inhibitory domain (an inhibitory TCR). In some embodiments, the inhibitory TCR comprises an inhibitory intracellular domain and/or an inhibitory transmembrane domain. In some embodiments, the inhibitory intracellular domain is fused to the intracellular domain of TCR alpha, TCR beta, CD3 delta, CD3 gamma or CD3 epsilon or a portion thereof a TCR. In some embodiments, the inhibitory intracellular domain is fused to the transmembrane domain of TCR alpha, TCR beta, CD3 delta, CD3 gamma or CD3 epsilon.

In some embodiments, the second receptor is a TCR comprising an inhibitory domain (an inhibitory TCR). In some embodiments, the inhibitory domain is isolated or derived from LILRB1.

LILRB1 Inhibitory receptors

[0341] The disclosure provides a second, inhibitory receptor comprising a LILRB1 inhibitory domain, and optionally, a LILRB1 transmembrane and/or hinge domain, or functional variants thereof. The inclusion of the LILRB1 transmembrane domain and/or the LILRB1 hinge domain in the inhibitory receptor may increase the inhibitory signal generated by the inhibitory receptor compared to a reference inhibitory receptor having another transmembrane domain or another hinge domains. The second, inhibitory receptor comprising the LILRB1 inhibitory domain may be a CAR or TCR, as described herein. Any suitable ligand binding domain, as described herein, may be fused to the LILRB1-based second, inhibitory receptors.

[0342] Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1), also known as Leukocyte immunoglobulin-like receptor B1, as well as ILT2, LIR1, MIR7, PIRB, CD85J, ILT-2 LIR-1, MIR-7 and PIR-B, is a member of the leukocyte immunoglobulin-like receptor (LIR) family. The LILRB1 protein belongs to the subfamily B class of LIR receptors. These receptors contain two to four extracellular immunoglobulin domains, a transmembrane domain, and two to four cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). The LILRB1 receptor is expressed on immune cells, where it binds to MHC class I molecules on antigen-presenting cells and transduces a negative signal that inhibits stimulation of an immune response. LILRB1 is thought to regulate inflammatory responses, as well as cytotoxicity, and to play a role in limiting auto-reactivity. Multiple transcript variants encoding different isoforms of LILRB1 exist, all of which are contemplated as within the scope of the instant disclosure.

[0343] In some embodiments of the inhibitory receptors described herein, the inhibitory receptor comprises one or more domains isolated or derived from LILRB1. In some embodiments of the receptors having one or more domains isolated or derived from LILRB1, the one or more domains of LILRB1 comprise an amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 54. In some embodiments, the one or more domains of LILRB1 comprise an amino acid sequence that is identical to a sequence or subsequence of SEQ ID NO: 54. In some embodiments, the one or more domains of LILRB1 consist of an amino acid sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 54. In some embodiments, the one or more domains of LILRB1 consist of an amino acid sequence that is identical to a sequence or subsequence of SEQ ID NO: 54.

[0344] In some embodiments of the receptors having one or more domains isolated or derived from LILRB1, the one or more domains of LILRB1 are encoded by a polynucleotide sequence that is at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or is identical to a sequence or subsequence of SEQ ID NO: 55.

[0345] In some embodiments of the receptors having one or more domains of LILRB1, the one or more domains of LILRB1 are encoded by a polynucleotide sequence that is identical to a sequence or subsequence of SEQ ID NO: 55.

[0346] In various embodiments, an inhibitory receptor is provided, comprising a polypeptide, wherein the polypeptide comprises one or more of: an LILRB1 hinge domain or functional variant thereof; an LILRB1 transmembrane domain or a functional variant thereof; and an LILRB1 intracellular domain or an intracellular domain comprising at least one, or at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0347] As used herein an “immunoreceptor tyrosine-based inhibitory motif” or “ITIM” refers to a conserved sequence of amino acids with a consensus sequence of S/I/V/LxYxxI/V/L (SEQ ID NO: 547), or the like, that is found in the cytoplasmic tails of many inhibitory receptors of the immune system. After ITIM-possessing inhibitory receptors interact with their ligand, the ITIM motif is phosphorylated, allowing the inhibitory receptor to recruit other enzymes, such as the phosphotyrosine phosphatases SHP-1 and SHP-2, or the inositol-phosphatase called SHIP.

[0348] In some embodiments, the polypeptide comprises an intracellular domain comprising at least one immunoreceptor tyrosine-based inhibitory motif (ITIM), at least two ITIMs, at least 3 ITIMs, at least 4 ITIMs, at least 5 ITIMs or at least 6 ITIMs. In some embodiments, the intracellular domain has 1, 2, 3, 4, 5, or 6 ITIMs.

[0349] In some embodiments, the polypeptide comprises an intracellular domain comprising at least one ITIM selected from the group of ITIMs consisting of NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0350] In further particular embodiments, the polypeptide comprises an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0351] In some embodiments, the intracellular domain comprises both ITIMs NLYAAV (SEQ ID NO: 56) and VTYAEV (SEQ ID NO: 57). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 60. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 60.

[0352] In some embodiments, the intracellular domain comprises both ITIMs VTYAEV (SEQ ID NO: 57) and VTYAQL (SEQ ID NO: 58). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 61. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 61.

[0353] In some embodiments, the intracellular domain comprises both ITIMs VTYAQL (SEQ ID NO: 58) and SIYATL (SEQ ID NO: 59). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 62. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 62.

[0354] In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), and VTYAQL (SEQ ID NO: 58). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 63. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 63.

[0355] In some embodiments, the intracellular domain comprises the ITIMs VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59). In some

embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 64. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 64.

[0356] In some embodiments, the intracellular domain comprises the ITIMs NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59). In some embodiments, the intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 65. In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to SEQ ID NO: 65.

[0357] In some embodiments, the intracellular domain comprises a sequence at least 95% identical to the LILRB1 intracellular domain (SEQ ID NO: 70). In some embodiments, the intracellular domain comprises or consists essentially of a sequence identical to the LILRB1 intracellular domain (SEQ ID NO: 70).

[0358] LILRB1 intracellular domains or functional variants thereof of the disclosure can have at least 1, at least 2, at least 4, at least 4, at least 5, at least 6, at least 7, or at least 8 ITIMs. In some embodiments, the LILRB1 intracellular domain or functional variant thereof has 2, 3, 4, 5, or 6 ITIMs.

[0359] In particular embodiments, the intracellular domain comprises two, three, four, five, or six immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0360] In particular embodiments, the intracellular domain comprises at least three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0361] In particular embodiments, the intracellular domain comprises three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0362] In particular embodiments, the intracellular domain comprises four immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0363] In particular embodiments, the intracellular domain comprises five immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from

NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0364] In particular embodiments, the intracellular domain comprises six immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0365] In particular embodiments, the intracellular domain comprises at least seven immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0366] The LILRB1 protein has four immunoglobulin (Ig) like domains termed D1, D2, D3 and D4. In some embodiments, the LILRB1 hinge domain comprises an LILRB1 D3D4 domain or a functional variant thereof. In some embodiments, the LILRB1 D3D4 domain comprises a sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or identical to SEQ ID NO: 66. In some embodiments, the LILRB1 D3D4 domain comprises or consists essentially of SEQ ID NO: 66.

[0367] In some embodiments, the polypeptide comprises the LILRB1 hinge domain or functional variant thereof. In embodiments, the LILRB1 hinge domain or functional variant thereof comprises a sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical or identical to SEQ ID NO: 73, SEQ ID NO: 66, or SEQ ID NO: 67. In embodiments, the LILRB1 hinge domain or functional variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 73, SEQ ID NO: 66, or SEQ ID NO: 67.

[0368] In some embodiments, the LILRB1 hinge domain comprises a sequence identical to SEQ ID NO: 73, SEQ ID NO: 66, or SEQ ID NO: 67.

[0369] In some embodiments, the LILRB1 hinge domain consists essentially of a sequence identical to SEQ ID NO: 73, SEQ ID NO: 66, or SEQ ID NO: 67.

[0370] In some embodiments, the transmembrane domain is a LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical or at least 99% to SEQ ID NO: 74. In some embodiments, the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 74. In some embodiments, the LILRB1 transmembrane domain comprises a sequence identical to SEQ ID NO: 74. In

embodiments, the LILRB1 transmembrane domain consists essentially of a sequence identical to SEQ ID NO: 74.

[0371] In some embodiments, the transmembrane domain can be attached to the extracellular region of the second, inhibitory receptor, *e.g.*, the antigen binding domain or ligand binding domain, via a hinge, *e.g.*, a hinge from a human protein. For example, in some embodiments, the hinge can be a human immunoglobulin (Ig) hinge, *e.g.*, an IgG4 hinge, a CD8a hinge or an LILRB1 hinge.

[0372] In some embodiments, the second, inhibitory receptor comprises an inhibitory domain. In some embodiments, the second, inhibitory receptor comprises an inhibitory intracellular domain and/or an inhibitory transmembrane domain. In some embodiments, the inhibitory domain is isolated or derived from LILR1B.

Inhibitory Receptors Comprising Combinations of LILRB1 Domains

[0373] In some embodiments, the LILRB1-based inhibitory receptors of the disclosure comprise more than one LILRB1 domain or functional equivalent thereof. For example, in some embodiments, the inhibitory receptor comprises an LILRB1 transmembrane domain and intracellular domain, or an LILRB1 hinge domain, transmembrane domain and intracellular domain.

[0374] In particular embodiments, the inhibitory receptor comprises an LILRB1 hinge domain or functional variant thereof, and the LILRB1 transmembrane domain or a functional variant thereof. In some embodiments, the polypeptide comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical or identical to SEQ ID NO: 68. In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 68. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 68.

[0375] In further embodiments, the inhibitory receptor comprises: the LILRB1 transmembrane domain or a functional variant thereof, and an LILRB1 intracellular domain and/or an intracellular domain comprising at least one immunoreceptor tyrosine-based inhibitory motif (ITIM), wherein the ITIM is selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59). In some embodiments, the polypeptide comprises the LILRB1 transmembrane domain or a functional variant thereof, and an LILRB1 intracellular domain and/or an intracellular domain comprising at least two ITIM, wherein each ITIM is independently selected from NLYAAV (SEQ ID NO: 56), VTYAEV (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0376] In some embodiments, the inhibitory receptor comprises a LILRB1 transmembrane domain and intracellular domain. In some embodiments, the polypeptide comprises a sequence at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical or identical to SEQ ID NO: 69. In some embodiments, the polypeptide comprises a sequence at least 95% identical to SEQ ID NO: 69. In some embodiments, the polypeptide comprises a sequence identical to SEQ ID NO: 69.

[0377] In preferred embodiments, the inhibitory receptor comprises: an LILRB1 hinge domain or functional variant thereof; an LILRB1 transmembrane domain or a functional variant thereof; and an LILRB1 intracellular domain and/or an intracellular domain comprising at least two immunoreceptor tyrosine-based inhibitory motifs (ITIMs), wherein each ITIM is independently selected from LYAAV (SEQ ID NO: 56), VTYAE (SEQ ID NO: 57), VTYAQL (SEQ ID NO: 58), and SIYATL (SEQ ID NO: 59).

[0378] In some embodiments, the inhibitory receptor comprises a sequence at least 95% identical to SEQ ID NO: 71 or SEQ ID NO: 72, or at least 99% identical to SEQ ID NO: 71 or SEQ ID NO: 72, or identical to SEQ ID NO: 71 or SEQ ID NO: 72.

[0379] In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 68, or at least 99% identical to SEQ ID NO: 68, or identical to SEQ ID NO: 68.

[0380] In some embodiments, the polypeptide comprises a sequence at least 99% identical to SEQ ID NO: 69, or at least 99% identical to SEQ ID NO: 69, or identical to SEQ ID NO: 69.

Table 9: Polypeptide sequences for illustrative LILRB1-based inhibitory receptors

Name	Sequence
LILRB1	MTPILTVLICLGLSLGPRTHVQAGHLPKPTLWAEPGSVITQ GSPVTLRCQGGQETQEYRLYREKKTALWITRIPQELVKKG QFPIPSITWEHAGRYRCYYGSDTAGRSESSDPLELVVTGA YIKPTLSAQPSPVVNSGGNVILQCDSQVAFDGFSLCKEGED EHPQCLNSQPHARGSSRAIFSVGPVSPSRRWWYRCYAYDS NSPYEWSLPSDLLELLVLGVSKKPSLSVQPGPIVAPEETLT LQCGSDAGYNRFVLYKDGERDFLQLAGAQPQAGLSQANF TLGPVSRSYGGQYRCYGAHNLSSEWSAPSDPLDILIAGQF YDRVSLSVQPGPTVASGENVTLLCQSQGWMQTFLLTKEG AADDPWRLRSTYQSQKYQAEFPMGPVTSAHAGTYRC**YG SQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSGPE DQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLLLLLLLFLI

	LRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWR SSPAADAQEEN**LYAAV**KHTQPEDGVEMDTRSPHDEDPQA **VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQ**LHSLTLRREATEPPPSQEGPSP AVP**SIYAT**LAIHPSQEGPSPAVPSIYATLAIH SEQ ID NO: 54
LILRB1 hinge-transmembrane-intracellular domain	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG**VVIGILVAVILLLLLLLLL FLIL**RHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQ WRSSPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDEDP QAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDR QMDTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPS PAVPSIYATLAIH SEQ ID NO: 71
LILRB1 hinge-transmembrane-intracellular domain (w/o YGSQSSKPYLLTHPSD PLEL (SEQ ID NO: 66))	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LG**VVIGILVAVILLLLLLLLLFLIL**RHRRQGKHWTSTQRK ADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAV KHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMA SPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYA QLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH SEQ ID NO: 72
LILRB1 hinge domain	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG SEQ ID NO: 73
LILRB1 transmembrane domain	**VVIGILVAVILLLLLLLLLFLIL** SEQ ID NO: 74
LILRB1 intracellular domain	RHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRS SPAADAQEENLYAAVKHTQPEDGVEMDTRSPHDEDPQAV TYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQM DTEAAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSPA VPSIYATLAIH SEQ ID NO: 70
ITIM1	NLYAAV

	SEQ ID NO: 56
ITIM2	VTYAEV SEQ ID NO: 57
ITIM3	VTYAQL SEQ ID NO: 58
ITIM4	SIYATL SEQ ID NO: 59
ITIM1-2	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV** SEQ ID NO: 60
ITIM2-3	**VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQL** SEQ ID NO: 61
ITIM3-4	**VTYAQL**HSLTLRREATEPPPSQEGPSPAVP**SIYATL** SEQ ID NO: 62
ITIM1-3	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV**KHS RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQD**VTYAQL** SEQ ID NO: 63
ITIM2-4	**VTYAEV**KHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQ MDTEAAASEAPQD**VTYAQL**HSLTLRREATEPPPSQEGPSP AVP**SIYATL** SEQ ID NO: 64
ITIM1-4	**NLYAAV**KHTQPEDGVEMDTRSPHDEDPQA**VTYAEV**KHS RPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAASEA PQD**VTYAQL**HSLTLRREATEPPPSQEGPSPAVP**SIYATL** SEQ ID NO: 65
D3D4 domain	**YGSQSSKPYLLTHPSDPLEL** SEQ ID NO: 66
Short hinge	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LG SEQ ID NO: 67
Hinge (iTIM hinge)	YGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGP EDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 81)

Short hinge 2	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LGV (SEQ ID NO: 82)
Long hinge 1	AGSGGSGGSGGSPVPSTPPTPSPSTPPTPSPSGGSGNSSGSG GSPVPSTPPTPSPSTPPTPSPSASV (SEQ ID NO: 83)
Long hinge 2	AGSGGSGGSGGSPVPSTPPTNSSSTPPTPSPSPVPSTPPTNSS STPPTPSPSPVPSTPPTNSSSTPPTPSPSASV (SEQ ID NO: 84)
2X short hinge	VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH VVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LGV SEQ ID NO: 91
Hinge (truncated)	TTGPTSTSGPEDQPLTPTGSDPQSGLGRHLGV (SEQ ID NO: 90)
Hinge-transmembrane	**YGSQSSKPYLLTHPSDPLEL**VVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLG**VVIGILVAVILLLLLLLLL FLIL** SEQ ID NO: 68
Transmembrane-intracellular domain.	**VVIGILVAVILLLLLLLLLFLIL**RHRRQGKHWTSTQRKA DFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLYAAVK HTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMAS PPSPLSGEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYA QLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH SEQ ID NO: 69

[0381] Exemplary inhibitory receptors of the disclosure comprise the scFv specific to any of HLA-A, HLA-B or HLA-C non-target antigens, the sequences of which are set forth in Table 5, fused to the N terminus a LILRB1 hinge, transmembrane and intracellular domain. In some embodiments, the LILRB1 hinge comprises a sequence of SEQ ID NO: 73, the LILRB1 transmembrane domain comprises a sequence of SEQ ID NO: 74, and the LILRB1 intracellular domain comprises a sequence of SEQ ID NO: 70. For example, the second, inhibitory receptor comprises an scFv sequence of Table 5 fused to the N terminus of SEQ ID NO: 71.

[0382] As a further example, the non-target antigen comprises HLA-A*02, and the second inhibitory receptor comprises a sequence of:

DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTL
KISRVEAEDLGVYYCFQGSHVPRTSGGGTKLEIKGGGGSGGGGSGGGGSGGQVQLQQSGPELVKPGASVRISCKA
SGYTFTSYHIHWVKQRPGQGLEWIGWIYPGNVNTEYNEKFKGKATLTADKSSSTAYMHLSSLTSEDSAVYFCAREEI
TYAMDYWGQGTSVTVSSYGSQSSKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLG
RHLGVVIGILVAVILLLLLLLLLFLILRHRRQGKHWTSTQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEENLY
AAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEAAAS
EAPQDVTYAQLHSLTLRREATEPPPSQEGPSPAVPSIYATLAIH (SEQ ID NO: 348), or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the non-target antigen comprises HLA-A*02 and the second inhibitory receptor comprises a sequence of SEQ ID NO: 348.

Polynucleotides and Vectors

[0383] The disclosure provides polynucleotides encoding the sequence(s) of the first and second receptors of the disclosure. The disclosure provides immune cells comprising the polynucleotides and vectors described herein.

[0384] In some embodiments, the sequence of the first and/or second receptor is operably linked to a promoter. In some embodiments, the sequence encoding the first receptor is operably linked to a first promoter, and the sequence encoding the second receptor is operably linked to a second promoter.

[0385] The disclosure provides vectors comprising the polynucleotides described herein.

[0386] In some embodiments, the first receptor is encoded by a first vector and the second receptor is encoded by a second vector. In some embodiments, both receptors are encoded by a single vector. In some embodiments, the first and/or second vector comprises an shRNA, for example a B2M shRNA.

[0387] In some embodiments, both receptors are encoded by a single vector. In some embodiments the vector comprises an shRNA, for example a B2M shRNA.

[0388] In some embodiments, the first and second receptors are encoded by a single vector. Methods of encoding multiple polypeptides using a single vector will be known to persons of ordinary skill in the art, and include, *inter alia*, encoding multiple polypeptides under control of different promoters, or, if a single promoter is used to control transcription of multiple polypeptides, use of sequences encoding internal ribosome entry sites (IRES) and/or self-cleaving peptides. Exemplary self-cleaving peptides include T2A, P2A, E2A and F2A self-cleaving peptides. In some embodiments, the T2A self-cleaving peptide comprises a sequence of EGRGSLLTCGDVEENPGP (SEQ ID NO: 764). In some embodiments, the

P2A self-cleaving peptide comprises a sequence of ATNFSLLKQAGDVEENPGP (SEQ ID NO: 765). In some embodiments, the E2A self-cleaving peptide comprises a sequence of QCTNYALLKLAGDVESNPGP (SEQ ID NO: 766). In some embodiments, the F2A self-cleaving peptide comprises a sequence of VKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 767). In some embodiments, the T2A self-cleaving peptide comprises a sequence of EGRGSLLTCGDVEENPGP (SEQ ID NO: 764). Any of the foregoing can also include an N terminal GSG linker. For example, a T2A self-cleaving peptide can also comprise a sequence of GSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 351), which can be encoded by a sequence of GGATCCGGAGAGGGCAGAGGCAGCCTGCTGACATGTGGCGACGTGGAAGAGAACCCTGGCCCC (SEQ ID NO: 768).

[0389] In some embodiments, the vector is an expression vector, i.e. for the expression of the first and/or second receptor in a suitable cell.

[0390] Vectors derived from retroviruses such as the lentivirus are suitable tools to achieve long-term gene transfer since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity.

[0391] The expression of natural or synthetic nucleic acids encoding receptors is typically achieved by operably linking a nucleic acid encoding the receptor or portions thereof to a promoter, and incorporating the construct into an expression vector. The vectors can be suitable for replication and integration eukaryotes. Typical cloning vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence.

[0392] The polynucleotides encoding the receptors can be cloned into a number of types of vectors. For example, the polynucleotides can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

[0393] Further, the expression vector may be provided to cells, such as immune cells, in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook et al. (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals.

Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (e.g., WO 01/96584; WO 01/29058; and U.S. Pat. No. 6,326,193).

[0394] A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems. A selected gene can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either in vivo or ex vivo. A number of retroviral systems are known in the art. In some embodiments, adenovirus vectors are used. A number of adenovirus vectors are known in the art. In one embodiment, lentivirus vectors are used.

[0395] Additional promoter elements, e.g., enhancers, regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 basepairs (bp) upstream of the start site, although a number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the thymidine kinase (tk) promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can function either cooperatively or independently to activate transcription.

[0396] One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. Another example of a suitable promoter is Elongation Growth Factor-1α (EF-1α). However, other constitutive promoter sequences may also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, a U6 promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. Further, the disclosure should not be limited to the use of constitutive promoters. Inducible promoters are also contemplated as part of the disclosure. The use of an inducible promoter provides a molecular switch capable

of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0397] In order to assess the expression of a receptor, the expression vector to be introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co-transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and the like.

[0398] Reporter genes are used for identifying potentially transfected or transduced cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a polypeptide whose expression is manifested by some easily detectable property, e.g., enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. Suitable reporter genes may include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (e.g., Ui-Tei et al., 2000 FEBS Letters 479: 79-82). Suitable expression systems are well known and may be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5′ flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions may be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

[0399] Methods of introducing and expressing genes into a cell are known in the art. In the context of an expression vector, the vector can be readily introduced into a host cell, e.g., mammalian, bacterial, yeast, or insect cell by any method in the art. For example, the expression vector can be transferred into a host cell by physical, chemical, or biological means.

[0400] Physical methods for introducing a polynucleotide into a host cell include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and the like. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. See, for example, Sambrook et al. (2001, Molecular Cloning: A

Laboratory Manual, Cold Spring Harbor Laboratory, New York). One method for the introduction of a polynucleotide into a host cell is calcium phosphate transfection.

[0401] Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian, e.g., human cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and the like. See, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362.

[0402] Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (e.g., an artificial membrane vesicle).

[0403] Regardless of the method used to introduce exogenous nucleic acids into a host cell or otherwise expose a cell to the inhibitor of the present disclosure, in order to confirm the presence of the recombinant DNA sequence in the host cell, a variety of assays may be performed. Such assays include, for example, "molecular biological" assays well known to those of skill in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the presence or absence of a particular peptide, e.g., by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the disclosure.

Immune Cells

[0404] The disclosure provides immune cells comprising the receptors, vectors and polynucleotides described herein.

[0405] In some embodiments, the immune cells comprise: (a) first receptor, comprising a first extracellular ligand binding domain specific to a target antigen selected from: (i) a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); or (ii) MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and (b) a second receptor, comprising a second extracellular ligand binding specific to a non-target antigen selected from intercellular adhesion molecule 1 (ICAM1), catechol-O-methyltransferase (COMT), C-X-C motif chemokine ligand 16 (CXCL16), leucine rich repeat neuronal 4 (LRRN4) and uroplakin 3B UPK3B, or an antigen peptide thereof in a complex with a major

histocompatibility complex class I (MHC-I), or HLA-A*02. In some embodiments, the first receptor is a CAR or TCR. In some embodiments, the second receptor is an inhibitory receptor, such as an inhibitory chimeric antigen receptor or TCR.

[0406] The disclosure provides immune cells comprising a first receptor comprising a sequence of SEQ ID NO: 303, and second receptor comprising a sequence of SEQ ID NO: 348, or sequences having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. In some embodiments, the immune cells comprise an shRNA encoded by a sequence comprising SEQ ID NO: 349 or 350, or a sequence having at least 80%, at least 90%, or at least 95% identity thereto. In some embodiments, the immune cells comprise first receptor comprising a sequence of SEQ ID NO: 303, a second receptor comprising a sequence of SEQ ID NO: 348, and a sequence encoding an shRNA comprising a sequence of SEQ ID NO: 349 or 350. In some embodiments, the first receptor and second receptor are encoded by a single polynucleotide, and wherein the sequences encoding the first and second receptors are separated by a sequence encoding a self-cleaving polypeptide. In some embodiments, the self-cleaving polypeptide comprises a T2A self-cleaving polypeptide comprising a sequence of GSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 351).

[0407] As used herein, the term “immune cell” refers to a cell involved in the innate or adaptive (acquired) immune systems. Exemplary innate immune cells include phagocytic cells such as neutrophils, monocytes and macrophages, Natural Killer (NK) cells, polymophonuclear leukocytes such as neutrophils eosinophils and basophils and mononuclear cells such as monocytes, macrophages and mast cells. Immune cells with roles in acquired immunity include lymphocytes such as T-cells and B-cells.

[0408] As used herein, a “T-cell” refers to a type of lymphocyte that originates from a bone marrow precursor that develops in the thymus gland. There are several distinct types of T-cells which develop upon migration to the thymus, which include, helper CD4+ T-cells, cytotoxic CD8+ T cells, memory T cells, regulatory CD4+ T-cells and stem memory T-cells. Different types of T-cells can be distinguished by the ordinarily skilled artisan based on their expression of markers. Methods of distinguishing between T-cell types will be readily apparent to the ordinarily skilled artisan.

[0409] In some embodiments, the first receptor and the second receptor together specifically activate the immune cell in the presence of the target cell.

[0410] In some embodiments, the immune cell is CD4+, CD8+, a gamma delta T cell, an invariant T cells, an iNK cell , a NK cell, a macrophages, or combinations thereof. In some embodiments, the immune cell is a gamma delta (γδ) T cell. In some embodiments, the

immune cell is an invariant T cell. In some embodiments, the immune cell is an invariant natural killer T cell (iNKT cell). In some embodiments, the immune cell is a T cell. In some embodiments, the immune cell is a B cell. In some embodiments, the immune cell is a Natural Killer (NK) cell. In some embodiments, the immune cell is CD8-. In some embodiments, the immune cell is CD8+. In some embodiments, the immune cell is CD4+. In some embodiments, the immune cell is CD4-. In some embodiments, the immune cell is CD8-/CD4+. In some embodiments, the immune cell is a CD8+ CD4- T cell.

[0411] In some embodiments, the immune cell is non-natural. In some embodiments, the immune cell is isolated.

[0412] Methods transforming populations of immune cells, such as T cells, with the vectors of the instant disclosure will be readily apparent to the person of ordinary skill in the art. For example, CD3+ T cells can be isolated from PBMCs using a CD3+ T cell negative isolation kit (Miltenyi), according to manufacturer's instructions. T cells can be cultured at a density of 1 x 10^6 cells/mL in X-Vivo 15 media supplemented with 5% human A/B serum and 1% Pen/strep in the presence of CD3/28 Dynabeads (1:1 cell to bead ratio) and 300 Units/mL of IL-2 (Miltenyi). After 2 days, T cells can be transduced with viral vectors, such as lentiviral vectors using methods known in the art. In some embodiments, the viral vector is transduced at a multiplicity of infection (MOI) of 5. Cells can then be cultured in IL-2 or other cytokines such as combinations of IL-7/15/21 for an additional 5 days prior to enrichment. Methods of isolating and culturing other populations of immune cells, such as B cells, or other populations of T cells, will be readily apparent to the person of ordinary skill in the art. Although this method outlines a potential approach it should be noted that these methodologies are rapidly evolving. For example excellent viral transduction of peripheral blood mononuclear cells can be achieved after 5 days of growth to generate a >99% CD3+ highly transduced cell population.

[0413] Methods of activating and culturing populations of T cells comprising the TCRs, CARs, inhibitory receptors, receptors or vectors encoding same, will be readily apparent to the person of ordinary skill in the art.

[0414] Whether prior to or after genetic modification of T cells to express a TCR, the T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041, 10040846; and U.S. Pat. Appl. Pub. No. 2006/0121005.

[0415] In some embodiments, T cells of the instant disclosure are expanded and activated in vitro. Generally, the T cells of the instant disclosure are expanded in vitro by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a co-stimulatory molecule on the surface of the T cells. In particular, T cell populations may be stimulated as described herein, such as by contact with an anti-CD3 antibody. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besançon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

[0416] In some embodiments, the primary stimulatory signal and the co-stimulatory signal for the T cell may be provided by different protocols. For example, the agents providing each signal may be in solution or coupled to a surface. When coupled to a surface, the agents may be coupled to the same surface (i.e., in "cis" formation) or to separate surfaces (i.e., in "trans" formation). Alternatively, one agent may be coupled to a surface and the other agent in solution. In some embodiments, the agent providing the co-stimulatory signal is bound to a cell surface and the agent providing the primary activation signal is in solution or coupled to a surface. In certain embodiments, both agents can be in solution. In another embodiment, the agents may be in soluble form, and then cross-linked to a surface, such as a cell expressing Fc receptors or an antibody or other binding agent which will bind to the agents. In this regard, see for example, U.S. Patent Application Publication Nos. 20040101519 and 20060034810 for artificial antigen presenting cells (aAPCs) that are contemplated for use in activating and expanding T cells in the present disclosure.

[0417] In some embodiments, the two agents are immobilized on beads, either on the same bead, i.e., "cis," or to separate beads, i.e., "trans." By way of example, the agent providing the primary activation signal is an anti-CD3 antibody or an antigen-binding fragment thereof and the agent providing the co-stimulatory signal is an anti-CD28 antibody or antigen-binding fragment thereof; and both agents are co-immobilized to the same bead in equivalent molecular amounts. In one embodiment, a 1:1 ratio of each antibody bound to the beads for CD4+ T cell expansion and T cell growth is used. In some embodiments, the ratio of

CD3:CD28 antibody bound to the beads ranges from 100:1 to 1:100 and all integer values there between. In one aspect of the present disclosure, more anti-CD28 antibody is bound to the particles than anti-CD3 antibody, i.e., the ratio of CD3:CD28 is less than one. In certain embodiments of the disclosure, the ratio of anti CD28 antibody to anti CD3 antibody bound to the beads is greater than 2:1.

[0418] Ratios of particles to cells from 1:500 to 500:1 and any integer values in between may be used to stimulate T cells or other target cells. As those of ordinary skill in the art can readily appreciate, the ratio of particles to cells may depend on particle size relative to the target cell. For example, small sized beads could only bind a few cells, while larger beads could bind many. In certain embodiments the ratio of cells to particles ranges from 1:100 to 100:1 and any integer values in-between and in further embodiments the ratio comprises 1:9 to 9:1 and any integer values in between, can also be used to stimulate T cells. In some embodiments, a ratio of 1:1 cells to beads is used. One of skill in the art will appreciate that a variety of other ratios may be suitable for use in the present disclosure. In particular, ratios will vary depending on particle size and on cell size and type.

[0419] In further embodiments of the present disclosure, the cells, such as T cells, are combined with agent-coated beads, the beads and the cells are subsequently separated, and then the cells are cultured. In an alternative embodiment, prior to culture, the agent-coated beads and cells are not separated but are cultured together. In a further embodiment, the beads and cells are first concentrated by application of a force, such as a magnetic force, resulting in increased ligation of cell surface markers, thereby inducing cell stimulation.

[0420] By way of example, cell surface proteins may be ligated by allowing paramagnetic beads to which anti-CD3 and anti-CD28 are attached to contact the T cells. In one embodiment the cells (for example, CD4+ T cells) and beads (for example, DYNABEADS CD3/CD28 T paramagnetic beads at a ratio of 1:1) are combined in a buffer. Again, those of ordinary skill in the art can readily appreciate any cell concentration may be used. In certain embodiments, it may be desirable to significantly decrease the volume in which particles and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and particles. For example, in one embodiment, a concentration of about 2 billion cells/ml is used. In another embodiment, greater than 100 million cells/ml is used. In a further embodiment, a concentration of cells of 10, 15, 20, 25, 30, 35, 40, 45, or 50 million cells/ml is used. In yet another embodiment, a concentration of cells from 75, 80, 85, 90, 95, or 100 million cells/ml is used. In further embodiments, concentrations of 125 or 150 million

cells/ml can be used. In some embodiments, cells that are cultured at a density of $1x10^6$ cells/mL are used.

[0421] In some embodiments, the mixture may be cultured for several hours (about 3 hours) to about 14 days or any hourly integer value in between. In another embodiment, the beads and T cells are cultured together for 2-3 days. Conditions appropriate for T cell culture include an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 15, (Lonza)) that may contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), interleukin-2 (IL-2), insulin, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGFβ, and TNF-α or any other additives for the growth of cells known to the skilled artisan. Other additives for the growth of cells include, but are not limited to, surfactant, plasmanate, and reducing agents such as N-acetyl-cysteine and 2-mercaptoethanol. Media can include RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, and X-Vivo 20, Optimizer, with added amino acids, sodium pyruvate, and vitamins, either serum-free or supplemented with an appropriate amount of serum (or plasma) or a defined set of hormones, and/or an amount of cytokine(s) sufficient for the growth and expansion of T cells. In some embodiments, the media comprises X-VIVO-15 media supplemented with 5% human A/B serum, 1% penicillin/streptomycin (pen/strep) and 300 Units/ml of IL-2 (Miltenyi).

[0422] The T cells are maintained under conditions necessary to support growth, for example, an appropriate temperature (e.g., 37° C.) and atmosphere (e.g., air plus 5% CO2).

[0423] In some embodiments, the T cells comprising TCRs, CARs and inhibitory receptors of the disclosure are autologous. Prior to expansion and genetic modification, a source of T cells is obtained from a subject. Immune cells such as T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present disclosure, any number of T cell lines available in the art, may be used. In certain embodiments of the present disclosure, T cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation.

[0424] In some embodiments, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In some embodiments, the cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent

processing steps. In some embodiments, the cells are washed with phosphate buffered saline (PBS). In alternative embodiments, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. As those of ordinary skill in the art would readily appreciate a washing step may be accomplished by methods known to those in the art, such as by using a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the Haemonetics Cell Saver 5) according to the manufacturer's instructions. After washing, the cells may be resuspended in a variety of biocompatible buffers, such as, for example, Ca2+-free, Mg2+-free PBS, PlasmaLyte A, or other saline solution with or without buffer. Alternatively, the undesirable components of the apheresis sample may be removed and the cells directly resuspended in culture media.

[0425] In some embodiments, immune cells such as T cells are isolated from peripheral blood lymphocytes by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLL™ gradient or by counterflow centrifugal elutriation. Specific subpopulations of immune cells, such as T cells, B cells, or CD4+ T cells can be further isolated by positive or negative selection techniques. For example, in one embodiment, T cells are isolated by incubation with anti-CD4 -conjugated beads, for a time period sufficient for positive selection of the desired T cells.

[0426] Enrichment of an immune cell population, such as a T cell population, by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One method is cell sorting and/or selection via negative magnetic immune-adherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4+ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD 14, CD20, CD 11b, CD 16, HLA-DR, and CD8.

[0427] For isolation of a desired population of immune cells by positive or negative selection, the concentration of cells and surface (e.g., particles such as beads) can be varied. In certain embodiments, it may be desirable to significantly decrease the volume in which beads and cells are mixed together (i.e., increase the concentration of cells), to ensure maximum contact of cells and beads.

[0428] In some embodiments, the cells may be incubated on a rotator for varying lengths of time at varying speeds at either 2-10° C or at room temperature.

[0429] T cells for stimulation, or PBMCs from which immune cells such as T cells are isolated, can also be frozen after a washing step. Wishing not to be bound by theory, the freeze and subsequent thaw step provides a more uniform product by removing granulocytes

and to some extent monocytes in the cell population. After the washing step that removes plasma and platelets, the cells may be suspended in a freezing solution. While many freezing solutions and parameters are known in the art and will be useful in this context, one method involves using PBS containing 20% DMSO and 8% human serum albumin, or culture media containing 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin and 7.5% DMSO, or 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40 and 5% Dextrose, 20% Human Serum Albumin, and 7.5% DMSO or other suitable cell freezing media containing for example, Hespan and PlasmaLyte A, the cells then are frozen to −80° C at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank. Other methods of controlled freezing may be used as well as uncontrolled freezing immediately at −20° C or in liquid nitrogen.

[0430] The disclosure provides an immune cell expressing the activator and/or blocker receptors described herein, wherein the immune cell has reduced expression and/or function the major histocompatibility (MHC) class I complex.

[0431] In some embodiments, the immune cell is autologous. For example, the immune cells is isolated or derived from same subject who will receive the cell as part of a therapeutic regimen. It can be advantageous to modify autologous immune cells to have reduced expression and/or function of MHC class I with the blocker receptor is specific to an MHC class I antigen. Without wishing to be bound by theory, modification of autologous immune cells to have reduced expression and/or function of MHC class I reduces binding of the blocker receptor by MHC class I expressed by the immune cells, either in cis or in trans .

[0432] In some embodiments, the immune cell is all allogeneic. Allogeneic immune cells can be derived from a donor other than the subject to which the immune cells will be administered. Allogeneic immune cells have been commonly referred to in cell therapy as “off-the-shelf” or “universal” because of the possibility for allogeneic cells to be prepared and stored for use in subjects of a variety of genotypes.

[0433] Any suitable methods of reducing expression and/or function the MHC class I complex are envisaged as within the scope of the instant disclosure, and include, inter alia, expression of interfering RNAs that knock down one or more RNAs encoding MHC class I components, or modifications of genes encoding MHC class I components.

[0434] The major histocompatibility complex (MHC) is a locus on the vertebrate genome that encodes a set of polypeptides required for the adaptive immune system. Among these are MHC class I polypeptides that include HLA-A, HLA-B, and HLA-C and alleles thereof. MHC class I alleles are highly polymorphic and expressed in all nucleated cells. MHC class I

polypeptides encoded by HLA-A, HLA-B, and HLA-C and alleles thereof form heterodimers with β2 microglobulin (B2M) and present in complex with antigens on the surface of cells. As referred to herein, an MHC class I gene or polypeptide may refer to any polypeptide found in the MHC or the corresponding gene encoding said polypeptide. In some embodiments, the immune cells of the disclosure are inactivated by an inhibitor ligand comprising an MHC class I polypeptide, e.g. HLA-A, HLA-B, and HLA-C and alleles thereof. HLA-A alleles can be, for example and without limitation, HLA-A*02, HLA-A*02:01, HLA-A*02:01:01, HLA-A*02:01:01:01, and/or any gene that encodes protein identical or similar to HLA-A*02 protein. Thus, to prevent autocrine signaling/binding as described herein, it is desirable to eliminate or reduce expression of polypeptides encoded by HLA-A, HLA-B, and HLA-C and alleles thereof in the immune cells.

Immune Cells with Reduced MHC Class I Polypeptide Expression

[0435] In some embodiments, the immune cells described herein are modified to inactivate, or reduce or eliminate expression or function of an endogenous gene encoding an allele of an endogenous MHC class I polypeptide. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A, HLA-B, and/or HLA-C. HLA-A, HLA-B and HLA-C are encoded by the HLA-A, HLA-B and HLA-C loci. Each of HLA-A, HLA-B and HLA-C includes many variant alleles, all of which are envisaged as within the scope of the instant disclosure. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A*02. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A*02:01. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A*02:01:01. In some embodiments, the gene encoding the MHC class I polypeptide is HLA-A*02:01:01:01.

[0436] In some embodiments, the genetically engineered immune cells described herein are modified to reduce or eliminate expression of the B2M gene product. The beta-2 microglobulin (B2M) gene encodes a protein that associates with the major histocompatibility complex (MHC) class I, i.e. MHC-I complex. The MHC-I complex is required for presentation of antigens on the cell surface. The MHC -I complex is disrupted and non-functional when the B2M is deleted (Wang D et al. Stem Cells Transl Med. 4:1234-1245 (2015)). Furthermore, the B2M gene can be disrupted with high efficiency using gene editing techniques known in the art (Ren et al. Clin. Cancer Res. 23:2255-2266 (2017)). Reducing or eliminating B2M can reduce, or eliminate functional MHC I on the surface of the immune cell.

[0437] The disclosure provides gene editing systems for editing an endogenous target gene in an immune cell. The disclosure provides interfering RNAs specific to sequences of target genes. Gene editing systems such as CRISPR/Cas systems, TALENs and zinc fingers can be used to generate double strand breaks, which, through gene repair mechanisms such as homology directed repair or non-homologous end joining (NHEJ), can be used to introduce mutations. NHEJ after resection of the ends of the break, or improper end joining, can be used to introduce deletions. In some embodiments, the target gene comprises a gene encoding a subunit of the MHC-I complex.

[0438] Target gene sequences include, but are not limited to, promoters, enhancers, introns, exons, intron/exon junctions, transcription products (pre-mRNA, mRNA, and splice variants), and/or 3' and 5' untranslated regions (UTRs). Any gene element or combination of gene elements may be targeted for the purpose of genetic editing in the immune cells described herein. Modifications to the target genes can be accomplished using any method known in the art to edit the target gene that results in altered or disrupted expression or function the target gene or gene product.

[0439] In some embodiments, modifying the gene encoding the MHC class I polypeptide comprises deleting all or a portion of the gene. In some embodiments, modifying the gene encoding the MHC class I polypeptide comprises introducing a mutation in the gene. In some embodiments, the mutation comprises a deletion, insertion, substitution, or frameshift mutation. In some embodiments, modifying the gene comprises using a nucleic acid guided endonuclease.

[0440] Gene sequences for the target genes described herein are known in the art. The sequences can be found at public databases, such as NCBI GenBank or the NCBI nucleotide database. Sequences may be found using gene identifiers, for example, the HLA-A gene has NCBI Gene ID: 3105, the HLA-B gene has NCBI Gene ID: 3106, the HLA-C gene has NCBI Gene ID: 3107, and the *B2M* gene has NCBI Gene ID: 567 and NCBI Reference Sequence: NC_000015.10. Gene sequences may also be found by searching public databases using keywords. For example, HLA-A alleles may be found in the NCBI nucleotide database by searching keywords, "HLA-A*02", "HLA-A*02:01", "HLA-A*02:01:01", or "HLA-A*02:01:01:01." These sequences can be used for targeting in various gene editing techniques known in the art. Table 10 provides non-limiting illustrative sequences of HLA-A allele and B2M gene sequences targeted for modification as described herein.

Table 10. Exemplary Target Gene Sequences

B2M mRNA	SEQ ID NO: 769

B2M Gene (GenBank: 567)	SEQ ID NO: 770
HLA-A*02:01:01:01 sequence encoding mRNA	SEQ ID NO: 771
HLA-A*02 (GenBank: LK021978.1)	SEQ ID NO: 772

[0441] The person of ordinary skill in the art will appreciate that T can be substituted for U to convert an RNA sequence to a DNA sequence and vice versa, and both are envisaged as target gene sequences of the disclosure.

[0442] In some embodiments, a target gene is edited in the immune cells described herein using a nucleic acid guided endonuclease. Exemplary nucleic acid guided endonucleases include Class II endonucleases, such as CRISPR/Cas9.

[0443] "CRISPR" or "CRISPR gene editing" as used herein refers to a set of clustered regularly interspaced short palindromic repeats, or a system comprising such a set of repeats. "Cas", as used herein, refers to a CRISPR-associated protein. A "CRISPR/Cas" system refers to a system derived from CRISPR and Cas which can be used to silence, knock out, or mutate a target gene. This system is a type of prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. The CRISPR/Cas system has been modified for use in gene editing. This is accomplished by introducing into the eukaryotic cell a one or more specifically designed guide nucleic acids (gNAs), typically guide RNAs (gRNAs), and an appropriate Cas endonuclease which forms a ribonucleoprotein complex with the gNA. The gNA guides the gNA-endonuclease protein complex to a target genomic location, and the endonuclease introduces strand breakage at the target genomic location. This strand breakage can be repaired by cellular mechanisms such non-homologous end joining (leading to deletions) or homologous repair (which can generate insertions), thereby introducing genetic modifications into the host cell genome.

[0444] CRISPR/Cas systems are classified by class and by type. Class 2 systems currently represent a single interference protein that is categorized into three distinct types (types II, V and VI). Any class 2 CRISPR/Cas system suitable for gene editing, for example a type II, a type V or a type VI system, is envisaged as within the scope of the instant disclosure. Exemplary Class 2 type II CRISPR systems include Cas9, Csn2 and Cas4. Exemplary Class 2, type V CRISPR systems include, Cas12, Cas12a (Cpf1), Cas12b (C2c1), Cas12c (C2c3), Cas12d (CasY), Cas12e (CasX), Cas12f, Cas12g, Cas12h, Cas12i and Cas12k (C2c5). Exemplary Class 2 Type VI systems include Cas13, Cas13a (C2c2) Cas13b, Cas13c and Cas13d.

[0445] The CRISPR sequence, sometimes called a CRISPR locus, comprises alternating repeats and spacers. In a naturally-occurring CRISPR, the spacers usually comprise sequences foreign to the bacterium such as a plasmid or phage sequence. As described herein, spacer sequences may also be referred to as "targeting sequences." In CRISPR/Cas systems for a genetic engineering, the spacers are derived from the target gene sequence (the gNA).

[0446] An exemplary Class 2 type II CRISPR system relies on the protein Cas9, which is a nuclease with two active cutting sites, one for each strand of the double helix. Combining Cas9 and modified CRISPR locus RNA can be used in a system for gene editing. Pennisi (2013) Science 341: 833-836. In some embodiments, the Cas protein used to modify the immune cells is Cas9.

[0447] The CRISPR/Cas system can thus be used to edit a target gene, such as a gene targeted for editing in the immune cells described herein, by adding or deleting a base pair, or introducing a premature stop which thus decreases expression of the target. The CRISPR/Cas system can alternatively be used like RNA interference, turning off a target gene in a reversible fashion. In a mammalian cell, for example, the RNA can guide the Cas protein to a target gene promoter, sterically blocking RNA polymerases.

[0448] A Cas protein may be derived from any bacterial or archaeal Cas protein. Any suitable CRISPR/Cas system is envisaged as within the scope of the instant disclosure. In other aspects, Cas protein comprises one or more of Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas9, Cas10, Cas12a (Cpf1), Cas13, Csy1, Csy2, Csy3, Cse1, Cse2, Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, CasX, CasY, homologs thereof, or modified versions thereof. In some embodiments, the Cas protein is a Cas9 protein, a Cpf1 protein, a C2c1 protein, a C2c2 protein, a C2c3 protein, Cas3, Cas3-HD, Cas 5, Cas7, Cas8, Cas10, or combinations or complexes of these. In some embodiments, the Cas protein is a Cas9 protein.

[0449] Artificial CRISPR/Cas systems can be generated which inhibit a target gene, using technology known in the art, *e.g.*, that described in U.S. Publication No. 20140068797, and Cong (2013) Science 339: 819-823. Other artificial CRISPR/Cas systems that are known in the art may also be generated which inhibit a target gene, *e.g.*, that described in Tsai (2014) Nature Biotechnol., 32:6 569-576, U.S. Pat. Nos. 8,871,445; 8,865,406; 8,795,965; 8,771,945; and 8,697,359. Methods of designing suitable gNAs for a particular Cas protein will be known by persons of ordinary skill in the art.

[0450] The present disclosure provides gene-targeting guide nucleic acids (gNAs) that can direct the activities of an associated polypeptide (e.g., nucleic acid guided endonuclease) to a specific target gene sequence within a target nucleic acid genome. The genome-targeting nucleic acid can be an RNA. A genome-targeting RNA is referred to as a "guide RNA" or "gRNA" herein. A guide RNA can comprise at least a targeting sequence that hybridizes to a target nucleic acid sequence of interest, and a CRISPR repeat sequence. In some Type II systems, the gRNA also comprises a second RNA called the tracrRNA sequence, also referred to herein as a "scaffold" sequence. In the Type II guide RNA (gRNA), the CRISPR repeat sequence and scaffold sequence hybridize to each other to form a duplex. In the Type V guide RNA (gRNA), the crRNA forms a duplex. In both systems, the duplex can bind a site-directed polypeptide, such that the guide RNA and site-directed polypeptide form a complex. The gene-targeting nucleic acid can provide target specificity to the complex by virtue of its association with the site-directed polypeptide. The gene-targeting nucleic acid thus can direct the activity of the site-directed polypeptide.

[0451] In some embodiments, the disclosure provides a guide RNA comprising a targeting sequence and a guide RNA scaffold sequence, wherein the targeting sequence is complementary to the sequence of a target gene.

[0452] Exemplary guide RNAs include targeting sequences of about 15-20 bases. As is understood by the person of ordinary skill in the art, each gRNA can be designed to include a targeting sequence complementary to its genomic target sequence. For example, each of the targeting sequences, e.g., the RNA version of the DNA sequences presented in Tables 11 and 14, minus the three 3' nucleotides which represent that PAM site, can be put into a single RNA chimera or a crRNA.

[0453] The gene targeting nucleic acid can be a double-molecule guide RNA. The gene targeting nucleic acid can be a single-molecule guide RNA. The gene targeting nucleic acid can be any known configuration of guide RNA known in the art, such as, for example, including paired gRNA, or multiple gRNAs used in a single step. Although it is clear from genomic sequences where the coding sequences and splice junctions are, other features required for gene expression may be idiosyncratic and unclear.

[0454] A double-molecule guide RNA can comprise two strands of RNA. The first strand comprises a sequence in the 5′ to 3′ direction, an optional spacer extension sequence, a targeting sequence and a minimum CRISPR repeat sequence. The second strand can comprise a minimum tracrRNA sequence (complementary to the minimum CRISPR repeat sequence), a 3′ tracrRNA sequence and an optional tracrRNA extension sequence.

[0455] A single-molecule guide RNA (sgRNA) in a Type II system can comprise, in the 5′ to 3′ direction, an optional spacer extension sequence, a targeting sequence, a minimum CRISPR repeat sequence, a single-molecule guide linker, a minimum tracrRNA sequence, a 3′ tracrRNA sequence and an optional tracrRNA extension sequence. The optional tracrRNA extension can comprise elements that contribute additional functionality (e.g., stability) to the guide RNA. The single-molecule guide linker can link the minimum CRISPR repeat and the minimum tracrRNA sequence to form a hairpin structure. The optional tracrRNA extension can comprise one or more hairpins.

[0456] In some embodiments, guide RNA or single-molecule guide RNA (sgRNA) can comprise a targeting sequence and a scaffold sequence. In some embodiments, the scaffold sequence is a Cas9 gRNA sequence. In some embodiments, the scaffold sequence is encoded by a DNA sequence that comprises a sequence that shares at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTT (SEQ ID NO: 773). In some embodiments, the scaffold sequence is encoded by a DNA sequence that comprises GTTTTAGAGCTAGAAATAGCAAGTTAAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTT (SEQ ID NO: 773).

[0457] In some embodiments, for example those embodiments where the CRISPR/Cas system is a Cas9 system, the sgRNA can comprise a 20 nucleotide targeting sequence at the 5′ end of the sgRNA sequence. The sgRNA can comprise a less than a 20 nucleotide targeting sequence at the 5′ end of the sgRNA sequence. The sgRNA can comprise a more than 20 nucleotide targeting sequence at the 5′ end of the sgRNA sequence. The sgRNA can comprise a variable length targeting sequence with 17-30 nucleotides at the 5′ end of the sgRNA sequence.

[0458] Suitable scaffold sequences, and arrangement of scaffold targeting sequences, will depend on choice of endonuclease, and will be known to persons of skill in the art.

[0459] A single-molecule guide RNA (sgRNA) in a Type II system, *e.g.* Cas9, can comprise, in the 5′ to 3′ direction, a minimum CRISPR repeat sequence and a targeting sequence.

[0460] By way of illustration, guide RNAs used in the CRISPR/Cas9 or CRISPR/Cpf1 system, or other smaller RNAs can be readily synthesized by chemical means, as illustrated below and described in the art. While chemical synthetic procedures are continually expanding, purifications of such RNAs by procedures such as high performance liquid chromatography (HPLC, which avoids the use of gels such as PAGE) tends to become more

challenging as polynucleotide lengths increase significantly beyond a hundred or so nucleotides. One approach used for generating RNAs of greater length is to produce two or more molecules that are ligated together. Much longer RNAs, such as those encoding a Cas9 or Cpf1 endonuclease, are more readily generated enzymatically. Various types of RNA modifications can be introduced during or after chemical synthesis and/or enzymatic generation of RNAs, e.g., modifications that enhance stability, reduce the likelihood or degree of innate immune response, and/or enhance other attributes, as described in the art.

[0461] The targeting sequence of a gRNA hybridizes to a sequence in a target nucleic acid of interest. The targeting sequence of a genome-targeting nucleic acid can interact with a target nucleic acid in a sequence-specific manner via hybridization (i.e., base pairing). The nucleotide sequence of the targeting sequence can vary depending on the sequence of the target nucleic acid of interest.

[0462] In a Cas9 system described herein, the targeting sequence can be designed to hybridize to a target nucleic acid that is located 5′ of the reverse complement of a PAM of the Cas9 enzyme used in the system. The targeting sequence may perfectly match the target sequence or may have mismatches. Each CRISPR/Cas system protein may have a particular PAM sequence, in a particular orientation and position, that it recognizes in a target DNA. For example, S. pyogenes Cas9 recognizes in a target nucleic acid a PAM that comprises the sequence 5′-NRG-3′, where R comprises either A or G, where N is any nucleotide and N is immediately 3′ of the target nucleic acid sequence targeted by the targeting sequence. Selection of appropriate PAM sequences will be apparent to the person of ordinary skill in the art.

[0463] The target sequence is complementary to, and hybridizes with, the targeting sequence of the gRNA. The target nucleic acid sequence can comprise 20 nucleotides. The target nucleic acid can comprise less than 20 nucleotides. The target nucleic acid can comprise more than 20 nucleotides. The target nucleic acid can comprise at least: 5, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30 or more nucleotides. In some embodiments, for example those embodiments where the CRISPR/Cas system is a Cas9 system, the target nucleic acid sequence can comprise 20 nucleotides immediately 5′ of the first nucleotide of the reverse complement of the PAM sequence. This target nucleic acid sequence is often referred to as the PAM strand or a target strand, and the complementary nucleic acid sequence is often referred to the non-PAM strand or non-target strand. One of skill in the art would recognize that the targeting sequence hybridizes to the non-PAM strand of the target nucleic acid, see *e.g.*, US20190185849A1.

[0464] In some examples, the percent complementarity between the targeting sequence and the target nucleic acid is at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, or 100%. In some examples, the percent complementarity between the targeting sequence and the target nucleic acid is at most about 30%, at most about 40%, at most about 50%, at most about 60%, at most about 65%, at most about 70%, at most about 75%, at most about 80%, at most about 85%, at most about 90%, at most about 95%, at most about 97%, at most about 98%, at most about 99%, or 100%. In some examples, the percent complementarity between the targeting sequence and the target nucleic acid is 100% over the six contiguous 5′-most nucleotides of the target sequence of the complementary strand of the target nucleic acid. The percent complementarity between the targeting sequence and the target nucleic acid can be at least 60% over about 20 contiguous nucleotides. The length of the targeting sequence and the target nucleic acid can differ by 1 to 6 nucleotides, which may be thought of as a bulge or bulges.

[0465] The targeting sequence can be designed or chosen using computer programs known to persons of ordinary skill in the art. The computer program can use variables, such as predicted melting temperature, secondary structure formation, predicted annealing temperature, sequence identity, genomic context, chromatin accessibility, % GC, frequency of genomic occurrence (e.g., of sequences that are identical or are similar but vary in one or more spots as a result of mismatch, insertion or deletion), methylation status, presence of SNPs, and the like. Available computer programs can take as input NCBI gene IDs, official gene symbols, Ensembl Gene IDs, genomic coordinates, or DNA sequences, and create an output file containing sgRNAs targeting the appropriate genomic regions designated as input. The computer program may also provide a summary of statistics and scores indicating on- and off-target binding of the sgRNA for the target gene (Doench et al. *Nat Biotechnol.* 34:184-191 (2016)).The disclosure provides guide RNAs comprising a targeting sequence. In some embodiments, the guide RNA further comprises a guide RNA scaffold sequence. In some embodiments, the targeting sequence is complementary to the sequence of a target gene selected from the group consisting of HLA-A, HLA-B, HLA-C, B2M or an allele thereof. In some embodiments, the target gene is an HLA-A gene. In some embodiments, the target gene is an HLA-B gene. In some embodiments, the target gene is an HLA-C gene. In some embodiments the target gene is HLA-A, HLA-B, HLA-C, or a combination thereof. In some embodiments, targeting sequence comprises a sequence that shares about 90%, about 95%,

about 96%, about 97%, about 98%, about 99% identity to or is identical to a sequence disclosed in Tables 11 and14.

[0466] In some embodiments, the gNAs specifically target the sequence of an endogenous HLA-A locus. In some embodiments, the gNAs that specifically target the sequence of an HLA-A locus comprise a sequence that shares about 90%, about 95%, about 96%, about 97%, about 98%, or about 99% identity to a sequence selected from the sequences disclosed in Table 11. In some embodiments, the gNAs that specifically target the sequence of an HLA-A locus comprise a sequence selected from the sequences disclosed in Table 11.

[0467] In some embodiments, the gNAs specifically target a sequence of HLA-A*02 alleles. For example, the gRNAs specifically target, and hybridize to, a sequence shared by all HLA-A*02 alleles, but that is not shared by HLA-A*02 and HLA-A*03 alleles. In some embodiments, the gNAs specifically target a sequence of HLA-A*02:01 alleles. In some embodiments, the gNAs specifically target a sequence of HLA-A*02:01:01 alleles. In some embodiments, the gNAs specifically target a sequence of HLA-A*02:01:01:01 alleles. In some embodiments, the gNAs specifically target a sequence of HLA-A*02:01:01:01 alleles.

[0468] In some embodiments, the gNAs specifically target a coding DNA sequence of HLA-A*02.

[0469] In some embodiments, the gNAs specifically target a coding DNA sequence that is shared by more than 1000 HLA-A*02 alleles. In some embodiments, the gNAs that specifically target a coding DNA sequence in greater than 1000 HLA-A*02 alleles comprise a sequence that shares about 90%, about 95%, about 96%, about 97%, about 98%, about 99% identity or is identical to a sequence selected from the sequences set forth in Table 11.

[0470] The sequences in Tables 11-14 are presented as DNA sequences. The skilled artisan will understand that thymine (T) can be replaced with uracil (U) in any DNA sequence including those set forth in Tables 11-14, to arrive at the corresponding RNA sequence.

[0471] Table 11. Illustrative sequences targeting HLA-A and HLA-A alleles

SEQ ID NO	Guide Nucleic Acid Targeting Sequences
774	TGGACGACACGCAGTTCGTG
775	CAGATACCTGGAGAACGGGA
776	TCCCGTTCTCCAGGTATCTG
777	CCGCCGCGGTCCAAGAGCGC
778	CCTGCGCTCTTGGACCGCGG
779	GGACCTGCGCTCTTGGACCGC
780	AAGGAGACGCTGCAGCGCACGGG
781	GAAGGAGACGCTGCAGCGCACGG
782	GCGGGCGCCGTGGATAGAGCAGG
783	TGCTCTATCCACGGCGCCCGCGG
784	CGATGAAGCGGGGCTCCCCGCGG
785	CGTGTCCCGGCCCGGCCGCGGGG
786	CGGCTCCATCCTCTGGCTCGCGG
787	GATGTAATCCTTGCCGTCGTAGG
788	ACAGCGACGCCGCGAGCCAGAGG
789	GGATGGAGCCGCGGGCGCCGTGG
790	GGCGCCGTGGATAGAGCAGGAGG
791	GCGCCGTGGATAGAGCAGGAGGG
792	CGGCTACTACAACCAGAGCGAGG
793	CTGGTTGTAGTAGCCGCGCAGGG
794	TACTACAACCAGAGCGAGGCCGG
795	CTACCTGGAGGGCACGTGCGTGG
796	CACGCACGTGCCCTCCAGGTAGG
797	GCAGGGTCCCCAGGTCCACTCGG
798	GTGGACCTGGGGACCCTGCGCGG
799	TGGAGGGCACGTGCGTGGAGTGG
800	GTATGGCTGCGACGTGGGGTCGG
801	CTGAGCTGCCATGTCCGCCGCGG
802	GGATTACATCGCCCTGAAAGAGG
803	CAAGTGGGAGGCGGCCCATGTGG
804	GTGGGAGGCGGCCCATGTGGCGG
805	CAGTTGAGAGCCTACCTGGAGGG
806	GCAGTTGAGAGCCTACCTGGAGG
807	TACCACCAGTACGCCTACGACGG
808	TGCCGTCGTAGGCGTACTGGTGG
809	CCAGTACGCCTACGACGGCAAGG
810	GGATGTGAAGAAATACCTCATGG
811	ATTTCTTCACATCCGTGTCCCGG
812	AGGCGTACTGGTGGTACCCGCGG
813	CGTACTGGTGGTACCCGCGGAGG
814	GAGGATGTATGGCTGCGACGTGG
815	GGATGTATGGCTGCGACGTGGGG
816	CTCAGACCACCAAGCACAAGTGG
817	TCAGACCACCAAGCACAAGTGGG
818	CACCAAGCACAAGTGGGAGGCGG
819	GACCACCAAGCACAAGTGGGAGG
820	GAGCCCCGCTTCATCGCAGTGGG
821	GTAGCCCACTGCGATGAAGCGGG
822	TAGCCCACTGCGATGAAGCGGGG
823	CGTAGCCCACTGCGATGAAGCGG
824	CTTCATCGCAGTGGGCTACGTGG
825	GGAGCCCCGCTTCATCGCAGTGG
826	CGGGGAGACACGGAAAGTGAAGG
827	AGTATTGGGACGGGGAGACACGG
828	AGGGTCCGGAGTATTGGGACGGG
829	GAGGGTCCGGAGTATTGGGACGG
830	GGACCCTCCTGCTCTATCCACGG
831	GTGGATAGAGCAGGAGGGTCCGG
832	AGACTCACCGAGTGGACCTGGGG
833	CACTCGGTGAGTCTGTGAGTGGG
834	CAGACTCACCGAGTGGACCTGGG
835	CCACTCACAGACTCACCGAGTGG
836	CCACTCGGTGAGTCTGTGAGTGG
837	TCGGACTGGCGCTTCCTCCGCGG
838	GCAGCCATACATCCTCTGGACGG
839	TCTCAACTGCTCCGCCACATGGG
840	ACCCTCATGCTGCACATGGCAGG
841	ACCTGCCATGTGCAGCATGAGGG
842	CACCTGCCATGTGCAGCATGAGG
843	GGAGGACCAGACCCAGGACACGG
844	GGATGGGGAGGACCAGACCCAGG
845	GACCTGGCAGCGGGATGGGGAGG
846	AGATCACACTGACCTGGCAGCGG
847	GATCACACTGACCTGGCAGCGGG
848	AGGTCAGTGTGATCTCCGCAGGG
849	AAGCCCCTCACCCTGAGATGGGG
850	CTGCGGAGATCACACTGACCTGG
851	CAGCAATGATGCCCACGATGGGG
852	CCAGCAATGATGCCCACGATGGG
853	GCCAGCAATGATGCCCACGATGG
854	GGATGGAACCTTCCAGAAGTGGG
855	GGGATGGAACCTTCCAGAAGTGG
856	ATGCCCACGATGGGGATGGTGGG
857	CAGCCCACCATCCCCATCGTGGG
858	CCAGCCCACCATCCCCATCGTGG
859	GATGCCCACGATGGGGATGGTGG

SEQ ID NO	Guide Nucleic Acid Targeting Sequences
860	CAGGGCCCAGCACCTCAGGGTGG
861	AATGATGCCCACGATGGGGATGG
862	GGCCCTGACCCAGACCTGGGCGG
863	GACCCAGGACACGGAGCTCGTGG
864	ACACGGAGCTCGTGGAGACCAGG
865	CGTGGAGACCAGGCCTGCAGGGG
866	TCGTGGAGACCAGGCCTGCAGGG
867	AGCTGTGATCACTGGAGCTGTGG
868	AAAAGGAGGGAGCTACTCTCAGG
869	ATGTGGAGGAGGAAGAGCTCAGG
870	GTGTCTCTCACAGCTTGTAAAGG
871	GAGAGACACATCAGAGCCCTGGG
872	CTCCGCAGGGTAGAAGCTCAGGG
873	GGCCCTGAGCTTCTACCCTGCGG
874	GCTCAGGGCCCAGCACCTCAGGG
875	TATCTCTGCTCCTGTCCAGAAGG
876	AGTAGCAGGACGAGGGTTCGGGG

SEQ ID NO	Guide Nucleic Acid Targeting Sequences
877	CCCCGAGAGTAGCAGGACGAGGG
878	CCCTCGTCCTGCTACTCTCGGGG
879	CCTCGTCCTGCTACTCTCGGGGG
880	CTGTGGTCGCTGCTGTGATGTGG
881	TCGCTGCTGTGATGTGGAGGAGG
882	TGGTCGCTGCTGTGATGTGGAGG
883	CACAGCCGCCCACTTCTGGAAGG
884	CCAGAAGTGGGCGGCTGTGGTGG
885	TGGAACCTTCCAGAAGTGGGCGG
886	TCACAGCTCCAAAGAGAACCAGG
887	CTGACCATGAAGCCACCCTGAGG
888	GCAAACCCTCATGCTGCACATGG
889	TGAAGCCACCCTGAGGTGCTGGG
890	GGTGAGTCATATGCGTTTTGGGG
891	GTGAGTCATATGCGTTTTGGGGG
892	CTTCATGGTCAGAGACAGCGTGG
893	TCTGGCCCTGACCCAGACCTGGG

[0472] The sequences disclosed in Table 11 include the corresponding genomic sequences, inclusive of the PAM sequence. The skilled artisan will understand that the targeting sequence of the gRNA does not include three 3' terminal nucleotides of the sequences in Table 11, which represent the corresponding PAM site for the gRNA.

[0473] The disclosure provides gNAs comprising a targeting sequence specific to the *B2M* gene. In some embodiments, the gNAs specifically target the coding sequence (CDS) sequence of the B2M gene. In some embodiments, the gNA comprises a sequence that targets the *B2M* gene promoter sequence.

[0474] In some embodiments the gNA comprise a targeting sequence and a gNA scaffold sequence. In some embodiments, the targeting sequence comprises a sequence set forth in Table 12, or a sequence shares about 90%, about 95%, about 96%, about 97%, about 98%, about 99% identity thereto.

[0475] In some embodiments, the targeting sequence is complementary to a sequence of the *B2M* gene. In some embodiments, the *B2M* gene comprises a sequence that shares about 90%, about 95%, about 96%, about 97%, about 98%, about 99% identity to the B2M sequence set forth in Table 10.

Table 12. Illustrative sequences targeting *B2M*

SEQ ID NO	Sequence
894	CGCGAGCACAGCTAAGGCCA
895	GAGTAGCGCGAGCACAGCTA
896	AGGGTAGGAGAGACTCACGC
897	CTGAATCTTTGGAGTACCTG
898	TCACGTCATCCAGCAGAGAA
899	TCCTGAATTGCTATGTGTCT
900	AAGTCAACTTCAATGTCGGA
901	GTCTTTTCCCGATATTCCTC
902	TGGAGTACCTGAGGAATATC
903	CAGCCCAAGATAGTTAAGTG
904	ACAAAGTCACATGGTTCACA
905	ACTCTCTCTTTCTGGCCTGG
906	TGGGCTGTGACAAAGTCACA
907	GGCCGAGATGTCTCGCTCCG
908	CAGTAAGTCAACTTCAATGT
909	ACTCACGCTGGATAGCCTCC
910	CATACTCATCTTTTTCAGTG
911	CACAGCCCAAGATAGTTAAG
912	TTCAGACTTGTCTTTCAGCA
913	AGTCACATGGTTCACACGGC
914	ATACTCATCTTTTTCAGTGG
915	GGCATACTCATCTTTTTCAG
916	ACAGCCCAAGATAGTTAAGT
917	GCTACTCTCTCTTTCTGGCC
918	TGGAGAGAGAATTGAAAAAG
919	ACTTGTCTTTCAGCAAGGAC
920	GAAGTTGACTTACTGAAGAA
921	GGCCACGGAGCGAGACATCT
922	GCATACTCATCTTTTTCAGT
923	CGTGAGTAAACCTGAATCTT
924	TTACCCCACTTAACTATCTT
925	TTGGAGTACCTGAGGAATAT
926	ACCCAGACACATAGCAATTC
927	TTTGACTTTCCATTCTCTGC
928	TTCCTGAATTGCTATGTGTC
929	CTCAGGTACTCCAAAGATTC
930	CTTACCCCACTTAACTATCT
931	CTCGCGCTACTCTCTCTTTC
932	TCGATCTATGAAAAAGACAG
933	GAGACATGTAAGCAGCATCA
934	ACATGTAAGCAGCATCATGG
935	GAAGTCCTAGAATGAGCGCC
936	GAGCGCCCGGTGTCCCAAGC
937	AGCGCCCGGTGTCCCAAGCT
938	GCGCCCGGTGTCCCAAGCTG
939	CTGGGGCGCGCACCCCAGAT

SEQ ID NO	Sequence
940	GGGCGCGCACCCCAGATCGG
941	GGCGCGCACCCCAGATCGGA
942	CATCACGAGACTCTAAGAAA
943	TAAGAAAAGGAAACTGAAAA
944	AAGAAAAGGAAACTGAAAAC
945	GAAAGTCCCTCTCTCTAACC
946	CTAACCTGGCACTGCGTCGC
947	CTGGCACTGCGTCGCTGGCT
948	TGCGTCGCTGGCTTGGAGAC
949	GCTGGCTTGGAGACAGGTGA
950	GAGACAGGTGACGGTCCCTG
951	AGACAGGTGACGGTCCCTGC
952	CCTGCGGGCCTTGTCCTGAT
953	CGGGCCTTGTCCTGATTGGC
954	GGGCCTTGTCCTGATTGGCT
955	GGGCACGCGTTTAATATAAG
956	CACGCGTTTAATATAAGTGG
957	TATAAGTGGAGGCGTCGCGC
958	AAGTGGAGGCGTCGCGCTGG
959	AGTGGAGGCGTCGCGCTGGC
960	TTCCTGAAGCTGACAGCATT
961	TCCTGAAGCTGACAGCATTC
962	GCCCGAATGCTGTCAGCTTC
963	AAACGCGTGCCCAGCCAATC
964	GTGCCCAGCCAATCAGGACA
965	CCAATCAGGACAAGGCCCGC
966	CAATCAGGACAAGGCCCGCA
967	CAAGCCAGCGACGCAGTGCC
968	CGCAGTGCCAGGTTAGAGAG
969	GCAGTGCCAGGTTAGAGAGA
970	GAGTCTCGTGATGTTTAAGA
971	TAAGAAGGCATGCACTAGAC
972	AAGAAGGCATGCACTAGACT
973	TGAGTTTGCTGTCTGTACAT
974	TACATCGGCGCCCTCCGATC
975	ACATCGGCGCCCTCCGATCT
976	CATCGGCGCCCTCCGATCTG
977	CTGGGGTGCGCGCCCCAGCT
978	TGGGGTGCGCGCCCCAGCTT
979	CGCGCCCCAGCTTGGGACAC
980	GCGCCCCAGCTTGGGACACC
981	CAAGTCACTTAGCATCTCTG
982	ACAGAAGTTCTCCTTCTGCT
983	ATTCAAAGATCTTAATCTTC
984	TTCAAAGATCTTAATCTTCT
985	TTTTCTCGAATGAAAAATGC

SEQ ID NO	Sequence
986	TGCAGGTCCGAGCAGTTAAC
987	GGTCCGAGCAGTTAACTGGC
988	GTCCGAGCAGTTAACTGGCT
989	TCCGAGCAGTTAACTGGCTG
990	AGCAAGTCACTTAGCATCTC
991	GCAAGTCACTTAGCATCTCT
992	TGGGGCCAGTCTGCAAAGCG
993	GGGGCCAGTCTGCAAAGCGA
994	GGGCCAGTCTGCAAAGCGAG
995	GGCCAGTCTGCAAAGCGAGG
996	GGACACCGGGCGCTCATTCT
997	GGCGCTCATTCTAGGACTTC
998	CTCATTCTAGGACTTCAGGC
999	ATTCTAGGACTTCAGGCTGG
1000	TTCAGGCTGGAGGCACATTA
1001	TGCCCCCTCGCTTTGCAGAC
1002	GATGCTAAGTGACTTGCTAA
1003	GCCCCAGCCAGTTAACTGCT
1004	GCATTTTTCATTCGAGAAAA
1005	TTTGAATGCTACCTAGCAGA
1006	TTCTGTTTATAACTACAGCT
1007	TCTGTTTATAACTACAGCTT

[0476] In some embodiments, the immune cells described herein are edited using TALEN gene editing.

[0477] "TALEN" or "TALEN gene editing" refers to a transcription activator-like effector nuclease, which is an artificial nuclease used to edit a target gene.

[0478] TALENs are produced artificially by fusing a TAL effector DNA binding domain to a DNA cleavage domain. Transcription activator-like effectors (TALEs) derived from Xanthomonas bacteria can be engineered to bind any desired DNA sequence, including a portion of target genes such as TCR subunits, MHC class I complex components, or CD52. By combining an engineered TALE with a DNA cleavage domain, a restriction enzyme can be produced which is specific to any desired DNA sequence, including a target gene sequence. These can then be introduced into a cell, wherein they can be used for genome editing.

[0479] To produce a TALEN, a TALE protein is fused to a nuclease (N), which is a wild-type or mutated Fold endonuclease. Several mutations to FokI have been made for its use in TALENs; these, for example, improve cleavage specificity or activity.

[0480] The FokI domain functions as a dimer, requiring two constructs with unique DNA binding domains for sites in the target genome with proper orientation and spacing. Both the number of amino acid residues between the TALE DNA binding domain and the FokI cleavage domain and the number of bases between the two individual TALEN binding sites appear to be important parameters for achieving high levels of activity.

[0481] TALENs specific to sequences in a target gene can be constructed using any method known in the art, including various schemes using modular components.

[0482] In some embodiments, a target gene is edited in the immune cells described herein using ZFN gene editing.

[0483] "ZFN" or "Zinc Finger Nuclease" or "ZFN gene editing" refer to a zinc finger nuclease, an artificial nuclease which can be used to edit a target gene.

[0484] Like a TALEN, a ZFN comprises a Fold nuclease domain (or derivative thereof) fused to a DNA-binding domain. In the case of a ZFN, the DNA-binding domain comprises one or more zinc fingers.

[0485] A zinc finger is a small protein structural motif stabilized by one or more zinc ions. A zinc finger can comprise, for example, Cys2His2, and can recognize an approximately 3-bp sequence. Various zinc fingers of known specificity can be combined to produce multi-finger polypeptides which recognize about 6, 9, 12, 15 or 18-bp sequences. Various selection and modular assembly techniques are available to generate zinc fingers (and combinations thereof)

recognizing specific sequences, including phage display, yeast one-hybrid systems, bacterial one-hybrid and two-hybrid systems, and mammalian cells.

[0486] Like a TALEN, a ZFN must dimerize to cleave DNA. Thus, a pair of ZFNs are required to target non-palindromic DNA sites. The two individual ZFNs must bind opposite strands of the DNA with their nucleases properly spaced apart.

[0487] Also like a TALEN, a ZFN can create a double-stranded break in the DNA, which can create a frame-shift mutation if improperly repaired, leading to a decrease in the expression and amount of a target gene or gene product in a cell. ZFNs can also be used with homologous recombination to mutate in a target gene.

[0488] ZFNs specific to sequences in a target gene can be constructed using any method known in the art.

[0489] In some embodiments, the expression and of function of one or more MCH-I components are reduced using RNA interference. “RNAi” or “RNA interference” refers to the process of sequence-specific post-transcriptional gene silencing, mediated by double-stranded RNA (dsRNA). Duplex RNAs such as siRNA (small interfering RNA), miRNA (micro RNA), shRNA (short hairpin RNA), ddRNA (DNA- directed RNA), piRNA (Piwi-interacting RNA), or rasiRNA (repeat associated siRNA) and modified forms thereof are all capable of mediating RNA interference. These dsRNA molecules may be commercially available or may be designed and prepared based on known sequence information. The anti-sense strand of these molecules can include RNA, DNA, PNA, or a combination thereof. DNA/RNA chimeric polynucleotides include, but are not limited to, a double-strand polynucleotide composed of DNA and RNA that inhibits the expression of a target gene. dsRNA molecules can also include one or more modified nucleotides, as described herein, which can be incorporated on either or both strands.

[0490] In RNAi gene silencing or knockdown, dsRNA comprising a first (anti-sense) strand that is complementary to a portion of a target gene and a second (sense) strand that is fully or partially complementary to the first anti-sense strand is introduced into an organism. After introduction into the organism, the target gene-specific dsRNA is processed into relatively small fragments (siRNAs) and can subsequently become distributed throughout the organism, decrease messenger RNA of target gene, leading to a phenotype that may come to closely resemble the phenotype arising from a complete or partial deletion of the target gene.

[0491] Certain dsRNAs in cells can undergo the action of Dicer enzyme, a ribonuclease III enzyme. Dicer can process the dsRNA into shorter pieces of dsRNA, i.e. siRNAs. RNAi also involves an endonuclease complex known as the RNA induced silencing complex (RISC). Following cleavage by Dicer, siRNAs enter the RISC complex and direct cleavage of a single

stranded RNA target having a sequence complementary to the anti-sense strand of the siRNA duplex. The other strand of the siRNA is the passenger strand. Cleavage of the target RNA takes place in the middle of the region complementary to the anti-sense strand of the siRNA duplex. siRNAs can thus down regulate or knock down gene expression by mediating RNA interference in a sequence-specific manner.

[0492] As used herein with respect to RNA interference, “target gene” or “target sequence” refers to a gene or gene sequence whose corresponding RNA is targeted for degradation through the RNAi pathway using dsRNAs or siRNAs as described herein. Exemplary target gene sequences are shown in Table 10. To target a gene, for example using an siRNA, the siRNA comprises an anti-sense region complementary to, or substantially complementary to, at least a portion of the target gene or sequence, and sense strand complementary to the anti-sense strand. Once introduced into a cell, the siRNA directs the RISC complex to cleave an RNA comprising a target sequence, thereby degrading the RNA. The disclosure provides interfering RNAs. The double stranded RNA molecule of the disclosure may be in the form of any type of RNA interference molecule known in the art. In some embodiments, the double stranded RNA molecule is a small interfering RNA (siRNA). In other embodiments, the double stranded RNA molecule is a short hairpin RNA (shRNA) molecule. In other embodiments, the double stranded RNA molecule is a Dicer substrate that is processed in a cell to produce an siRNA. In other embodiments the double stranded RNA molecule is part of a microRNA precursor molecule.

[0493] In some embodiments, the shRNA is a length to be suitable as a Dicer substrate, which can be processed to produce a RISC active siRNA molecule. See, e.g., Rossi et al., US2005/0244858.

[0494] A Dicer substrate double stranded RNA (*e.g.* a shRNA) can be of a length sufficient that it is processed by Dicer to produce an active siRNA, and may further include one or more of the following properties: (i) the Dicer substrate shRNA can be asymmetric, for example, having a 3' overhang on the anti-sense strand, (ii) the Dicer substrate shRNA can have a modified 3' end on the sense strand to direct orientation of Dicer binding and processing of the dsRNA to an active siRNA, for example the incorporation of one or more DNA nucleotides, and (iii) the first and second strands of the Dicer substrate ds RNA can be from 21-30 bp in length..

[0495] In some embodiments, the interfering RNAs comprise a sequence complementary to a sequence of a B2M mRNA. In some embodiments, the interfering RNA is capable of inducing RNAi-mediated degradation of the B2M mRNA. In some embodiments, the B2M mRNA sequence comprises a coding sequence. In some embodiments, the B2M mRNA sequence comprises an untranslated region.

[0496] In some embodiments, the interfering RNAs comprise a sequence complementary to a sequence of an HLA-A*02 mRNA. In some embodiments, the interfering RNA is capable of inducing RNAi-mediated degradation of the HLA-A*02 mRNA. In some embodiments, the HLA-A*02 mRNA sequence comprises a coding sequence. In some embodiments, the HLA-A*02 mRNA sequence comprises an untranslated region.

[0497] In some embodiments, the interfering RNA is a short hairpin RNA (shRNA). In some embodiments, the shRNA comprises a first sequence, having from 5' to 3' end a sequence complementary to the B2M mRNA; and a second sequence, having from 5' to 3' end a sequence complementary to the first sequence, wherein the first sequence and second sequence form the shRNA.

[0498] In some embodiments, the first sequence is 18, 19, 20, 21, or 22 nucleotides. In some embodiments, the first sequence is complementary to a sequence selected from the sequences set forth in Tables 13 and 14. In some embodiments, the first sequence has GC content greater than or equal to 25% and less than 60%. In some embodiments, the first sequence is complementary to a sequence selected from the sequences set forth in Tables 13 and 14. In some embodiments, the first sequence does not comprise four nucleotides of the same base or a run of seven C or G nucleotide bases. In some embodiments, the first sequence is 21 nucleotides.

[0499] Illustrative target B2M sequences complementary to the first sequence are shown in Table 13.

[0500] In some cases, the first sequence may have 100% identity, i.e. complete identity, homology, complementarity to the target nucleic acid sequence. In other cases, there may be one or more mismatches between the first sequence and the target nucleic acid sequence. For example, there may be 1, 2, 3, 4, 5, 6, or 7 mismatches between the sense region and the target nucleic acid sequence.

[0501] The sequences set forth in Table 13 are presented as DNA sequences. In all sequences set forth in Table 13, thymine (T) may be replaced by uracil (U) to arrive at the sequence of the target mRNA sequence.

Table 13. Illustrative target B2M sequences complementary to first sequence

SEQ ID NO	Sequence
1008	AGAGAATGGAAAGTCAAATTT
1009	ATGGACATGATCTTCTTTATA
1010	TGGACATGATCTTCTTTATAA
1011	GGACATGATCTTCTTTATAAT
1012	TGACAGGATTATTGGAAATTT
1013	TTGTGGTTAATCTGGTTTATT
1014	TGTGGTTAATCTGGTTTATTT

SEQ ID NO	Sequence
1015	GCAGAGAATGGAAAGTCAAAT
1016	CAGAGAATGGAAAGTCAAATT
1017	GAGAATGGAAAGTCAAATTTC
1018	GTCACAGCCCAAGATAGTTAA
1019	TGCTTATACACTTACACTTTA
1020	GCTTATACACTTACACTTTAT
1021	CTTATACACTTACACTTTATG

SEQ ID NO	Sequence
1022	ACATGGACATGATCTTCTTTA
1023	CATGGACATGATCTTCTTTAT
1024	ATCAACATCTTGGTCAGATTT
1025	CTTGCACTCAAAGCTTGTTAA
1026	AGTTAAGCGTGCATAAGTTAA
1027	GCATAAGTTAACTTCCAATTT
1028	TACATACTCTGCTTAGAATTT
1029	ACATACTCTGCTTAGAATTTG
1030	TTGACAGGATTATTGGAAATT
1031	GACAGGATTATTGGAAATTTG
1032	TAAGGCATGGTTGTGGTTAAT
1033	GTTGTGGTTAATCTGGTTTAT
1034	GTTCCACAAGTTAAATAAATC
1035	TCCAGCGTACTCCAAAGATTC
1036	TACTCCAAAGATTCAGGTTTA
1037	ACTCCAAAGATTCAGGTTTAC
1038	CACGTCATCCAGCAGAGAATG
1039	GGTTTCATCCATCCGACATTG
1040	CCGACATTGAAGTTGACTTAC
1041	TGAAGAATGGAGAGAGAATTG
1042	GAGCATTCAGACTTGTCTTTC
1043	TTCAGCAAGGACTGGTCTTTC
1044	GCAAGGACTGGTCTTTCTATC
1045	CGTGTGAACCATGTGACTTTG
1046	CTTTGTCACAGCCCAAGATAG
1047	TCACAGCCCAAGATAGTTAAG
1048	AGTGGGATCGAGACATGTAAG
1049	AGGTTTGAAGATGCCGCATTT
1050	GGTTTGAAGATGCCGCATTTG
1051	TTGATATGCTTATACACTTAC
1052	TGAGTGCTGTCTCCATGTTTG
1053	TGTCTCCATGTTTGATGTATC
1054	TCAACATCTTGGTCAGATTTG
1055	TCAGATTTGAACTCTTCAATC
1056	TTCAATCTCTTGCACTCAAAG
1057	TTGCACTCAAAGCTTGTTAAG
1058	ACTCAAAGCTTGTTAAGATAG
1059	AGATAGTTAAGCGTGCATAAG
1060	TGCATAAGTTAACTTCCAATT
1061	GTTAACTTCCAATTTACATAC
1062	ATTGACAGGATTATTGGAAAT
1063	GTAAGGCATGGTTGTGGTTAA
1064	GGTTGTGGTTAATCTGGTTTA
1065	TTCCTGAAGCTGACAGCATTC
1066	GCTATCCAGCGTACTCCAAAG
1067	CATCCAGCAGAGAATGGAAAG
1068	CAAATTTCCTGAATTGCTATG
1069	ATTGCTATGTGTCTGGGTTTC
1070	GAAGATGCCGCATTTGGATTG
1071	CAATTTACATACTCTGCTTAG
1072	TATCCAGCGTACTCCAAAGAT
1073	ATCCAGCGTACTCCAAAGATT
1074	CTCCAAAGATTCAGGTTTACT
1075	TGCTATGTGTCTGGGTTTCAT
1076	TTTCATCCATCCGACATTGAA
1077	GAAGTTGACTTACTGAAGAAT

SEQ ID NO	Sequence
1078	GAAGAATGGAGAGAGAATTGA
1079	AGAATGGAGAGAGAATTGAAA
1080	CAGCAAGGACTGGTCTTTCTA
1081	AGCAAGGACTGGTCTTTCTAT
1082	ACTTTGTCACAGCCCAAGATA
1083	TTGTCACAGCCCAAGATAGTT
1084	TGTCACAGCCCAAGATAGTTA
1085	CACAGCCCAAGATAGTTAAGT
1086	GCAGCATCATGGAGGTTTGAA
1087	CCGCATTTGGATTGGATGAAT
1088	TTGAGTGCTGTCTCCATGTTT
1089	AGTGCTGTCTCCATGTTTGAT
1090	CTGTCTCCATGTTTGATGTAT
1091	TCTAGGAGGGCTGGCAACTTA
1092	CAACATCTTGGTCAGATTTGA
1093	GTCAGATTTGAACTCTTCAAT
1094	TCTTGCACTCAAAGCTTGTTA
1095	TGCACTCAAAGCTTGTTAAGA
1096	GCACTCAAAGCTTGTTAAGAT
1097	CACTCAAAGCTTGTTAAGATA
1098	TCAAAGCTTGTTAAGATAGTT
1099	CAAAGCTTGTTAAGATAGTTA
1100	GATAGTTAAGCGTGCATAAGT
1101	ATAGTTAAGCGTGCATAAGTT
1102	TAGTTAAGCGTGCATAAGTTA
1103	TTAAGCGTGCATAAGTTAACT
1104	TAAGCGTGCATAAGTTAACTT
1105	ATTTACATACTCTGCTTAGAA
1106	TTTACATACTCTGCTTAGAAT
1107	ACAGGATTATTGGAAATTTGT
1108	CAGGATTATTGGAAATTTGTT
1109	AGGCATGGTTGTGGTTAATCT
1110	CAGCAGAGAATGGAAAGTCAA
1111	TCCGACATTGAAGTTGACTTA
1112	CTGGTCTTTCTATCTCTTGTA
1113	CCGTGTGAACCATGTGACTTT
1114	CCCAAGATAGTTAAGTGGGAT
1115	GGTTGCTCCACAGGTAGCTCT
1116	GCTCCACAGGTAGCTCTAGGA
1117	GGGAGCAGAGAATTCTCTTAT
1118	GGAGCAGAGAATTCTCTTATC
1119	GAGCAGAGAATTCTCTTATCC
1120	GAGAATTCTCTTATCCAACAT
1121	GAATTCTCTTATCCAACATCA
1122	AAGTGGAGCATTCAGACTTGT
1123	AAGGACTGGTCTTTCTATCTC
1124	AAGCTTGTTAAGATAGTTAAG
1125	AAGCGTGCATAAGTTAACTTC
1126	AAGATGCCGCATTTGGATTGG
1127	AAGAATGGAGAGAGAATTGAA
1128	AACATCAACATCTTGGTCAGA
1129	AAGGCATGGTTGTGGTTAATC
1130	AAGCAGCATCATGGAGGTTTG
1131	AAGATGAGTATGCCTGCCGTG
1132	AAGTTGACTTACTGAAGAATG
1133	AAGATAGTTAAGCGTGCATAA

SEQ ID NO	Sequence
1134	AACTTCCAATTTACATACTCT
1135	AACATCTTGGTCAGATTTGAA
1136	AACTCTTCAATCTCTTGCACT
1137	AATTTCCTGAATTGCTATGTG
1138	AATGGAAAGTCAAATTTCCTG
1139	AACCATGTGACTTTGTCACAG

SEQ ID NO	Sequence
1140	AATTGACAGGATTATTGGAAA
1141	AATTCTCTTATCCAACATCAA
1142	AAAGTGGAGCATTCAGACTTG
1143	AAAGTCAAATTTCCTGAATTG
1144	GTTGCTCCACAGGTAGCTCTA
1145	AATTTACATACTCTGCTTAGA

[0502] An exemplary sequence encoding a B2M shRNA comprises a sequence of GCACTCAAAGCTTGTTAAGATCGAAATCTTAACAAGCTTTGAGTGC (SEQ ID NO: 349), or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto. A further exemplary sequence encoding a B2M shRNA comprises a sequence of GTTAACTTCCAATTTACATACCGAAGTATGTAAATTGGAAGTTAAC (SEQ ID NO: 350), or a sequence having at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0503] In some embodiments, the interfering RNAs comprise a sequence complementary to a sequence of an HLA-A*02 mRNA. In some embodiments, the interfering RNA is capable of inducing RNAi-mediated degradation of the HLA-A*02 mRNA. In some embodiments, the HLA-A*02 mRNA sequence comprises a coding sequence. In some embodiments, the HLA-A*02 mRNA sequence comprises an untranslated region.

[0504] In some embodiments, the interfering RNA is a short hairpin RNA (shRNA). In some embodiments, the shRNA comprises a first sequence, having from 5' to 3' end a sequence complementary to the HLA-A*02 mRNA; and a second sequence, having from 5' to 3' end a sequence complementary to the first sequence, wherein the first sequence and second sequence form the shRNA

[0505] Illustrative target HLA sequences complementary to the first sequence are shown in Table 14.

Table 14. Illustrative target HLA sequences complementary to first sequence

SEQ ID NO	Sequence
1146	CTTCTTCCTTCCCTATTAAAA
1147	TCTCACTCCATGAGGTATTTC
1148	CTCTCACTCCATGAGGTATTT
1149	GAGGAGGAAGAGCTCAGATAG
1150	GCTCTCACTCCATGAGGTATT
1151	AGGATTACATCGCCCTGAAAG
1152	ACACCGTCCAGAGGATGTATG
1153	AGGGTCCTTCTTCCTGGATAC
1154	CCTACGACGGCAAGGATTACA
1155	TCACTCCATGAGGTATTTCTT
1156	CTACGACGGCAAGGATTACAT

SEQ ID NO	Sequence
1157	CTCACTCCATGAGGTATTTCT
1158	GGAGGAAGAGCTCAGATAGAA
1159	CACACCGTCCAGAGGATGTAT
1160	CACGCTGTCTCTGACCATGAA
1161	CTGGACAGGAGCAGAGATACA
1162	TGGAGGAGGAAGAGCTCAGAT
1163	GGCTCTCACTCCATGAGGTAT
1164	CATCTCTGTCTCAACTTCATG
1165	TACGACGGCAAGGATTACATC
1166	GGATTACATCGCCCTGAAAGA
1167	GATTACATCGCCCTGAAAGAG

SEQ ID NO	Sequence
1168	CTCAGACCACCAAGCACAAGT
1169	TCACACCGTCCAGAGGATGTA
1170	ACTCCATGAGGTATTTCTTCA
1171	CACTCCATGAGGTATTTCTTC
1172	CCATGAGGTATTTCTTCACAT
1173	ACTTCTTCCTTCCCTATTAAA
1174	GTGTCTCTCACAGCTTGTAAA
1175	CTGTGTTCGTGTAGGCATAAT
1176	TGTGTTCGTGTAGGCATAATG
1177	TAACTTCTTCCTTCCCTATTA
1178	TCTGGACAGGAGCAGAGATAC
1179	TTGCTGGCCTGGTTCTCTTTG
1180	TGTCTCTCACAGCTTGTAAAG
1181	ACTTGAAGAACCCTGACTTTG
1182	GAAGAACCCTGACTTTGTTTC
1183	TCTGTGTTCGTGTAGGCATAA
1184	CATGGTGCACTGAGCTGTAAC
1185	GTAACTTCTTCCTTCCCTATT
1186	CATGTGCAGCATGAGGGTTTG
1187	TTGTTCCTGCCCTTCCCTTTG
1188	ACCCAGTTCTCACTCCCATTG
1189	GGGTTTCCAGAGAAGCCAATC
1190	TTCTCCCTCTCCCAACCTATG
1191	GTCTCTCACAGCTTGTAAAGT
1192	TGTGTCTCTCACAGCTTGTAA
1193	GAGGAAGAGCTCAGATAGAAA
1194	TGAAGAACCCTGACTTTGTTT
1195	TTGAAGAACCCTGACTTTGTT
1196	GTGTTCGTGTAGGCATAATGT
1197	TGGTGCACTGAGCTGTAACTT
1198	CTCCCTCTCCCAACCTATGTA
1199	AGGAGGAAGAGCTCAGATAGA
1200	ACCTATGTAGGGTCCTTCTTC
1201	GGGTCCTTCTTCCTGGATACT
1202	GGTCCTTCTTCCTGGATACTC
1203	GTCCTTCTTCCTGGATACTCA
1204	AAGCCAATCAGTGTCGTCGCG
1205	AAGAGGACCTGCGCTCTTGGA
1206	AAGTGTGAGACAGCTGCCTTG
1207	AAGGCACCTGCATGTGTCTGT
1208	AATCATCTTTCCTGTTCCAGA
1209	AAAGGCACCTGCATGTGTCTG
1210	AAAGAGGACCTGCGCTCTTGG
1211	AAACGCATATGACTCACCACG
1212	GGAAGAGCTCAGATAGAAA
1213	GGGAGACACGGAAAGTGAA
1214	CACCTGCCATGTGCAGCATGA
1215	GGAGATCACACTGACCTGGCA
1216	GGATTACATCGCCCTGAAAG
1217	GCAGGAGGGTCCGGAGTATT
1218	GGACGGGGAGACACGGAAAG
1219	GAAAGTGAAGGCCCACTCA

SEQ ID NO	Sequence
1220	GATACCTGGAGAACGGGAAG
1221	GCTGTGGTGGTGCCTTCTGG
1222	GCTACTACAACCAGAGCGAG
1223	GTGGCTCCGCAGATACCTG
1224	GCCAATCAGTGTCGTCGCG
1225	GAGGACCTGCGCTCTTGGA
1226	GTGTGAGACAGCTGCCTTG
1227	GGCACCTGCATGTGTCTGT
1228	TCATCTTTCCTGTTCCAGA
1229	AGGCACCTGCATGTGTCTG
1230	AGAGGACCTGCGCTCTTGG
1231	ACGCATATGACTCACCACG

[0506] In some embodiments, the first sequence and second sequence are separated by a linker, sometimes referred to as a loop. In some embodiments, both the first sequence and the second sequence are encoded by one single-stranded RNA or DNA vector. In some embodiments, the loop is between the first and second sequences. In these embodiments, and the first sequence and the second sequence hybridize to form a duplex region. The first sequence and second sequence are joined by a linker sequence, forming a "hairpin" or "stem-loop" structure. The shRNA can have complementary first sequences and second sequences at opposing ends of a single stranded molecule, so that the molecule can form a duplex region with the complementary sequence portions, and the strands are linked at one end of the duplex region by a linker (*i.e.* loop sequence). The linker, or loop sequence, can be either a nucleotide or non-nucleotide linker. The linker can interact with the first sequence, and optionally, second sequence through covalent bonds or non-covalent interactions.

[0507] Any suitable nucleotide loop sequence is envisaged as within the scope of the disclosure. An shRNA of this disclosure may include a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the first sequence of the shRNA to the second sequence of the shRNA. A nucleotide loop sequence can be ≥ 2 nucleotides in length, for example about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides in length. Illustrative loop sequences are disclosed in Table 16.

[0508] In some embodiments, the shRNA further comprises a 5' flank sequence and a 3' flank sequence. In some embodiments, wherein the 5' flank sequence is joined to the 5' end of the first sequence, and wherein the 3' flank sequence is joined to the 3' end of the second sequence.

[0509] Without wishing to be bound by theory, it is thought that flanking shRNA stem loop sequence with 5' and 3' sequences similar to those found in microRNAs can target the shRNA for processing by the endogenous microRNA processing machinery, increasing the effectiveness of shRNA processing. Alternatively, or in addition, flanking sequences may increase shRNA compatibility with polymerase II or polymerase III promoters, leading to more effective regulation of shRNA expression.

[0510] In some embodiments, the 5' flank sequence is selected from the sequences set forth in Table 15. Illustrative flank sequence are shown in Table 15.

Table 15. Illustrative flank sequences

SEQ ID NO	**5' Flank Sequence**
1232	GG

1233	ACACCAUGUUGCCAGUCUCUAGG
1234	UGAUAGCAAUGUCAGCAGUGCCU
1235	UAUUGCUGUUGACAGUGAGCGAC
SEQ ID NO	**3' Flank Sequence**
1236	UGGCGUCUGGCCCAACCACAC
1237	GUAAGGUUGACCAUACUCUAC

[0511] In some embodiments, the first and second sequence are present on a single stranded polynucleotide, wherein the first sequence and second sequence are separated by 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides, wherein the 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides form a loop region in the shRNA. In some embodiments, the loop region comprises a sequence selected from the sequences set forth in Table 16.

Table 16. Illustrative loop region sequences

SEQ ID NO	**Loop Region Sequence**
1238	CGAA
1239	UUCAAGA
1240	AUAUUCA
1241	UGUGCUGUC
1242	CUCGAG
1243	CUUCCUGUCAGA
1244	CUUCCCUUUGUCAGA
1245	GUGUUAUUCUUG
1246	GUGUCUUAAUUG
1247	GUGUUAGUCUUG
1248	UCAAGAG
1249	GGACAUCCAGGG
1250	GUGAAGCCACAGAUG
1251	GAUUCUAAAA

[0512] shRNAs of the disclosure may be generated exogenously by chemical synthesis, by in vitro transcription, or by cleavage of longer double-stranded RNA with Dicer or another appropriate nuclease with similar activity. Chemically synthesized siRNAs, produced from protected ribonucleoside phosphoramidites using a conventional DNA/RNA synthesizer, may be obtained from commercial suppliers such as Millipore Sigma (Houston, Tex.), Ambion Inc. (Austin, Tex.). Invitrogen (Carlsbad, Calif.), or Dharmacon (Lafayette, Colo.). siRNAs can be purified by extraction with a solvent or resin, precipitation, electrophoresis, chromatography, or a combination thereof, for example. Alternatively, siRNAs may be used with little if any purification to avoid losses due to sample processing.

[0513] In some embodiments, shRNAs of the disclosure can be produced using an expression vector into which a nucleic acid encoding the double stranded RNA has been cloned, for example under control of a suitable promoter.

Pharmaceutical Compositions

[0514] The disclosure provides pharmaceutical compositions comprising immune cells comprising the first and second receptors of the disclosure and a pharmaceutically acceptable diluent, carrier or excipient.

[0515] Such compositions may comprise buffers such as 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; and preservatives.

[0516] In some embodiments, the immune cell expresses both the first receptor and the second receptor. In some embodiments, at least about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the immune cells express both the first receptor and the second receptor. In some embodiments, at least 90% of the immune cells express both the first receptor and the second receptor.

Treating Cancer

[0517] Provided herein are methods of killing a plurality of cancer cells, or treating cancer, in a subject, comprising administering to the subject a therapeutically effective amount of a composition comprising immune cells comprising the first and second receptors of the disclosure. The immune cells express both receptors in the same cell.

[0518] Cancer is a disease in which abnormal cells divide without control and spread to nearby tissue. In some embodiments, the cancer comprises a liquid tumor or a solid tumor. Exemplary liquid tumors include leukemias and lymphomas. Cancers can arise in virtually an organ in the body, including epithelial tissues. Any cancer wherein a plurality of the cancer cells express the first, activator, ligand and do not express the second, inhibitor ligand is envisaged as within the scope of the instant disclosure. For example, MSLN positive cancers that can be treated using the methods described herein include mesothelioma, ovarian cancer, cervical cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancers such as lung adenocarcinomas, colorectal cancer and cholangiocarcinoma.

[0519] In some embodiments, the plurality of cancer cells express the target antigen. In some embodiments, the plurality cancer cells of the subject express MSLN. MSNL positive cancers

include mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, lung adenocarcinomas, colorectal cancer, or cholangiocarcinoma, as well as other solid epithelial tumors. Further cancers that express MSLN include relapsed, refractory or metastatic gastric, esophageal, head and neck and kidney cancers. In some embodiments, the MSLN positive cancer comprises an epithelial tumor, for example a carcinoma.

[0520] Provided herein are methods of treating MSLN+ cancer in a subject having a MSLN+ tumor, the tumor having loss of heterozygosity at an MHC class I locus. In some embodiments, the methods comprise administering to the subject an effective amount of the immune cells or pharmaceutical compositions described herein. In some embodiments, the methods comprise (a) determining HLA-A, HLA-B, or HLA-C genotype or expression of normal cells and a plurality of cancer cells of the subject; (b) determining the expression of MSLN in a plurality of cancer cells of the subject; and (c) administering to the subject an effective amount of the immune cells or pharmaceutical compositions of the disclosure if the normal cells express an HLA-A, HLA-B or HLA-C non-target antigen and the plurality of cancer cells do not express the HLA-A, HLA-B or HLA-C non-target antigen, and the plurality of cancer cells are also MSLN-positive. In some embodiments, for example those embodiments where the cancer is known to be MSLN+, the methods comprise (a) determining HLA-A, HLA-B or HLA-C genotype or expression of normal cells and a plurality of cancer cells of the subject; and (b) administering to the subject an effective amount of the immune cells or pharmaceutical compositions of the disclosure if the normal cells express an HLA-A, HLA-B or HLA-C non-target antigen and the plurality of cancer cells do not express the non-target antigen. In some embodiments, the non-target antigen comprises HLA-A*02, HLA-A*01, HLA-A*03, HLA-A*11, HLA-B*07 or HLA-C*07.

[0521] In some embodiments, a plurality of cancer cells do not express a polymorphic allele of ICAM1, COMT or CXCL16. For example, the cancer cells have lost an allele of CAM1, COMT or CXCL16 through loss of heterozygosity at that locus.

[0522] In some embodiments, the plurality of cancer cells do not express, or have lower expression than normal cells, of LRRN4 or UPK3B.

[0523] The disclosure provides methods of treating a cancer in a subject comprising: (a) determining the genotype of normal cells and a plurality of cancer cells of the subject at a polymorphic locus selected from the group consisting of a polymorphic locus of ICAM1, a polymorphic locus of COMT and a polymorphic locus of CXCL16; (b) determining the

expression of MSLN in a plurality of cancer cells; and (c) administering a plurality of immune cells to the subject if the normal cells are heterozygous for the polymorphic locus and the plurality of cancer cells are hemizygous for the polymorphic locus, and the plurality of cancer cells are MSLN positive, wherein the plurality of immune cells comprise: (i) a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and (ii) a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding specific to a non-target antigen selected from ICAM1, COMT, and CXCL16, or an antigen peptide thereof in a complex with an a major histocompatibility complex class I (MHC-I), wherein the non-target antigen comprises a polymorphism.

[0524] Methods of genotyping cancer cells and normal cells from a subject for the presence or absence of SNPs will be readily apparent to persons of ordinary skill in the art. SNP genotyping methods include, *inter alia*, PCR based methods such as dual-probe TaqMan assays, array based hybridization methods and sequencing.

[0525] Methods of measuring the expression of the target antigen in cancer or normal cells from a subject will be readily apparent to persons of ordinary skill in the art. These include, *inter alia*, methods of measuring RNA expression such as RNA sequencing and reverse transcription polymerase chain reaction (RT-PCR), as well as methods of measuring protein expression such as immunohistochemistry based methods. Methods of measuring loss of heterozygosity in a plurality of cancer cells, include, inter alia, high throughput sequencing of genomic DNA extracted from cancer cells using methods known in the art.

[0526] The disclosure provides methods of treating a cancer in a subject comprising measuring the expression level of the non-target antigen in a plurality of cancer cells, and treating the subject when the expression level of the non-target antigen in the plurality of cancer cells is less than the expression level of the non-target antigen in the plurality of cancer cells is less than the expression level of the non-target antigen a plurality of healthy cells. In some embodiments, the non-target antigen comprises LRRN4 or UPKB3, or a peptide antigen of LRRN4 or UPKB3. In some embodiments, the methods comprise determining the expression of MSLN in a plurality of cancer cells; and administering a plurality of immune cells to the subject if the plurality of cancer cells have low or no expression of the non-target antigen, and the plurality of cancer cells are MSLN positive. Methods of measuring the expression of the target antigen in cancer or cells from a subject will be readily apparent to persons of ordinary skill in the art. These include, *inter alia*,

methods of measuring RNA expression such as RNA sequencing and reverse transcription polymerase chain reaction (RT-PCR), as well as methods of measuring protein expression such as immunohistochemistry based methods.

[0527] In some embodiments, the immune cells are T cells.

[0528] In some embodiments, the immune cells are allogeneic or autologous.

[0529] In some embodiments, the second receptor increases the specificity of the immune cells for the MSLN positive cancer cells compared to immune cells that express the first receptor but do not express the second receptor. In some embodiments, the immune cells have reduced side effects compared to immune cells that express the first receptor but do not express the second receptor.

[0530] Administration of the immune cells or pharmaceutical compositions described herein can arrest the growth of a tumor in the subject. For example, the immune cells or pharmaceutical compositions can kill tumor cells, so that the tumor stops growing, or is reduced in size. In some cases, immune cells or pharmaceutical compositions can prevent formation of additional tumors, or reduce the total number of tumors in the subject.

[0531] Administration of the immune cells or pharmaceutical compositions described herein can result in selective killing of a cancer cell but not a wild-type cell in the subject. In some embodiments, about 60% of the cells killed are cancer cells, about 65% of the cells killed are cancer cells, about 70% of the cells killed are cancer cells, about 75% of the cells killed are cancer cells, about 80% of the cells killed are cancer cells, about 85% of the cells killed are cancer cells, about 90% of the cells killed are cancer cells, about 95% of the cells killed are cancer cells, or about 100% of the cells killed are cancer cells.

[0532] Administration of the immune cells or pharmaceutical compositions described herein can result in the killing of about 40%, about 50%, about 60%, about 70%, about 80%, about 90% or all of the cancer cells of the subject.

[0533] Administration of the immune cells or pharmaceutical compositions described herein can result in fewer side effects for the subject than administration of an otherwise equivalent immune cell comprising the first activator receptor but no second inhibitory receptor. For example, administering the immune cells or pharmaceutical compositions described herein can reduce dose limited toxicity relative to the MSLN CAR, or MSLN TCR administered without the second inhibitory receptor.

[0534] Treating cancer can result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as “tumor regression”. Preferably, after treatment, tumor size is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor size is

reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0535] Treating cancer can result in a reduction in tumor volume. Preferably, after treatment, tumor volume is reduced by 5% or greater relative to its size prior to treatment; more preferably, tumor volume is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0536] Administration of the immune cells or pharmaceutical compositions described herein can reduce the size of a tumor in the subject. In some embodiments, the size of the tumor is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, relative to the size of the tumor before administration of the immune cells or pharmaceutical compositions. In some embodiments, the tumor is eliminated.

[0537] Treating cancer results in a decrease in number of tumors. Preferably, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; more preferably, tumor number is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0538] Treating cancer can result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. Preferably, after treatment, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; more preferably, the number of metastatic lesions is reduced by 10% or greater; more preferably, reduced by 20% or greater; more preferably, reduced by 30% or greater; more preferably, reduced by 40% or greater; even more preferably, reduced by 50% or greater; and most

preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. Preferably, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0539] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0540] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0541] Treating cancer can result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the average survival time is increased by more than 30 days; more preferably, by more than 60 days; more preferably, by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by

calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0542] Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the present disclosure, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof. Preferably, the mortality rate is decreased by more than 2%; more preferably, by more than 5%; more preferably, by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

[0543] Treating cancer can result in a decrease in tumor growth rate. Preferably, after treatment, tumor growth rate is reduced by at least 5% relative to number prior to treatment; more preferably, tumor growth rate is reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate can be measured according to a change in tumor diameter per unit time.

[0544] Treating cancer can result in a decrease in tumor regrowth. Preferably, after treatment, tumor regrowth is less than 5%; more preferably, tumor regrowth is less than 10%; more preferably, less than 20%; more preferably, less than 30%; more preferably, less than 40%; more preferably, less than 50%; even more preferably, less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

[0545] Treating or preventing a cancer can result in a reduction in the rate of cellular proliferation. Preferably, after treatment, the rate of cellular proliferation is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0546] Treating or preventing cancer can result in a reduction in the proportion of proliferating cells. Preferably, after treatment, the proportion of proliferating cells is reduced by at least 5%; more preferably, by at least 10%; more preferably, by at least 20%; more preferably, by at least 30%; more preferably, by at least 40%; more preferably, by at least 50%; even more preferably, by at least 50%; and most preferably, by at least 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. Preferably, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample. The proportion of proliferating cells can be equivalent to the mitotic index.

[0547] Treating or preventing cancer can result in a decrease in size of an area or zone of cellular proliferation. Preferably, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. The size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0548] Treating or preventing cancer can result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. Preferably, after treatment, the number of cells having an abnormal morphology is reduced by at least 5% relative to its size prior to treatment; more preferably, reduced by at least 10%; more preferably, reduced by at least 20%; more preferably, reduced by at least 30%; more preferably, reduced by at least 40%; more preferably, reduced by at least 50%; even more preferably, reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular

morphology can be measured by microscopy, *e.g.*, using an inverted tissue culture microscope. An abnormal cellular morphology can take the form of nuclear pleiomorphism.

Dosage and Administration

[0549] The immune cells and of the present disclosure may be administered in a number of ways depending upon whether local or systemic treatment is desired.

[0550] In general, administration may be parenteral.

[0551] Methods for administration of cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions. For example, adoptive T cell therapy methods are described, e.g., in US Patent Application Publication No. 2003/0170238 to Gruenberg et al and U.S. Pat. No. 4,690,915 to Rosenberg.

[0552] The compositions of the disclosure are suitable for parenteral administration. As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue, thus generally resulting in the direct administration into the blood stream, into muscle, or into an internal organ. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intraperitoneal, intramuscular, intrasternal, intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intracranial, intratumoral, intrasynovial injection or infusions; and kidney dialytic infusion techniques. In some embodiments, parenteral administration of the compositions of the present disclosure comprises intravenous or intraarterial administration.

[0553] The disclosure provides pharmaceutical compositions comprising a plurality of immune cells of the disclosure, and a pharmaceutically acceptable carrier, diluent or excipient.

[0554] Formulations of a pharmaceutical composition suitable for parenteral administration typically generally comprise of immune cells combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampoules or in multi-dose containers containing a preservative. Formulations for parenteral

administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and the like. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. Parenteral formulations also include aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents. Exemplary parenteral administration forms include solutions or suspensions in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0555] In some embodiments, the formulated composition comprising the immune cells is suitable for administration via injection. In some embodiments, the formulated composition comprising the immune cells is suitable for administration via infusion.

[0556] The pharmaceutical compositions of the present disclosure, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the immune cells with the pharmaceutical carrier(s) or excipient(s), such as liquid carriers.

[0557] Aqueous suspensions may further contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

[0558] The compositions of the present disclosure may additionally contain other adjunct components conventionally found in pharmaceutical compositions. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present disclosure, such as dyes, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the immune cells of the compositions of the present disclosure.

[0559] The formulation or composition may also contain more than one active ingredient useful for the particular indication, disease, or condition being treated with the immune cells, where the respective activities do not adversely affect one another. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

Thus, in some embodiments, the pharmaceutical composition further includes other pharmaceutically active agents or drugs, such as chemotherapeutic agents.

[0560] The pharmaceutical composition in some aspects can employ time-released, delayed release, and sustained release delivery systems such that the delivery of the composition occurs prior to, and with sufficient time to cause, sensitization of the site to be treated. Many types of release delivery systems are available and known. Such systems can avoid repeated administrations of the composition, thereby increasing convenience to the subject and the physician.

[0561] Administration can be effected in one dose, continuously or intermittently throughout the course of treatment. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

[0562] The pharmaceutical composition in some embodiments contains the immune cells in amounts effective to treat or prevent a cancer, such as a therapeutically effective or prophylactically effective amount. Therapeutic or prophylactic efficacy in some embodiments is monitored by periodic assessment of treated subjects. For repeated administrations over days, weeks or months, depending on the condition, the treatment can be repeated until a desired suppression of cancer signs or symptoms occurs. However, other dosage regimens may be useful and can be determined. The desired dosage can be delivered by a single bolus administration or infusion of the composition or by multiple bolus administrations or infusions of the composition.

[0563] The cells or population of cells can be administrated in one or more doses. In some embodiments, an effective amount of cells can be administrated as a single dose. In some embodiments, an effective amount of cells can be administrated as more than one doses over a period time. Timing of administration is within the judgment of a managing physician and depends on the clinical condition of the patient.

[0564] The cells or population of cells may be obtained from any source, such as a blood bank or a donor, or the patient themselves.

[0565] An effective amount means an amount which provides a therapeutic or prophylactic benefit. The dosage administered will be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. In some embodiments, an effective amount of cells or composition comprising those cells are administrated parenterally. In some embodiments, administration can be an intravenous administration. In some embodiments, administration can be directly done by injection within a tumor.

[0001] For purposes of the disclosure, an assay, which comprises, for example, comparing the extent to which target cells are lysed or one or more cytokines are secreted by immune cells expressing the receptors, upon administration of a given dose of such immune cells to a mammal, among a set of mammals of which is each given a different dose of the immune cells, can be used to determine a starting dose to be administered to a mammal.

[0002] In some embodiments, the cells are administered as part of a combination treatment, such as simultaneously with or sequentially with, in any order, another therapeutic intervention, such as an antibody or engineered cell or receptor or agent, such as a cytotoxic or therapeutic agent. The immune cells of the disclosure are in some embodiments are co-administered with one or more additional therapeutic agents or in connection with another therapeutic intervention, either simultaneously or sequentially in any order. In some contexts, the immune cells are co-administered with another therapy sufficiently close in time such that the immune cell populations enhance the effect of one or more additional therapeutic agents, or vice versa. In some embodiments, the immune cells are administered prior to the one or more additional therapeutic agents. In some embodiments, the immune cells are administered after to the one or more additional therapeutic agents.

[0566] In embodiments, a lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (*e.g.*, infusion) of adoptive immune cells. In an example, the lymphodepleting chemotherapy is administered to the subject prior to administration of the immune cells. For example, the lymphodepleting chemotherapy ends 1-4 days (*e.g.*, 1, 2, 3, or 4 days) prior to adoptive cell infusion. In embodiments, multiple doses of adoptive cells are administered, *e.g.*, as described herein. In embodiments, a lymphodepleting chemotherapy is administered to the subject prior to, concurrently with, or after administration (*e.g.*, infusion) of the immune cells described herein. Examples of lymphodepletion include, but may not be limited to, nonmyeloablative lymphodepleting chemotherapy, myeloablative lymphodepleting chemotherapy, total body irradiation, etc. Examples of lymphodepleting agents include, but are not limited to, antithymocyte globulin, anti-CD3 antibodies, anti-CD4 antibodies, anti-CD8 antibodies, anti-CD52 antibodies, anti-CD2 antibodies, TCRαβ blockers, anti-CD20 antibodies, anti-CD19 antibodies, Bortezomib, rituximab, anti-CD 154 antibodies, rapamycin, CD3 immunotoxin, fludarabine, cyclophosphamide, busulfan, melphalan, Mabthera, Tacrolimus, alefacept, alemtuzumab, OKT3, OKT4, OKT8, OKT11, fingolimod, anti-CD40 antibodies, anti-BR3 antibodies, Campath-1H, anti-CD25 antibodies, calcineurin inhibitors, mycophenolate, and steroids, which may be used alone or in combination. As a further example, a lymphodepletion

regimen can include, administration of alemtuzumab, cyclophosphamide, benduamustin, rituximab, pentostatin, and/or fludarabine. Lymphodepletion regimen can be administered in one or more cycles until the desired outcome of reduced circulating immune cells. In some embodiments, the lymphodepletion comprises administering an agent that specifically targets, and reduces or eliminates CD52+ cells in the subject, and the immune cells are modified to reduce or eliminate CD52 expression.

[0567] In some embodiments, an immune stimulating therapy is administered to the subject prior to, concurrently with, or after administration (*e.g.* infusion) of adoptive immune cells. In some embodiments, the immune stimulating therapy comprises homeostatic cytokines. In some embodiments, the immune stimulating therapy comprises immune-stimulatory molecules. In some embodiments, the immune stimulating therapy comprises IL-2, IL-7, IL-12, IL-15, IL-21, IL-9, or a functional fragment thereof. In some embodiments, the immune stimulating therapy comprises IL-2, IL-7, IL-12, IL-15, IL-21, IL-9, or combinations thereof. In some embodiments, the immune stimulating therapy comprises IL-2, or a functional fragment thereof.

[0568] Methods for adoptive cell therapy using autologous cells includes isolating immune cells from patient blood, performing a series of modifications on the isolated cells including transducing the cells with one or more vectors encoding the dual receptor system described herein, and administering the cells to a patient. Providing immune cells from a subject suffering from or at risk for cancer or a hematological malignancy requires isolation of immune cell from the patient's blood, and can be accomplished through methods known in the art, for example, by leukapheresis. During leukapheresis, blood from a subject is extracted and the peripheral blood mononuclear cells (PBMCs) are separated, and the remainder of the blood is returned to the subject's circulation. The PBMCs are stored either frozen or cryopreserved as a sample of immune cells and provided for further processing steps, such as, *e.g.* the modifications described herein.

[0569] In some embodiments, the method of treating a subject described herein comprises modifications to immune cells from the subject comprising a series of modifications comprising enrichment and/or depletion, activation, genetic modification, expansion, formulation, and cryopreservation.

[0570] The disclosure provides enrichment and/or depletion steps that can be, for example, washing and fractionating methods known in the art for preparation of subject PBMCs for downstream procedures, *e.g.* the modifications described herein. For example, without limitation, methods can include devices to remove gross red blood cells and platelet

contaminants, systems for size-based cell fractionation for the depletion of monocytes and the isolation of lymphocytes, and/or systems that allow the enrichment of specific subsets of T cells, such as, *e.g.* CD4+, CD8+, CD25+, or CD62L+ T cells. Following the enrichment steps, a target sub-population of immune cells will be isolated from the subject PMBCs for further processing. Those skilled in the art will appreciate that enrichment steps, as provided herein, may also encompass any newly discovered method, device, reagent or combination thereof.

[0571] The disclosure provides activation steps that can be any method known in the art to induce activation of immune cells, *e.g.* T cells, required for their ex vivo expansion. Immune cell activation can be achieved, for example, by culturing the subject immune cells in the presence of dendritic cells, culturing the subject immune cells in the presence of artificial antigen-presenting cells (AAPCs), or culturing the immune cells in the presence of irradiated K562-derived AAPCs. Other methods for activating subject immune cells can be, for example, culturing the immune cells in the presence of isolated activating factors and compositions, *e.g.* beads, surfaces, or particles functionalized with activating factors. Activating factors can include, for example, antibodies, *e.g.* anti-CD3 and/or anti-CD28 antibodies. Activating factors can also be, for example, cytokines, *e.g.* interleukin (IL)-2 or IL-21. Activating factors can also be costimulatory molecules, such as, for example, CD40, CD40L, CD70, CD80, CD83, CD86, CD137L, ICOSL, GITRL, and CD134L. Those skilled in the art will appreciate that activating factors, as provided herein, may also encompass any newly discovered activating factor, reagent, composition, or combination thereof that can activate immune cells.

[0572] The disclosure provides genetic modification steps for modifying the subject immune cells. In some embodiments, the genetic modification comprises transducing the immune cell with a vector comprising a shRNA described herein complementary to B2M or HLA-A. In some embodiments, the genetic modification comprises modifying the genome of the immune cells to induce mutations in B2M or HLA-A using CRISPR/Cas mediated genome engineering. In some embodiments, the method comprises transducing the immune cell with one or more vectors encoding the activator and inhibitory receptors, thereby producing immune cells expressing the activator and inhibitory receptors.

[0573] The disclosure provides expansion steps for the genetically modified subject immune cells. Genetically modified subject immune cells can be expanded in any immune cell expansion system known in the art to generate therapeutic doses of immune cells for administration. For example, bioreactor bags for use in a system comprising controller

pumps, and probes that allow for automatic feeding and waste removal can be used for immune cell expansion. Cell culture flasks with gas-permeable membranes at the base may be used for immune cell expansion. Any such system known in the art that enables expansion of immune cells for clinical use is encompassed by the expansion step provided herein. Immune cells are expanded in culture systems in media formulated specifically for expansion. Expansion can also be facilitated by culturing the immune cell of the disclosure in the presence of activation factors as described herein. Those skilled in the art will appreciate that expansion steps, as provided herein, may also encompass any newly discovered culture systems, media, or activating factors that can be used to expand immune cells.

[0574] The disclosure provides formulation and cryopreservation steps for the expanded genetically modified subject immune cells. Formulation steps provided include, for example, washing away excess components used in the preparation and expansion of immune cells of the methods of treatment described herein. Any pharmaceutically acceptable formulation medium or wash buffer compatible with immune cell known in the art may be used to wash, dilute/concentration immune cells, and prepare doses for administration. Formulation medium can be acceptable for administration of the immune cells, such as, for example crystalloid solutions for intravenous infusion. Cryopreservation can optionally be used to store immune cells long-term. Cryopreservation can be achieved using known methods in the art, including for example, storing cells in a cryopreservation medium containing cryopreservation components. Cryopreservation components can include, for example, dimethyl sulfoxide or glycerol. Immune cells stored in cryopreservation medium can be cryopreserved by reducing the storage temperature to -80ºC to -196 ºC.

[0575] In some embodiments, the method of treatment comprises determining the HLA germline type of the subject. In some embodiments, the HLA germline type is determined in bone marrow.

[0576] In some embodiments, the method of treatment comprises determining the level of expression of MSLN. In some embodiments, the level of expression of MSLN is determined in tumor tissue samples from the subject. In some embodiments, the expression level of MSLN is determined using next generation sequencing. In some embodiments, the expression level of MSLN is determined using RNA sequencing. In some embodiments, the level of MSLN is determined using immunohistochemistry.

[0577] In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-A*02 inhibitory receptor to a subject in need thereof, wherein the subject is determined to be HLA germline HLA-

A*02 heterozygous and have cancer cells with loss of HLA-A*02. In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-A*01 inhibitory receptor to a subject in need thereof, wherein the subject is determined to be HLA germline HLA-A*01 heterozygous and have cancer cells with loss of HLA-A*01. In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-A*03 to a subject in need thereof, wherein the subject is determined to be HLA germline HLA-A*03 heterozygous and have cancer cells with loss of HLA-A*03. In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-A*07 inhibitory receptor to a subject in need thereof, wherein the subject is determined to be HLA germline HLA-A*07 heterozygous and have cancer cells with loss of HLA-A*07. In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-C*07 inhibitory receptor to a subject in need thereof, wherein the subject is determined to be HLA germline HLA-C*07 heterozygous and have cancer cells with and loss of HLA-C*07. In some embodiments, the method of treatment comprises administering a therapeutically effective dose of immune cells comprising an HLA-B*07 inhibitory receptor in a subject in need thereof, wherein the subject is determined to be HLA germline HLA-B*07 heterozygous and have cancer cells with loss of HLA-B*07.

[0578] In various embodiments, the disclosure provides method of treatment of heterozygous HLA-A*02 patients with malignancies that express MSLN and have lost HLA-A*02 expression; and/or of treatment of heterozygous HLA-A*02 adult patients with recurrent unresectable or metastatic solid tumors that express MSLN and have lost HLA-A*02 expression.

[0579] In some embodiments, a therapeutically effective dose of the immune cells described herein are administered. In some embodiments, the immune cells of the disclosure are administered by intravenous injection. In some embodiments, the immune cells of the disclosure are administered by intraperitoneal injection. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells, about 1×10^6 cells, about 2×10^6 cells, about 3×10^6 cells, 4×10^6 cells, about 5×10^6 cells, about 6×10^6 cells, about 7×10^6 cells, about 8×10^6 cells, about 9×10^6 cells, about 1×10^7, about 2×10^7, about 3×10^7, about 4×10^7, about 5×10^7, about 6×10^7, about 7×10^7, about 8×10^7, about 9×10^7, about 1×10^8 cells, about 2×10^8 cells, about 3×10^8 cells, about 4×10^8 cells, about 5×10^8 cells, about 6×10^8 cells, about

7×10^8 cells, about 8×10^8 cells, about 9×10^8 cells, about 1×10^9 cells, about 2×10^9 cells, about 3×10^9 cells, about 3×10^9 cells, about 4×10^9 cells, about 5×10^9 cells, about 5×10^9 cells, about 6×10^9 cells, about 7×10^9 cells, about 8×10^9 cells, about 9×10^9 cells, about 1×10^{10} cells, about 2×10^{10} cells, about 3×10^{10} cells, about 4×10^{10} cells, about 5×10^{10} cells, about 6×10^{10} cells, about 7×10^{10} cells, about 8×10^{10} cells, or about 9×10^{10} cells.

[0580] In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 9×10^{10} cells, about 1×10^6 cells to about 5×10^{10} cells, about 2×10^6 cells to about 5×10^9 cells, about 3×10^6 cells to about 5×10^9 cells, about 4×10^6 cells to about 3×10^9 cells, about 5×10^6 cells to about 2×10^9 cells, about 6×10^6 cells to about 1×10^9 cells, 0.5×10^6 cells to about 6×10^9 cells, about 1×10^6 cells to about 5×10^9 cells, about 2×10^6 cells to about 5×10^9 cells, about 3×10^6 cells to about 4×10^9 cells, about 4×10^6 cells to about 3×10^9 cells, about 5×10^6 cells to about 2×10^9 cells, about 6×10^6 cells to about 1×10^9 cells, 0.5×10^6 cells to about 6×10^8 cells, about 1×10^6 cells to about 5×10^8 cells, about 2×10^6 cells to about 5×10^8 cells, about 3×10^6 cells to about 4×10^8 cells, about 4×10^6 cells to about 3×10^8 cells, about 5×10^6 cells to about 2×10^8 cells, about 6×10^6 cells to about 1×10^8 cells, about 7×10^6 cells to about 9×10^8 cells, about 8×10^6 cells to about 8×10^8 cells, about 9×10^6 cells to about 7×10^8 cells, about 1×10^7 cells to about 6×10^8 cells, about 2×10^7 cells to about 5×10^8 cells, about 7×10^6 cells to about 9×10^7 cells, about 8×10^6 cells to about 8×10^7 cells, about 9×10^6 cells to about 7×10^7 cells, about 1×10^7 cells to about 6×10^7 cells, or about 2×10^7 cells to about 5×10^7 cells.

[0581] In some embodiments, a therapeutically effective dose comprises about 0.5×10^5 cells to about 9×10^{10} cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 1×10^{10} cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 5×10^9 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 1×10^9 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 6×10^8 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^6 cells to about 9×10^{10} cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^7 cells to about 1×10^{10} cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^7 cells to about 5×10^9 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^7 cells to about 1×10^9 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^7 cells to about 6×10^8 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^8 cells to about 9×10^{10} cells. In some

embodiments, a therapeutically effective dose comprises about 0.5×10^8 cells to about 1×10^{10} cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^8 cells to about 5×10^9 cells. In some embodiments, a therapeutically effective dose comprises about 0.5×10^8 cells to about 1×10^9 cells. The term "about" as referred to in a therapeutically dose, can be, for example, $\pm 0.5\times10^6$ cells, $\pm 0.5\times10^7$ cells, or $\pm 0.5\times10^8$ cells.

Kits and Articles of Manufacture

[0582] The disclosure provides kits and articles of manufacture comprising the polynucleotides and vectors encoding the receptors described herein, and immune cells comprising the receptors described herein. In some embodiments, the kit comprises articles such as vials, syringes and instructions for use.

[0583] In some embodiments, the kit comprises a polynucleotide or vector comprising a sequence encoding one or more receptors of the disclosure.

[0584] In some embodiments, the kit comprises a plurality of immune cells comprising the first and second receptors as described herein. In some embodiments, the plurality of immune cells comprises a plurality of T cells.

[0585] In some embodiments, the kit further comprises instructions for use.

ENUMERATED EMBODIMENTS

[0586] The disclosure can be understood with reference to the following illustrative, enumerated embodiments:

[0587] 1. An immune cell responsive to loss of heterozygosity in a cancer cell, comprising:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to a target antigen selected from:

i. a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); or

ii. Mesothelin (MSLN), or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen selected from ICAM1, COMT, and CXCL16, or a peptide antigen thereof in a complex with a major

histocompatibility complex class I (MHC-I) , wherein the non-target antigen comprises a polymorphism.

[0588] 2. The immune cell of embodiment 1, wherein the non-target antigen is lost from the cancer cell through loss of heterozygosity (LOH).

[0589] 3. The immune cell of embodiment 1 or 2, wherein the non-target antigen is an ICAM1 antigen that shares at least 95% identity to SEQ ID NO: 27 and the polymorphism comprises a K or E at position 469 of SEQ ID NO: 27.

[0590] 4. The immune cell of embodiment 1 or 2, wherein the non-target antigen is a COMT antigen that shares at least 95% identity to SEQ ID NO: 28 and the polymorphism comprises a V or M at position 158 of SEQ ID NO: 28.

[0591] 5. The immune cell of embodiment 1 or 2, wherein the non-target antigen is a CXCL16 antigen that shares at least 95% identity to SEQ ID NO: 29 and the polymorphism is selected from the group consisting of:

a. an I or T at position 142 of SEQ ID NO: 29; and

b. an A or V at position 200 of SEQ ID NO: 29.

[0592] 6. The immune cell of any one of embodiments 1-5, wherein the non-target antigen is expressed in a non-target cell.

[0593] 7. The immune cell of any one of embodiments 1-6, wherein the non-target cell expresses both target antigen and the non-target antigen.

[0594] 8. An immune cell responsive to low or no expression of a protein in a cancer cell, comprising:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to a target antigen selected from:

i. a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); or

ii. MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen selected from LRRN4 and UPK3B, or peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I), wherein the non-target antigen is expressed at a lower level by the cancer cell than by a non-target cell.

[0595] 9. The immune cell of embodiment 8, wherein the non-target antigen is not expressed by the cancer cell.

[0596] 10. The immune cell of embodiment 9, wherein the non-target cell expresses both the target antigen and the non-target antigen.

[0597] 11. The immune cell of any one of embodiments 1-10, wherein the target antigen is a cancer cell-specific antigen.

[0598] 12. The immune cell of embodiment 11, wherein the target antigen is a peptide antigen of a cancer cell-specific antigen in a complex with a major histocompatibility complex class I (MHC-I).

[0599] 13. The immune cell of any one of embodiments 1-12, wherein the cancer cell is a mesothelioma cancer cell, an ovarian cancer cell, a cervical cancer cell, a colorectal cancer cell, an esophageal cancer cell, a head and neck cancer cell, a kidney cancer cell, an uterine cancer cell, a gastric cancer cell, a pancreatic cancer cell, a lung cancer cell, a colorectal cancer cell or a cholangiocarcinoma cell.

[0600] 14. The immune cell of any one of embodiments 1-13, wherein the cancer cell expresses MSLN.

[0601] 15. The immune cell of any one of embodiments 1-14, wherein the first receptor and the second receptor together specifically activate the immune cell in the presence of the cancer cell.

[0602] 16. The immune cell of embodiment 15, wherein the immune cell is a T cell.

[0603] 17. The immune cell of embodiment 16, wherein the T cell is a CD8+ CD4- T cell.

[0604] 18. The immune cell of any one of embodiments 1-17, wherein the MSLN comprises a sequence that shares at least 95% identity to SEQ ID NO: 1 or SEQ ID NO: 2.

[0605] 19. The immune cell of any one of embodiments 1-18, wherein the first receptor is a T cell receptor (TCR).

[0606] 20. The immune cell of any one of embodiments 1-18, wherein the first receptor is a chimeric antigen receptor (CAR).

[0607] 21. The immune cell of embodiment 19 or 20, wherein the extracellular ligand binding domain of the first receptor comprises an antibody fragment, a single chain Fv antibody fragment (scFv), a β chain variable domain (Vβ), or a TCR α chain variable domain and a TCR β chain variable domain.

[0608] 22. The immune cell of embodiment 19 or 20, wherein the extracellular ligand binding domain comprises an scFv.

[0609] 23. The immune cell of embodiment 22, wherein the scFv comprises a sequence selected from the group consisting of SEQ ID NOs: 3-6, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0610] 24. The immune cell of embodiment 22, wherein the scFv comprises or consists essentially of a sequence selected from the group consisting of SEQ ID NOs: 3-6.

[0611] 25. An immune cell responsive to loss of heterozygosity in a cancer cell, comprising:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to Mesothelin (MSLN), or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen, wherein the non-target antigen comprises HLA-A*02.

[0612] 26. The immune cell of embodiment 25, wherein the extracellular ligand binding domain of the first receptor comprises an antibody fragment, a single chain Fv antibody fragment (scFv), a β chain variable domain (Vβ), or a TCR α chain variable domain and a TCR β chain variable domain.

[0613] 27. The immune cell of embodiment 25, wherein the extracellular ligand binding domain of the first receptor comprises an scFv.

[0614] 28. The immune cell of embodiment 27, wherein the scFv comprises a sequence selected from the group consisting of SEQ ID NOs: 3-6, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto.

[0615] 28. The immune cell of embodiment 27, wherein the scFv comprises or consists essentially of a sequence selected from the group consisting of SEQ ID NOs: 3-6.

[0616] 29. The immune cell of any one of embodiments 25-28, wherein the extracellular ligand binding domain of the second receptor comprises an antibody fragment, a single chain Fv antibody fragment (scFv), a β chain variable domain (Vβ), or a TCR α chain variable domain and a TCR β chain variable domain.

[0617] 30. The immune cell of any one of embodiments 25-28, wherein the extracellular ligand binding domain of the second receptor comprises an scFv.

[0618] 31. The immune cell of embodiment 30, wherein the scFv comprises a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity to any one of SEQ ID NOs: 30-41.

[0619] 32. The immune cell of embodiment 30, wherein the scFv comprises or consists essentially of a sequence of any one of SEQ ID NOs: 30-41.

[0620] 33. The immune cell of any one of embodiments 25-32, wherein the extracellular ligand binding domain of the second receptor comprises CDRs selected from the group consisting of SEQ ID NOs: 42-53.

[0621] 34. The immune cell of any one of embodiments 25-33, wherein the second receptor comprises a LILRB1 intracellular domain or a functional variant thereof.

[0622] 35. The immune cell of embodiment 34, wherein the LILRB1 intracellular domain comprises a sequence at least 95% identical to SEQ ID NO: 65.

[0623] 36. The immune cell of any one of embodiments 25-35, wherein the second receptor comprises a LILRB1 transmembrane domain or a functional variant thereof.

[0624] 37. The immune cell of embodiment 36, wherein the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 95% identical to SEQ ID NO: 74.

[0625] 38. The immune cell of any one of embodiments 25-37, wherein the second receptor comprises a LILRB1 hinge domain or functional fragment or variant thereof.

[0626] 39. The immune cell of embodiment 38, wherein the LILRB1 hinge domain comprises a sequence at least 95% identical to SEQ ID NO: 73, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NOS: 81-84, or SEQ ID NOS: 90-91.

[0627] 40. The immune cell of any one of embodiments 25-39, wherein the second receptor comprises a LILRB1 intracellular domain and a LILRB1 transmembrane domain, or a functional variant thereof.

[0628] 41. The immune cell of embodiment 40, wherein the LILRB1 intracellular domain and LILRB1 transmembrane domain comprises SEQ ID NO: 69 or a sequence at least 95% identical to SEQ ID NO: 69.

[0629] 42. The immune cell of any one of embodiments 25-41, wherein the cancer cell is a mesothelioma cancer cell, an ovarian cancer cell, a cervical cancer cell, a colorectal cancer cell, an esophageal cancer cell, a head and neck cancer cell, a kidney cancer cell, an uterine cancer cell, a gastric cancer cell, a pancreatic cancer cell, a lung cancer cell, a colorectal cancer cell or a cholangiocarcinoma cell.

[0630] 43. wherein the cancer cell is a colorectal cancer cell.

[0631] 44. The immune cell of any one of embodiments 25-43, wherein the cancer expresses MSLN.

[0632] 45. The immune cell of any one of embodiments 25-44, wherein the cancer cell does not express HLA-A*02.

[0633] 46. The immune cell of any one of embodiments 25-45, wherein non-target cells express MSLN and HLA-A*02.

[0634] 47. The immune cell of any one of embodiments 25-46, wherein the first receptor and the second receptor together specifically activate the immune cell in the presence of the target cell.

[0635] 48. The immune cell of embodiment 47, wherein the immune cell is a T cell.

[0636] 49. The immune cell of embodiment 48, wherein the T cell is a CD8+ CD4- T cell.

[0637] 50. The immune cell of any one of embodiments 25-49, wherein the MSLN comprises a sequence that shares at least 95% identity to SEQ ID NO: 1.

[0638] 51. The immune cell of any one of embodiments 25-50, wherein the first receptor is a chimeric antigen receptor (CAR) or a TCR.

[0639] 52. A pharmaceutical composition, comprising a therapeutically effective amount of the immune cells of any one of embodiments 1-51.

[0640] 53. The pharmaceutical composition of embodiment 52, further comprising a pharmaceutically acceptable carrier, diluent or excipient.

[0641] 54. The pharmaceutical composition of embodiment 52 or 53, for use as a medicament in the treatment of cancer.

[0642] 55. A polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to a target antigen selected from:

i. a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); or

ii. MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen selected from ICAM1, COMT and CXCL16, or an antigen peptide thereof in a complex with a major histocompatibility complex class I (MHC-I), wherein the non-target antigen comprises a polymorphism.

[0643] 56. A polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to a target antigen selected from:

i. a cancer cell-specific antigen, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); or

ii. MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen selected from LRRN4 and UPK3B, or peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I), wherein the non-target antigen is expressed at a lower level by the cancer cell than by a non-target cell.

[0644] 57. A polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding:

a. a first receptor, optionally a chimeric antigen receptor (CAR) or T cell receptor (TCR), comprising an extracellular ligand binding domain specific to MSLN, or a peptide antigen thereof in a complex with a major histocompatibility complex class I (MHC-I); and

b. a second receptor, optionally an inhibitory chimeric antigen receptor, comprising an extracellular ligand binding domain specific to a non-target antigen, wherein the non-target antigen comprises HLA-A*02.

[0645] 58. A vector, comprising the one or more polynucleotides of any one of embodiments 55-57.

[0646] 59. A method of killing a plurality of cancer cell and/or treating cancer in a subject, comprising administering to the subject an effective amount of the immune cell of any one of embodiments 1-51 or the pharmaceutical composition of any one of embodiments 52-54.

[0647] 60. The method of embodiment 59, wherein a plurality of cancer cells express the target antigen.

[0648] 61. The method of embodiment 59 or 60, wherein a plurality of cancer cells do not express the non-target antigen.

[0649] 62. A method of making a plurality of immune cells, comprising:

a. providing a plurality of immune cells, and

b. transforming the plurality of immune cells with the polynucleotide system of any one of embodiments 55-57, or the vector of embodiment 58.

[0650] 63. A kit comprising the immune cell of any one of embodiments 1-51 or the pharmaceutical composition of any one of embodiments 52-54.

[0651] 62. The kit of embodiment 63, further comprising instructions for use.

EXAMPLES

[0652] The following Examples are intended for illustration only and do not limit the scope of the invention. Throughout the examples, the term "blocker antigen" is used to describe embodiments of a non-target antigen.

Example 1: Identification of Differentially Expressed Blockers

[0653] Candidate blocker targets were identified using a bioinformatics pipeline. In brief, publicly available expression databases, as described below, were searched for genes with loss of expression in tumor versus normal colon tissue. These genes were filtered for membrane proteins, and for expression in the TCGA-MESO dataset (mesothelioma). A diagram of this process is shown in FIG. 14. Candidate blocker targets are expressed in the mesothelium in healthy tissues, but are not expressed in Mesothelin (MSLN) positive cancers, which include ovarian cancers and pancreatic cancers, and approximately three-quarters of lung and colorectal cancers.

[0654] In brief, the total set of human proteins was filtered to identify predicted cell surface proteins. These proteins were examined for expression using The Cancer Genome Atlas (TCGA) database. Expression of candidate genes was examined in mesotheliomas, and genes whose expression was greater than 2 transcripts per kilobase million (TPM), or greater than 5 TPM in greater than 50% of the samples in the were included for further analysis. Expression of candidate genes in colorectal, ovarian, pancreatic and lung adenocarcinoma tumors was also evaluated, and genes whose expression in these tumor types was less than 2 TPM were included for further analysis. A summary of these genes is shown in FIG. 1. FIG. 2 shows RNA expression of MSLN in normal tissues (data from the Genotype-Tissue Expression, GTEx project, gtexportal.org/home). Mesothelin is expressed in normal adipose, fallopian tube, lung and salivary gland tissues. Thus, candidate blockers that can prevent MSLN CAR

or TCR T cells from targeting these tissues should also be expressed in health tissues that express MSLN.

[0655] MSLN expression in tumor versus normal tissues was examined (FIG. 3, TCGA database). MSLN expression in a variety of cell lines was also examined (FIG. 4, Cancer Cell Line Encyclopedia, or CCLE). The cell line rank order of expression shown in FIG. 4 correlated roughly with MSLN tumor rank expression seen in FIG. 3.

[0656] LRRN4 and UPK3B were identified as a candidate blocker target. FIG. 5 shows LRRN expression in normal tissues from the GTex portal (www.gtexportal.org/home/), while FIGS. 6 and 7 show LRRN4 expression in TCGA samples, and FIG. 8 shows LRRN4 expression in CCLE cell lines. As can be seen in FIGS. 5-7, LRRN4, like MSLN, is highly expressed in adipose and lung tissues. Moreover, LRRN4 has a large extracellular domain that contains multiple leucine rich repeat (LRR) and fibronectin type-III domains (FIG. 9).

Example 2: Identification of Candidate Blocker Targets Lost in Cancer Cells Due to Loss of Heterozygosity

[0657] Candidate blocker targets that are lost in MSLN positive cancers due to loss of heterozygosity were identified using a bioinformatics pipeline.

[0658] The following databases were used to identify candidate blocker targets: dbSNP, a database of single nucleotide polymorphisms that includes human single nucleotide variations and small-scale insertions and deletions along with publication, population frequency, molecular consequence, and genomic mapping information. Common variations were defined as having a minor allele frequency (MAF) of greater than or equal to 0.01 in at least one major population and with at least two unrelated individuals having the minor allele in NCBI. MAF of greater than or equal to 0.1 was used as the criterion for common variations. Uniprot (The Universal Protein Resource) was used as a resource for protein sequence and annotation data hosted by EMBL-EBI, SIB and PIR. GTEx (The Genotype-Tissue Expression) was used as a public resource for tissue-specific gene expression and regulation. It contains samples from 54 non-diseased tissue sites across nearly 1000 individuals. TCGA (The Cancer Genome Atlas) was used as resource for over 20,000 primary cancer and matched normal samples spanning 33 cancer types. CCLE (Cancer cell line Encyclopedia) contains information on 57 Colorectal Cancer (CRC) cell lines. Xena UCSC has renormalized TCGA and GTEx expression data (FPKM). The Broad GDAC Firehose Legacy data was used for copy number analysis.

[0659] The NCBI dbSNP database was downloaded and searched for common variants. Only variants in chromosomes identified based on a search in the Tumor Copy number portal with high loss of heterozygosity (greater than or equal to 0.5) were included, variants with a minor allele frequency of less than 0.1 were removed. VEP (Variant Effect Predictor) was used to filter for missense variants that are in protein coding regions. Genes without transmembrane domains were removed, as were genes that are not highly expressed in mesothelioma (TCGA-MESO expression level <5 TPM). Genes with an LOH frequency of less than or equal to 0.5 were removed. Genes expressed Golgi, ER, Nucleus, Cytoplasm, Mitochondrion, helical, Lysosome, and as propeptides were removed. LOH frequency was checked in the TCGA Copy Number Portal.

[0660] Genes that passed the filters were checked for other variants in Ensembl Genome Browser or VEP analysis output, as well as the locations of the variations in the gene. 11 genes passed all filters. A summary of this process is shown in FIG. 13.

[0661] Candidate blocker targets ICAM1, COMT and CXCL16 were identified. As summary of the frequency of LOH in various cancers for ICAM1, COMT and CXCL16 is shown in Table 17 below.

Table 17: Frequency of LOH

			LOH Freq	
		ICAM1	**COMT**	**CXCL16**
Ovarian (all)		0.33	0.64	0.74
Pancreatic (all)		0.15	0.25	0.48
Mesothelioma (all)		0.09	0.7	0.21
Lung (3/4)		0.46	0.3	0.58
Colorectal (3/4)		0.12	0.33	0.58
Blood cancers				0.1
AML				0.07
variant		K/E	V/M	I/T
MAF		0.36	0.37	0.46

Table 18: Summary of ICAM1, COMT and CXCL16 variants

Gene Name	Variant	Protein Position	Change	MAF
CXCL16	rs2277680, rs1050998	1. 200, 2. 142	1. A/V, 2. I/T	1. 0.4615, 2. 0.4633
COMT	rs4680	158	V/M	0.369
ICAM1	rs5498	469	K/E	0.359

Example 3: Identification of Blocker Ligand Binding Domains

[0662] Publicly available antibodies to candidate blocker antigens are sequenced, if CDR sequences are unknown. If no antibodies to candidate blocker targets are available, these antibodies are generated by immunization of mice, rats, or rabbits with purified protein (*e.g.*, ICAM1, CXCL16, and COMT1). Sera from immunized animals is used to screen for mAbs for binding to blocker targets. Antibodies to blocker targets are also generated using the huTARG™ system. Antibodies with the desired specificity are then isolated and sequenced to determine CDR sequences.

[0663] CDR sequence from antibodies to blocker targets are used to generate scFv using standard molecular biology techniques. Candidate scFv are fused to inhibitor receptor hinge or transmembrane domains to generate inhibitory receptors using standard molecular biology techniques. Candidate scFv are also fused to activator receptor hinge or transmembrane domains (e.g., CAR) to generate full length activator receptors to use as a positive control for scFv binding to target antigens. The ability of candidate scFv to work in the context of an inhibitory receptor is assayed in Jurkat cells using the NFAT-luciferase reporter assay.

Example 4: HLA-A*02 Blocker can Block MSLN Activator Mediated Activation of Jurkat Cells

[0664] Cell culture

[0665] Jurkat cells encoding an NFAT Luciferase reporter were obtained from BPS Bioscience. In culture, Jurkat cells were maintained in RPMI media supplemented with 10% FBS, 1% Pen/Strep and 0.4mg/mL G418/Geneticin. All other cell lines used in this study were obtained from ATCC, and maintained as suggested by ATCC.

[0666] Jurkat cell transfection

[0667] Jurkat cells were transiently transfected via 100uL format Neon electroporation system (Thermo Fisher Scientific) according to manufacturer's protocol using the following settings: 3 pulses, 1500V, 10 msec. Cotransfection was performed with 1-3ug of activator CAR or TCR construct and 1-3ug of blocker constructs or empty vector per 1e6 cells and recovered in RPMI media supplemented with 20% heat-inactivated FBS and 0.1% Pen/Strep.

[0668] Jurkat-NFAT-luciferase activation studies

[0669] Jurkat cells were resuspended in 15uL of RPMI supplemented with 10% heat-inactivated FBS and 0.1% Pen/Strep, added to the peptide-loaded beads and co-cultured for 6 hours. ONE-Step Luciferase Assay System (BPS Bioscience) was used to evaluate Jurkat luminescence. Assays were performed in technical duplicates.

[0670] Primary T cell transduction, expansion, and enrichment

[0671] Frozen PBMCs were thawed in 37°C water bath and cultured at 1e6 cells/mL in LymphoONE (Takara) with 1% human serum and activated using 1:100 of T cell TransAct (Miltenyi) supplemented with IL-15 (10ng/mL) and IL-21 (10ng/mL). After 24 hours, lentivirus was added to PBMCs at a MOI of 5. PBMCs were cultured for 2-3 additional days to allow cells to expand under TransAct stimulation. Post expansion, activator and blocker transduced primary T cells were enriched using anti-PE microbeads (Miltenyi) according to manufacturer's instructions. Briefly, primary T cells were incubated with CD19-Fc (R&D Systems) at 1:100 dilution for 30 minutes at 4°C in MACS buffer (0.5% BSA + 2mM EDTA in PBS). Cells were washed 3 times in MACS buffer and incubated in secondary antibody (1:200) for 30 minutes at 4°C in MACS buffer. Cells were then incubated in anti-PE microbeads and passed through the LS column (Miltenyi).

[0672] Primary T cell in *vitro* cytotoxicity studies

[0673] For cytotoxicity studies with pMHC targets, enriched primary T cells were incubated with SiHa or HeLa cells expressing renilla luciferase (Biosettia), and GFP or RFP. Live luciferase-expressing SiHa or HeLa cells were quantified using a Renilla Luciferase Reporter Assay System (Promega). Enriched primary T cells were incubated with SiHa or HeLa ("tumor" cells) or HLA-A*02 transduced SiHa or HeLa cells ("normal" cells). WT "tumor" SiHa or HeLa cells stably expressing GFP or RFP and renilla luciferase (Biosettia) or HLA-A*02 "normal" SiHa or HeLa cells stably expressing RFP and luciferase (Biosettia) were imaged together with unlabeled primary T cells using an IncuCyte live cell imager.

[0674] Activation of Jurkat effector cells expressing an MSLN CAR activator and a pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor was assayed using the NFAT Luciferase assay.

[0675] Jurkat cells were transfected with activator:blocker DNA at a ratio of 1:4, and activation was assayed in a cell-free bead based assay (FIG. 10A). Beads were loaded with either activator antigen, or activator and blocker antigens, and the ratio of beads to Jurkat cells was varied. In the cell-free bead based assay, the pMHC HLA-A*02 scFv LIR-1 based inhibitory receptor was able to block activation of the Jurkat cells when cells were contacted with beads carrying the pMHC HLA-A*02 blocker and MSLN activator in *cis*. Presence of

the pMHC HLA-A*02 blocker on the beads was able to shift E_{MAX} of MSLN CAR by greater than or equal to 12X (FIG. 10A).

[0676] Activation Jurkat cells transfected with the same activator and blocker at a 1:4 DNA ratio were assayed for activation using the chronic myelogenous leukemia cell line K562. K562 expresses MSLN, the activator antigen. The response of Jurkat effector cells to K562 cells transduced with HLA-A*02 to express both activator and blocker antigens (MSLN+ HLA-A*02+) and untransduced K562 (MSLN+ HLA-A*02-) that expressed the activator but not the blocker antigen was assayed. As can be seen in FIG. 10B, expression of HLA-A*02+ by the K562 cells was able to shift the MSLN CAR E_{MAX} by greater than 5X.

[0677] The ability of the pMHC HLA-A*02 inhibitory receptor to block activation via the MSNL scFv CAR was also assayed using effector primary T cells and SiHa or HeLa target cells. SiHa and HeLa cells endogenously express MSLN, and were transduced to express the HLA-A*02 inhibitory receptor target. Activation of primary effector T cells was assayed by looking at fold induction of IFNγ. As shown in FIG. 11, the pMHC HLA-A*02 LIR-1 inhibitory receptor was able to block activation of primary T cells when the primary T cells were presented with SiHa or HeLa target cells expressing HLA-A*02 (greater than 10X and 5X inhibition, respectively).

[0678] The pMHC HLA-A*02 inhibitory receptor was also able to inhibit killing by T cells expressing both the MSLN scFv CAR and the pMHC HLA-A*02 LIR-1 inhibitory receptor, when the T cells were presented with SiHa cells that expressed MSLN but not HLA-A*02 (FIG. 12).

Example 5: HLA-A*02 Blocker Inhibits MSLN CAR Activators Directed at MSLN Using K562 and HeLa Target Cells

[0679] *Cell culture*

[0680] MSLN CAR activator and HLA-A02 LIR-1 inhibitory receptor were examined, using Jurkat effector cells and K562 target cells (FIG. 15A). The ability of MSLN CAR T cells expressing MSLN CAR (with two different MSLN ligand binding domains) to kill HeLa cells expressing the blocker target, HLA-A*02, was also assayed (FIGS. 15B-15C). The MSLN ligand represents surface antigens that can extend into the realm of 100,000 epitopes/cell. The ratio of A to B module expression was varied using different DNA concentrations in transient transfection assays. The activator and inhibitory receptor system is

flexible enough to accommodate low and high target densities, in principle allowing optimization for pMHC targets as well as non-pMHC surface antigens.

[0681] Jurkat cells encoding an NFAT luciferase reporter were obtained from BPS Bioscience. All other cell lines used in this study were obtained from ATCC. In culture, Jurkat cells were maintained in RPMI media supplemented with 10% FBS, 1% Pen/Strep and 0.4mg/mL G418/Geneticin. K562 and HeLa cells were maintained as suggested by ATCC.

[0682] *MSLN antigen binding domains*

[0683] MSLN-activating CAR scFv were derived from human M5 (LBD1) as described Beatty, et al. WO2015/090230A1 and humanized SS1 (LBD2) as described in BioLuminate, 2019 (BioLuminate, version 3.6, version 3.6 ed. Schrödinger, LLC, New York, NY) and US 6,809,184 B1.

[0684] *Jurkat cell transfection and activation*

[0685] Jurkat cells were transiently transfected via 100uL format Neon electroporation system (Thermo Fisher Scientific) according to manufacturer's protocol using the following settings: 3 pulses, 1500V, 10 msec. Co-transfection was performed with 1-3ug of activator construct and 1-3 ug of blocker constructs or empty vector per 1e6 cells and recovered in RPMI media supplemented with 20% heat-inactivated FBS and 0.1% Pen/Strep. To confirm blocker surface expression, Jurkat cells were stained 18-24 hours post-transfection with 10ug/mL streptavidin-PE-HLA-A*02-pMHC tetramer for 60 minutes at 4°C in PBS with 1% BSA and characterized by flow cytometry (BD FACS Canto II). Jurkat cell activation was evaluated using the NFAT-luciferase assay system as described in Example 4.

[0686] *Primary T cell transduction, expansion, and enrichment*

[0687] Leukopaks were purchased from AllCells®. Collection protocols and donor informed consent were approved by an Institutional Review Board (IRB), with strict oversight. HIPAA compliance and approved protocols were also followed. Frozen PBMCs were thawed and cultured as described in Example 4. Cells were simultaneously co-transduced at a MOI = 5 for each lentivirus, i.e. lentiviral vectors including activator or blocker receptor. PBMCs were cultured for 2-3 additional days to allow cells to expand under TransAct stimulation. Post expansion, activator and blocker transduced primary T cells were enriched for blocker-positive T cells by positive selection using anti-PE microbeads (Miltenyi) according to manufacturer’s instructions. Briefly, primary T cells were incubated with 10ug/mL streptavidin-PE-HLA-A*02-pMHC tetramer for 60 minutes at 4°C in MACS buffer (0.5% BSA + 2mM EDTA in PBS). Cells were washed 3 times in MACS buffer and passed through

the LS column (Miltenyi) to separate blocker-positive cells (a mix of blocker-only and activator + blocker cells) from untransduced and activator-only cells.

[0688] *Primary T cell in vitro cytotoxicity studies*

[0689] For cytotoxicity studies with pMHC targets, enriched primary T cells were incubated with K562 or HeLa target cells expressing renilla luciferase (Biosettia). Target cells that were HLA-A*02 positive also expressed GFP and firefly luciferase (Biosettia), and target cells that were HLA-A*02 negative expressed RFP and firefly luciferase. Target cells were imaged together with unlabeled primary T cells using an IncuCyte live cell imager. Fluorescence intensity of live target cells over time was quantified using IncuCyte imaging software.

Example 6: Mouse SS1 MSLN Antigen Binding Domain Activator in 2nd and 3rd Generation CAR Architectures and HLA-A*02 Blocker

[0690] Originally, humanized M5 and SS1 scFv targeting MSLN were used with a third generation CAR architecture (CD28, 4-1BB and CD3 zeta). The effect of using a murine SS1 scFv antigen binding domain, and second generation CAR architecture (4-1BB and CD3zeta intracellular domains) was assayed.

[0691] HLA-A*02- donor T cells were transduced with MSLN third generation CAR activator (a CAR with CD28, 4-1BB and CD3 zeta intracellular domains) and an HLA-A*02 scFv LIR-1 blocker using a PA2.1 antigen binding domain. MSLN CAR activators with humanized M5, humanized SS1 and murine SS1 scFv were assayed (Table 1). HLA-A*02 blocker sequences are described in Table 5. T cells were transduced with activator and/or blocker constructs, cultured, and enriched as described in Examples 4 and 5. T cells were used on day 14 following transduction, and were cultured with MSLN + HeLa target cells at an effector: target ratio of 1:1. Cytotoxicity was assayed as described in Examples 4 and 5. FIG. 16 shows that inhibitor receptors were able to effectively block killing of HeLa cells by T cells expressing the MSLN third generation CAR when the HeLa cells also expressed HLA-A*02. Further, FIG. 16 shows that the murine SS1 generation 3 CAR (upper right plot, boxed) provides a better window than the humanized M5 and humanized SS1 CARs. Note, in FIG. 16, C-0883 is an HLA-A*02 CAR used as a positive control, additional sequences are described in Table 19.

[0692] The ability of T cells expressing the MSLN activator and HLA-A*02 LIR1 blocker to selectively kill MSLN+ HLA-A*02- Capan cells was also assayed (FIG. 17). T cells were transduced with activator and/or blocker receptor constructs, cultured, and enriched as

described in Examples 4 and 5. T cells were used on day 14 following transduction, and were cultured with Capan target cells at an effector: target ratio of 1:1. Cytotoxicity was assayed as described in Examples 4 and 5. FIG. 17 shows that inhibitor receptors were able to effectively block killing of Capan cells by T cells expressing the MSLN third generation CAR when the Capan cells also expressed HLA-A*02.

[0693] The murine SS1 MSLN1 scFv was also assayed in a generation 2 CAR (a CAR with a 4-1BB and CD3 zeta intracellular domain). FIG. 18 shows that killing of MSLN+ HLA-A*02+_HeLa cells, and HCT116 wild type cells (which natively express both MSLN and HLA-A*02) by T cells expressing the mSS1 2nd generation CAR was effectively blocked by HLA-A*02 scFv LIR-1 inhibitory receptor. As can be seen from FIG. 18, the 2nd generation mSS1 CAR was more effectively blocked by inhibitory receptors with a PA2.1 scFv antigen binding domain than by inhibitory receptors with a BB7.2 scFv antigen binding domain. The effect of short and long LIR-1 hinge sequences in the inhibitory receptor, and the arrangement of the VH and VL domains in the HLA-A*02 scFv, was also assayed.

[0694] Expression of the 2nd generation CAR with the murine SS1 scFv was also confirmed via FACS, and the results are shown in FIG. 19. The SS1 antigen binding domain was stained using a recombinant soluble MSLN ligand.

Table 19: Sequences of constructs

Name	Amino Acid Sequence	Nucleotide Sequence
PA2.1.14 (VL:VH) scFv LIR1 sHTICD	TEFTLTISSLQPDDFATYYCFQGSHVPRTFGQGTKV EVKGGGGSGGGGSGGGGSGGQVQLVQSGAEVKKPGS SVKVSCKASGYTFTSYHIHWVRQAPGQGLEWIGWIY PGNVNTEYNEKFKGKATITADESTNTAYMELSSLRS EDTAVYYCAREEITYAMDYWGQGTLVTVSSVVSGPS GGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRHL GVVIGILVAVILLLLLLLLFLILRHRRQGKHWTST QRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEEN LYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVKH SRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTEA AASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSPA VPSIYATLAIH (SEQ ID NO: 85)	(SEQ ID NO: 1252)
PA2.1.14 (VL:VH) scFv LIR1 HTICD	DIQMTQSPSTLSASVGDRVTITCRSSQSIVHSNGNT YLEWYQQKPGKAPKLLIYKVSNRFSGVPARFSGSGS GTEFTLTISSLQPDDFATYYCFQGSHVPRTFGQGTK VEVKGGGGSGGGGSGGGGSGGQVQLVQSGAEVKKPG SSVKVSCKASGYTFTSYHIHWVRQAPGQGLEWIGWI YPGNVNTEYNEKFKGKATITADESTNTAYMELSSLR SEDTAVYYCAREEITYAMDYWGQGTLVTVSSYGSQS SKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLL LLLLLFLILRHRRQGKHWTSTQRKADFQHPAGAVGP EPTDRGLQWRSSPAADAQEENLYAAVKHTQPEDGVE MDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPLS GEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYAQLH	(SEQ ID NO: 1253)

	SLTLRREATEPPPSQEGPSPAVPSIYATLAIH (SEQ ID NO: 86)	
MSLN_SsI CD8_HT 41BB CD3z	QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNW VKQSHGKSLEWIGLITPYNGASSYNQKFRGKATLTV DKSSSTAYMDLLSLTSEDSAVYFCARGGYDGRGFDY WGQGTTVTVSSGGGGSGGGGSGGGGSDIELTQSPAI MSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRW IYDTSKLASGVPGRFSGSGSGNSYSLTISSVEAEDD ATYYCQQWSGYPLTFGAGTKLEITTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIW APLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFM RPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADA PAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRR GKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 87)	(SEQ ID NO: 1254)
PA2.1.14 scFv LIR1 sHTICD	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIHW VRQAPGQGLEWIGWIYPGNVNTEYNEKFKGKATITA DESTNTAYMELSSLRSEDTAVYYCAREEITYAMDYW GQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS TLSASVGDRVTITCRSSQSIVHSNGNTYLEWYQQKP GKAPKLLIYKVSNRFSGVPARFSGSGSGTEFTLTIS SLQPDDFATYYCFQGSHVPRTFGQGTKVEVKVVSGP SGGPSSPTTGPTSTSGPEDQPLTPTGSDPQSGLGRH LGVVIGILVAVILLLLLLLLLFLILRHRRQGKHWTS TQRKADFQHPAGAVGPEPTDRGLQWRSSPAADAQEE NLYAAVKHTQPEDGVEMDTRSPHDEDPQAVTYAEVK HSRPRREMASPPSPLSGEFLDTKDRQAEEDRQMDTE AAASEAPQDVTYAQLHSLTLRREATEPPPSQEGPSP AVPSIYATLAIH (SEQ ID NO: 88)	(SEQ ID NO: 1255)
PA2.1.14 scFv LIR1 HTICD	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYHIHW VRQAPGQGLEWIGWIYPGNVNTEYNEKFKGKATITA DESTNTAYMELSSLRSEDTAVYYCAREEITYAMDYW GQGTLVTVSSGGGGSGGGGSGGGGSGGDIQMTQSPS TLSASVGDRVTITCRSSQSIVHSNGNTYLEWYQQKP GKAPKLLIYKVSNRFSGVPARFSGSGSGTEFTLTIS SLQPDDFATYYCFQGSHVPRTFGQGTKVEVKYGSQS SKPYLLTHPSDPLELVVSGPSGGPSSPTTGPTSTSG PEDQPLTPTGSDPQSGLGRHLGVVIGILVAVILLLL LLLLLFLILRHRRQGKHWTSTQRKADFQHPAGAVGP EPTDRGLQWRSSPAADAQEENLYAAVKHTQPEDGVE MDTRSPHDEDPQAVTYAEVKHSRPRREMASPPSPLS GEFLDTKDRQAEEDRQMDTEAAASEAPQDVTYAQLH SLTLRREATEPPPSQEGPSPAVPSIYATLAIH (SEQ ID NO: 89)	(SEQ ID NO: 258)

Example 7: Assaying the Effect of the LIR-1 Hinge on Blocking Activity

[0695] The effects of different LIR-1 hinges on the ability of HLA-A*02 scFv LIR-1 inhibitory receptors to block killing by Jurkat cells expressing a KRAS TCR activator was assayed using the Jurkat NFat Luciferase assays described *supra*. A humanized PA2.1 scFv LIR-1 receptor and humanized BB7.2 scFv LIR-1 with a shorter LIR-1 hinge were assayed in Jurkat cells as previously described, and the results are shown in FIGS. 20A-20B. Jurkat cells

were transfected with a KRAS TCR activator receptor and/or HLA-A*02 scFv LIR-1 inhibitory receptor (humanized PA2.1 or humanized BB7.2) with a variety of LIR-1 derived hinges, methods as described *supra*, and co-cultured with T2 target cells that were either HLA-A11 positive, or HA-A11 and HLA-A*02 positive. Inhibitory receptors with both the shorter and longer hinge behaved similarly (FIG. 20A-B). An inhibitory receptor with a mouse PA2.1 scFv and slightly longer hinges was also assayed functioned similarly to shorter LIR-1 hinges in the T2-Jurkat assay (FIG. 21A-B). Hinge sequences are shown in black in FIG. 20B and FIG. 21B, with the gray SS representing a linker between the antigen binding domain and the hinge, and the gray VIGIL the start of the LIR-1 transmembrane domain. Hinge, transmembrane domain and intracellular domain of the inhibitory receptors were all derived from LIR-1. FIGS. 20A-20B and 21A-21B show that LIR-1 hinge length can be varied without negatively effecting the LIR-1 inhibitory receptor. Shorter hinges can provide an advantage when packaging nucleic acid sequences encoding LIR-1 inhibitory receptors in lentiviral vectors for delivery.

Example 8: Identification of new anti-MSLN Antibodies

[0696] Mesothelin (MSLN) is a classic tumor-associated antigen that is expressed in lung cancer and many other solid tumors. However, MSLN is also expressed in normal mesothelium that surrounds and lubricates the surfaces of key internal organs. This normal expression creates significant risk of serious inflammation for MSLN-directed therapeutics. This example describes a dual-receptor (Tmod) system which exploits common LOH at the HLA locus in cancer cells, allowing T cells to recognize the difference between tumor and normal tissue. T cells engineered with the MSLN CAR Tmod construct described in this example contain: (i) a MSLN-activated CAR; and, (ii) an inhibitory receptor gated by HLA-A*02. Without wishing to be bound by theory, the Tmod system robustly protects “normal” cells even in mixed-cell populations in vitro and in a xenograft model. The MSLN CAR can also be paired with other HLA class I blockers, supporting extension of the approach to patients beyond HLA-A*02 heterozygotes. The Tmod mechanism exemplified by the MSLN CAR Tmod construct may provide an alternative route to leverage solid-tumor antigens such as MSLN in safer, more effective ways than previously possible. Mesothelin (MSLN) was proposed as a cancer target in 1992 [1], yet there is still no viable therapy that utilizes MSLN. Not only is it expressed on most mesotheliomas but also large subsets of ovarian, cervical, uterine, gastric, pancreatic and lung adenocarcinomas [2]. In normal adults, MSLN is present only in mesothelium, a tissue that itself may be nonessential [2,3]. However, immunotherapy

targeting MSLN carries the risk of inflammatory attack on MSLN(+) mesothelial cells that surround important internal organs [4]. Several investigational therapeutics directed at MSLN have been tested; for example, immunotoxin-conjugates [5, 6], antibody-drug conjugates [7], bispecific antibodies [8], CAR-Ts [9], and a hybrid TCR-scFv [10]. All active systemically administered therapeutics so far have been toxic. Recently, an approach to deliver MSLN CAR-Ts via intrapleural infusion has been reported [11].

[0697] This example describes an exemplary method to treat MSLN(+) cancers that does not depend on local administration of therapeutics, but instead exploits LOH. This approach seeks to avoid systemic toxicity to normal tissues by pairing a MSLN-targeted CAR with a LIR-1-based inhibitory receptor that blocks effector function against normal cells that express the HLA-A*02 allele (**FIG. 22A-22B**). This dual-receptor construct is intended to treat genetically defined cancer patients who have LOH of the HLA-A*02 allele in their MSLN(+) tumor. The difference in HLA-A*02 expression in tumor vs. normal tissues caused by LOH creates an all-or-nothing input to the effector cells that is believed to confer high selectivity for tumor killing.

RESULTS

Isolation and characterization of potent, selective MSLN CARs

[0698] To identify potent, selective MSLN-directed ligand-binding domains (LBDs) that function in CARs, mammalian surface display libraries encoding either IgG antibodies (mAbs) or scFvs were screened (**FIGS. 23A-23B**). Soluble biotinylated MSLN labeled with fluorochrome were used as probe to enrich for cells in the library that stained for MSLN via FACS. As negative probe, a mixture of soluble CEA and EGFR was used to deplete cells encoding mAbs or scFvs with non-specific binding properties. After two rounds of enrichment for MSLN-binding, 62 individual LBDs were selected, converted to scFv CARs, confirmed for surface expression in Jurkat cells, and assessed for functional activity in solid-state Jurkat cell assays (**FIGS. 23C-23D**). This step allowed for the selection of a subset of the most sensitive, selective binders for further functional characterization.

[0699] While most of the 62 binders resulted in a functional response to cell surface displayed MSLN, six were selected for further characterization; sequences binder CDRs (heavy chain (HC) CDRs and light chain (LC) CDRs) and are provided in Table 2, Table 3 (heavy chain; VH) and Table 4 (light chain; VL). In each case, the HC-CDRs or VH may be paired with any of the LC-CDRs or VL, as the heavy chains and light chains share similarity, with routine testing to confirm desired expression and binding activity.

[0700] Single chain variable fragments (scFvs) may be generated by inserting a linker (e.g., GGGGSGGGGSGGGGSGG (SEQ ID NO: 152) or another suitable linker) between the VH and VL segments to form a VH-VL scFv; or VL-VH scFvs may alternatively be constructed. The light chains have high sequence similarity; pairing of VL and VH to generate full antibodies have been determined without undue experimentation. Illustrative scFvs are provided in Table 1, illustrative heavy and light chains are provided in Tables 3 and 4, and illustrative CDR sequences are provided in Table 2. Sequences of illustrative chimeric antigen receptors using the MSLN scFv are provided as Table 20, below.

Table 20: Sequences of Receptors comprising single chain variable fragments (scFv)

#	SEQ ID NO	Receptor Sequence
1	286	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAP GKGLEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYL QMNSLKTEDTAVYYCTTDLPKLRNFHIWGQGTLVTVSSGGG GSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVV GGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
2	287	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAP GKGLEYVSAISSNGGSTYYANSVKGRFTISRDNSKNTLYLQM GSLRAEDMAVYYCASLEYHGFRQYGLRYWHWGQGTLVTVS SGGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFW VLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTP RRPGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRP VQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT YDALHMQALPPR
3	288	QLQLQESGSGLVKPSQTLSLTCAVSGGSISSGGYSWSWIRQPP GKGLEWIGYIYHSGSTYYNPSLKSRVTISVDRSKNQFSLKLSS VTAADTAVYYCASIKFWFAGINYFFPWGQGTLVTVSSGGGGS GGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR

#	SEQ ID NO	Receptor Sequence
		KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
4	289	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAP GKGLVWVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQM NSLRAEDTAVYYCASGFLGMGSNFIWGQGTLVTVSSGGGGS GGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
5	290	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHP GKGLEWIGYIYYSGSTYYNPSLKSLVTISVDTSKNQFSLKLSSV TAADTAVYYCASGDRARYFDLWGRGTLVTVSSGGGGSGGG GSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
6	291	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMHWVRQAP GKGLVWVSRINSDGSSTSYADSVKGRFTISRDNAKNTLYLQM NSLRAEDTAVYYCARYPRGYHQMVDAFDIWGQGTMVTVSS GGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRA SQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWV LVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR
7	292	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPG KGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVT AADTAVYYCARVRFLAARTTIPEANFLWGQGTLVTVSSGGG

#	SEQ ID NO	Receptor Sequence
		GSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVV GGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
8	293	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPG KGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARVLSRARFDYWGQGTLVTVSSGGGGSGGG GSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
9	294	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPG KGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARLRGRVFDPWGQGTLVTVSSGGGGSGGGG SGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR
10	295	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPG KGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVT AADTAVYYCARIKFTSFLYVHGFLWGQGTLVTVSSGGGGSG GGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM

#	SEQ ID NO	Receptor Sequence
		AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
11	296	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQA PGQRLEWMGWINAGNGNTKYSQKFQGRVTITRDTSASTAYM ELSSLRSEDTAVYYCARGQRWLYLGGIRRHWGQGTLVTVSS GGGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRA SQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWV LVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPV QTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQ LYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYN ELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTY DALHMQALPPR
12	297	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGK GLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTA ADTAVYYCAREWIPSRPYYFDYWGQGTLVTVSSGGGGSGGG GSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
13	298	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPP GKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCARESTGTGAFDIWGQGTMVTVSSGGGGSGGG GSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
14	299	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAP GKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQ MNSLRAEDTALYHCARERYRRVLHWYFDLWGRGTLVTVSSG GGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRAS QSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAP

#	SEQ ID NO	Receptor Sequence
		RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVL VVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRR PGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQ TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR
15	300	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQAT GQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYM ELSSLRSEDTAVYYCAREPDAFDIWGQGTMVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
16	301	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPP GKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCAREHMGTIPYYFDYWGQGTLVTVSSGGGGSG GGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
17	302	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQPP GKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCAREEFGYGDVLYWGQGTLVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR

#	SEQ ID NO	Receptor Sequence
18	303	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPP GKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCAREDVVKGAFDIWGQGTMVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
19	304	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPG KGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCAREDFSHKLGYFQHWGQGTLVTVSSGGGGS GGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
20	305	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDYDYVWGQGTLVTVSSGGGGSGGGGSG GGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTIASQ PLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLACY SLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPY APPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEY DVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
21	306	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSGDYYWSWIRQPP GKGLEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCARDRRDWDWFDPWGQGTLVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG

#	SEQ ID NO	Receptor Sequence
		CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
22	307	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPP GKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSV TAADTAVYYCARDQQALKYRVDWGQGTLVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
23	308	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAP GQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYM ELRSLRSDDTAVYYCARDLTLGCFDYWGQGTLVTVSSGGGG SGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
24	309	EVQLVESGGGLVQPGGSLRLSCAASGFTVSSNYMSWVRQAP GKGLEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARDGSNSWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
25	310	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAP GKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARAFLFLSFSVWGQGTLVTVSSGGGGS GGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS

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		YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
26	311	EVQLVESGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAP GKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNSLYLQM NSLRTEDTALYYCAKGIFYSSKEDFDYWGQGTLVTVSSGGGG SGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
27	312	EVQLVESGGVVVQPGGSLRLSCAASGFTFDDYTMHWVRQAP GKGLEWVSLISWDGGSTYYADSVKGRFTISRDNSKNSLYLQM NSLRTEDTALYYCAKDIWIFYSSNPKPTVYWGQGTLVTVSSG GGGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRAS QSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGT DFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVL VVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRR PGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQ TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQL YNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNE LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD ALHMQALPPR
28	313	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYAMNWVRQAP GQGLEWMGWINTNTGNPTYAQGFTGRFVFSFDTSVSTAYLQI CSLKAEDTAVYYCARKDQTLTYGNWFDPWGQGTLVTVSSGG GGSGGGGSGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQS ISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPP TPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVV VGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPG PTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYN ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ

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		KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
29	314	QVQLQESGPGLVKPSETLSLTCTVSGGSVSSGSYYWSWIRQPP GKGLEWIGYIYYSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSV TAADTAVYYCARDHYERGLYWGQGTLVTVSSGGGGSGGGG SGGGGSGGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQSYSTPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR
30	315	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARYMYNWYFDLWGRGTLVTVSSGGGGSGG GGSGGGGSGGDIQMTQSPSSVSASVGDRVTITCRASQGISSWL AWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQANSFPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
31	316	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDRRPAFDIWGQGTMVTVSSGGGGSGGGG SGGGGSGGDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQANSFPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR
32	317	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCAVHLKRRPYFDYWGQGTLVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI

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		ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
33	318	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASVHKKPIFDYWGQGTLVTVSSGGGGSGGG GSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
34	319	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASTSRRCTFQHWGQGTLVTVSSGGGGSGGG GSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
35	320	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASTSPRPLFQHWGQGTLVTVSSGGGGSGGG GSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR

#	SEQ ID NO	Receptor Sequence
36	321	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASPYQVRGVYFDYWGQGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
37	322	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASPYKKRRTVFDYWGQGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
38	323	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASLQRGLALFQHWGQGTLVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
39	324	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASILSVPYFDLWGRGTLVTVSSGGGGSGGGG SGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALAW YQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHY

#	SEQ ID NO	Receptor Sequence
		QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR
40	325	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCASGWIRVPLRLPLFQHWGQGTLVTVSSGGG GSGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGIS SALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVV GGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
41	326	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARVTIFAIFDIWGQGTMVTVSSGGGGSGGGG SGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALAW YQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQ PEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVLA CYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHY QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGR REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL PPR
42	327	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARVGRGFVHFDLWGRGTLVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
43	328	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARTSRGLCVLFDYWGQGTLVTVSSGGGGSG

#	SEQ ID NO	Receptor Sequence
		GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
44	329	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARSGPSSYWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
45	330	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARNIYMGGIWFDPWGQGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
46	331	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARLTVRTGAFDIWGQGTMVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM

#	SEQ ID NO	Receptor Sequence
		AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
47	332	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARLRTAHLDFDLWGRGTLVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
48	333	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDLIFPVVFDYWGQGTLVTVSSGGGGSGG GGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
49	334	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDGYRKYGYVFFDIWGQGTMVTVSSGGG GSGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGIS SALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVV GGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
50	335	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARDGRYRRFWHAFDIWGQGTMVTVSSGGG GSGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGIS SALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPT

#	SEQ ID NO	Receptor Sequence
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51	336	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPG KGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTAVYYCARAHIRGYFDLWGRGTLVTVSSGGGGSGGG GSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSALA WYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISSL QPEDFATYYCQQFNSYPLTFGGGTKVEIKTTTPAPRPPTPAPTI ASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGVL ACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
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53	338	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARTSRTTWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGV LACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR

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55	340	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKWGGRLYWYFDLWGRGTLVTVSSGGGG SGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISS ALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
56	341	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKVIRQLWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGV LACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR
57	342	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKVFANSWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGV LACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH

#	SEQ ID NO	Receptor Sequence
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59	344	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKRWGKDGPYWYFDLWGRGTLVTVSSGG GGSGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQG ISSALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPP TPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVV VGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPG PTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTT QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYN ELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQ KDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
60	345	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKRRDSYGPYWYFDLWGRGTLVTVSSGGG GSGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGIS SALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPT PAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVV GGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP TRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNE LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQK DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALH MQALPPR
61	346	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKNRPPPGYWYFDLWGRGTLVTVSSGGGG

#	SEQ ID NO	Receptor Sequence
		SGGGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISS ALAWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTP APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVG GVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTR KHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEE DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELN LGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDK MAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
62	347	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPG KGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKGRRFSWYFDLWGRGTLVTVSSGGGGSG GGGSGGGGSGGAIQLTQSPSSLSASVGDRVTITCRASQGISSAL AWYQQKPGKAPKLLIYDASSLESGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQFNNYPLTFGGGTKVEIKTTTPAPRPPTPAP TIASQPLSLRPEACRPAAGGAVHTRGLDFACDFWVLVVVGGV LACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKH YQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLG RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA LPPR

[0701] Six binders were expressed as third-generation (Gen3) chimeric antigen receptors (CAR1-CAR6) [corresponding to #16, 17, 18, 29, 55, and 59, respectively, in Tables 1-4 and 20], which were compared to anti-MSLN scFvs from the literature (SS1, M5 and m912) in Jurkat functional assays. The CARs displayed a range of sensitivities (EC_{50}) and maximal responses (E_{max}) (**FIG. 24A**). All constructs were Gen3 except SS1 (Gen2). Jurkat cell dose-response (RLU) was measured to assess the sensitivity in a 6 hour co-culture assay: **(1)** Titrated MSLN-encoding mRNA was used to transfect HEK293 cells; **(2)** QIFIKIT (quantitative analysis kit, Agilent®) was used to convert flow-cytometry based surface expression to MSLN molecules/cell; and, **(3)** The molecule/cell sensitivities (EC50) of 6 novel and three benchmark CARs were calculated from fitting the dose-response curves. For those CARs with sensitivities below the limit of detection of the assay, EC50 was reported as <3000 MSLN molecules/cell. Maximum signal (E_{max}) for each construct was also noted. Experiments were repeated 1-4 times.

[0702] Table 21 shows the selectivity window and killing efficiency of HeLa cells by transduced primary T cells. Quantification of the selectivity window between killing of

MSLN+ A2- and MSLN+ A2+ HeLa cells with activator and blocker+ primary T cells. Killing efficiency describes difference in killing of MSLN+ A2- HeLa cells by activator and blocker+ T cells compared to activator+ (only) T cells. Both measures are calculated up to the time corresponding to 80% maximum observed killing.

Table 21

Activator	**E:T (HeLa target)**	**Time (hours) to 80% max killing**	**Selectivity window**	**Killing efficiency**
hM5 CAR	4:1	28	6.9	1.2
mSS1 CAR	4:1	44	6.2	1.1
CAR 18	4:1	24	21.4	1.1
CAR 29	4:1	20	7.0	1.0
hM5 CAR	2:1	64	5.5	0.8
mSS1 CAR	2:1	72+	n/d	0.7
CAR 18	2:1	56	20.3	0.8
CAR 29	2:1	44	7.6	0.9

[0703] n/d = not determined due to poor overall killing

[0704] Six binders (CAR1-6) were compared to benchmark MSLN scFvs from the literature (SS1, M5 and m912) in Jurkat functional assays [12-14]. All were expressed as Gen3 CARs, with the exception of Gen2 SS1. For MSLN(+) target cells, HEK293 cells transfected with synthetic MSLN mRNA were used. The CARs displayed a range of sensitivities (EC_{50}) and maximal responses (E_{max}) (**FIG. 24A**). Of the six binders, all but CAR 16 exhibit higher sensitivity than hM5 and sSS1.

[0705] In short, an extensive campaign to identify anti-MSLN binders yielded hundreds of sequences identified in an NGS screen, and 62 candidate constructs were produced, all of which bind MSLN. Six of these shown superior activity. CAR 18 and CAR 29 demonstrated superior sensitivity to comparator CAR constructs.

[0706] Previous work suggested that E_{max} is related to surface expression of the receptor and EC_{50} to its binding and signal transduction properties, especially the LBD [15,16]. The EC_{50} was converted from relative response measured by luminescence in Jurkat cells to absolute molecules/cell using standard curves and QIFIKIT methodology necessary [27]. One of the benchmark CARs (m912) displayed low functional sensitivity, with an EC_{50} estimated at ~80K molecules/cell. The EC_{50}s for the other benchmarks and novel CARs ranged

downwards of ~6K molecules/cell. Several novel LBDs assayed as CARs in Jurkat cells had EC50s below the limit of detection (<3K molecules/cell). As an indicator of selectivity, CAR3 and the benchmark M5 were tested for responsiveness to a panel of MSLN(+) and (-) cell lines. Both CARs displayed MSLN-specific activation and were inactive against MSLN(-) lines (**FIG. 24B and 25A**).

MSLN Tmod constructs are blocked efficiently by HLA-A*02 antigen in Jurkat and primary T cells

[0707] CAR1-6 and the benchmark CARs were tested as components of Tmod constructs where the CARs were paired with an A*02-directed inhibitory receptor or "blocker" previously shown to inhibit functional response in Jurkat and primary T cells [18]. This blocker comprised an A*02-binding scFv fused to the hinge, transmembrane and intracellular domains of the ITIM-containing LIR-1 protein (**FIG. 22B**). As target cells we used cell lines characterized for MSLN surface expression (**FIGs. 25A and 25B, FIGs. 26A and 26B**). All the CARs were blocked in a ligand-dependent manner by the A*02-directed LIR-1 blocker (**FIG. 27A**). Because of the combination of high sensitivity, selectivity and effective functional pairing with the A*02 blocker, CAR3 was selected for further study as the MSLN Tmod lead activator construct.

[0708] The MSLN CAR3 Tmod construct was examined in detail in a series of quantitative mRNA titration experiments for activation and blocking sensitivity in Jurkat cells (**FIG. 27B and 27C**). For target cells, the cervical carcinoma HeLa cell line that, like most other cancer lines, expresses endogenous MSLN was used. This line is HLA-A*02(-). To control MSLN levels, a variant with MSLN inactivated by CRISPR was generated. mRNA titration experiments enabled estimation of EC_{50} and IC_{50} for the MSLN CAR3 Tmod construct and these parameters were viewed in the context of the expression levels of antigens on normal and tumor tissues derived from high-quality public databases (**FIG. 28A**).

[0709] To make these comparisons, a correlation between MSLN mRNA and surface protein levels was established as a first step (**FIG. 25B**). The same was done for HLA-A and the information used to plot the HLA-A and MSLN levels of different tissues relative to the EC_{50} and IC_{50} of the MSLN Tmod construct. The large majority of normal tissues expressed levels of MSLN well below the EC_{50} of MSLN Tmod. In contrast, certain tissues including lung expressed MSLN at a level well above the EC_{50} of the Tmod construct and, therefore, were considered high risk absent an effective blocker. However, these at-risk tissues also express HLA-A levels above the Tmod IC_{50}, suggesting they will be protected against

cytotoxicity by the A*02-targeted LIR-1 blocker component of Tmod. The cell lines (including transgenic HLA-A*02 HeLa and MS751) used to model normal and tumor tissues in functional assays are also shown on the graph.

[0710] The behavior of the MSLN CAR3 Tmod construct was then tested in primary T cells. Cytotoxicity was the principal readout, with IFN-γ secretion as a secondary measure. Target cells were HeLa cells and variants: (i) native MSLN(+)A*02(-) HeLa cells modeled tumor cells without blocker antigen; and, (ii) transgenic A*02(+) variant HeLa cells modeled normal mesothelial cells. Combinations of different constructs and target cells demonstrated that all MSLN CAR Tmod constructs kill tumor cells potently and block killing in an A*02-ligand-dependent fashion (**FIG. 28B**). Two other MSLN CARs from the literature (SS1 and M5) were used for comparison (**FIG. 29A**). Cytotoxicity was mirrored by IFN-γ release (**FIG. 29B**). Thus, the Tmod constructs composed of an HLA-A*02-directed blocker and different MSLN CAR activators displayed high potency and specificity for MSLN(+)A*02(-) target cells in both Jurkat and primary T cell assays.

The MSLN CAR3 Tmod construct mediates selective, reversible cytotoxicity in mixed-cell and serial cultures

[0711] A variety of other properties of the MSLN CAR3 Tmod construct important in the context of cancer cell therapy were tested. The construct mediated antigen-selective cytotoxicity in mixed cultures of tumor and normal target cells: Native MSLN(+)HLA-A*02(-) HeLa cells labeled with RFP were mixed at different ratios with MSLN(+)A*02(+) cells labeled with GFP. These cocultures were exposed to T cells engineered with different receptor constructs and imaged. Whereas CAR-only constructs killed indiscriminately, the Tmod constructs killed the native HeLa tumor cells only, leaving the A*02(+) cells unharmed (**FIG. 30A**). Selectivity was detectable even at normal:tumor cell ratios of 9:1 (**FIG. 30B**, **FIGs. 31A and 31B**).

[0712] The capacity of Tmod cells to switch between ON (active killing) and OFF (blocked) states was examined using cytotoxicity assays as readout. In these experiments the transduced T cells were transferred from one batch of target cells to another (**FIG. 32A, FIG. 33A**,). The Tmod cells displayed the capacity to activate and kill after being exposed for 2 days to normal cells where they were quiescent. The reverse was also true. Tmod cells engaged in killing tumor cells were able to quickly switch to the OFF state and refrain from

killing the normal cells after transfer and without a rest period. The ability to switch states was maintained through two cycles, over a total of four days.

[0713] It was investigated whether soluble MSLN (sMSLN), which is present in the blood of some cancer patients at high levels (median ~200ng/ml; range 20-2,000 ng/ml [19]), interfered with MSLN CAR3 Tmod cells. sMSLN added to the cultures at 500ng/ml had no effect on function of either the CAR or Tmod T cells **FIGs. 33B and 33C**). Together, these results suggested that MSLN CAR3 Tmod mediates selective, reversible cytotoxicity in mixed cultures of tumor and normal cells and is unaffected by sMSLN at levels observed in some cancer patients' blood. All of these features are consistent with a cell therapy that has the potential to be safe and efficacious in selected cancer patients.

MSLN CAR3 Tmod cells display no detectable off-target activity

[0714] To systematically explore off-target reactivity of MSLN CAR3 Tmod cells, Jurkat cell activation was tested by a panel of target cell lines chosen to encompass the large majority of adult gene expression (Wang et al., *in preparation*; see Methods). Positive controls were used to confirm that effector cells could be activated by MSLN(+) cell lines, and negative controls were used to set a baseline for response (**FIG. 26B**; **FIG. 32B**). No detectable responses were triggered in CAR3 Tmod Jurkat cells, despite high sensitivity of the assay, estimated at ~1,000 molecules/cell.

The MSLN CAR3 Tmod construct mediates selective killing of tumor cells in a xenograft model

[0715] To examine behavior of MSLN CAR3 Tmod cells in vivo, a mouse xenograft model was used. HeLa cells did not grow well in the immunocompromised (NSG) mice, so another cervical cancer cell line, MS751, was developed as grafted target cells. The native MSLN was used as the activator antigen and the blocker antigen HLA-A*02 was engineered by gene transfer to better approximate normal tissue levels. MSLN(+)A*02(-) MS751 cells, generated by CRISPR knockout of HLA-A*02, modeled tumor while the MSLN(+)A*02(+) transgenic variant modeled normal cells in these in vivo experiments.

[0716] The cell lines were engineered with luciferase to enable bioluminescence as an independent readout of tumor survival and growth. Mice (10/cohort) were implanted with tumor cells on their left flank and normal cells on their right flank in half of the mice in each cohort, and vice versa in the other half to control for flank growth variation (**FIG. 34A**). After xenografts reached ~100-150 mm^3 in volume, mice were infused via tail vein with 2E7

total T cells/mouse. After a short delay, both the CARs and the Tmod constructs killed the MSLN(+)A*02(-) tumor cells equally well measured by caliper and bioluminescence intensity (**FIGs. 34B and 34C**, **FIGs. 35B and 35C**). Whereas the CAR-only T cells killed both tumor and normal with equal effectiveness, Tmod cells killed only the tumor grafts, mirroring in vitro cytotoxicity (**FIG. 14A**). In the presence of Tmod cells, the normal cell grafts grew comparably to those in the control groups treated with untransduced T cells or saline. These results dramatically demonstrated selectivity of the MSLN Tmod system in a mammalian body, consistent with other activator-blocker pairs which have been observed (Sandberg et al., *submitted*; [18]).

Extension of the MSLN CAR Tmod platform

[0717] Use of an HLA-A*02-targeted blocker raises the possibility that the blocker may be bound *in cis* by endogenous HLA-A*02 molecules produced in autologous T cells. Indeed, decreased blocker binding was observed with HLA-A*02 tetramer in transfected transgenic A*02(+) Jurkat cells compared to native Jurkat A*02(-) cells (**FIG. 36**). A similar decrease was observed in primary T cells from HLA-A*02(+) donors transduced with MSLN CAR3 Tmod or SS1 Tmod constructs compared to A*02(-) donor T cells (**FIG. 36, FIG. 37A**). More importantly, this decreased binding translated to poor blocker function in both A*02(+) Jurkat and primary T cells relative to their A*02(-) counterparts (**FIG. 36, FIGs. 37B and 37C**). These observations illustrated how cis-binding may pose a problem for an autologous MSLN CAR3 Tmod product that utilizes an A*02-directed blocker.

[0718] To address this problem, we developed a solution based on CRISPR inactivation of endogenous β2 microglobulin (B2M). Because B2M is required for all HLA class I expression, this approach was expected to mitigate the cis-binding effect of HLA-A*02. As predicted, knockout of B2M in primary T cells restored blocker binding and function to levels comparable to A*02(-) donor T cells (**FIGs. 37A-37C**). Thus, CRISPR-mediated abrogation of cis-binding produced MSLN Tmod cells with functional properties in HLA-A*02(+) donors that were indistinguishable from function in HLA-A*02(-) donors. These results suggest that the MSLN CAR3 Tmod construct may be suitable for allogeneic cell therapy and autologous products, provided that a method is employed to reduce expression of A*02 in the patient's T cells.

The MSLN CAR3 can be paired with an HLA-A*11-directed blocker

[0719] The impressive performance of the MSLN CAR3 Tmod construct that utilizes an A*02-directed blocker suggested the possibility that CAR3 might be paired with blockers gated by other HLA class I alleles. If true, this would potentially allow the Tmod platform to be used to treat patients who are not heterozygous for HLA-A*02—a number estimated at >60% of the population [20]. For proof of concept of the modularity of the MSLN Tmod system, HLA-A*11, the most common class I allele in Asian populations was studied [20]. A screen for A*11-selective scFvs was carried out using the same method described for isolation of MSLN scFvs (see Methods, *infra*). A series of enrichment steps using the mammalian scFv-display library generated several A*11-specific scFvs (**FIGs. 38A**).

[0720] One high-performing scFv (A*11-LBD4) was fused to LIR-1 and paired with the MSLN CAR3 activator in Jurkat cells. This A*11 blocker demonstrated good function with an IC_{50} estimated at ~37,000 molecules/cell from mRNA titration experiments (**FIG. 38B**). Finally, the MSLN CAR3 paired with the A*11 blocker was confirmed to function well in Jurkat cell and primary T cells with potency and blockade comparable to the MSLN CAR3 Tmod construct that utilizes HLA-A*02 as blocker antigen (**FIGs. 39A-39C**). Encouraged by these results we converted two other anti-HLA-I monoclonal antibodies, targeting A*03 and B*07, to scFvs and tested them as MSLN Tmod blockers (**FIG. 39A**). These findings suggest that the Tmod system is sufficiently modular to accommodate pairings of one activator with multiple blockers, thereby extending the accessibility of the cell therapy platform to a larger number of patients.

DISCUSSION

[0721] Given the distribution of MSLN in the adult body [1, 2, 4], it is vital that the blocker functions well with a MSLN-targeted activator. The properties of the A*02 blocker described here suggest it will inhibit activation signals that arise from the CAR across a broad range of MSLN antigen levels. It is also likely that the blocker will inhibit other sources of T cell activation triggered by the CAR, including off-target. Because the HLA blocker antigen is ubiquitously expressed in nucleated cells, it should provide an inhibitory signal under all circumstances except when the blocker antigen is absent as in tumors selected for LOH. The blocker may also prevent cytokine-release syndrome, a continuing source of toxicity observed for T cell therapies [14, 33], if the stimulus involves normal cells or cell fragments.

[0722] The MSLN therapeutic candidate described here requires selection of patients who are germline heterozygous for the blocker-antigen allele and whose tumors have lost this allele via LOH. Fortunately, such diagnostic tests have been developed recently which utilize

the enormous power of DNA sequencing technology [27-29]. DNA-sequence-based LOH detection has sufficient sensitivity to distinguish most cases of clonal vs. subclonal LOH in the tumor, thereby enriching for patients most likely to benefit from the therapy. Because this diagnostic method utilizes genome sequence from the tumor, it detects any allelic variation and is not restricted to HLA-A*02. The lead MSLN Tmod construct described here is applicable to a subset of HLA-A*02(+) patients. With the goal of extending the Tmod platform to other patients, we have shown that the MSLN CAR3 activator can be paired with blockers directed at 3 other HLA-I allelic products including HLA-A*11. A*11 is the most frequent HLA-I allele in most Asian populations and represents a significant opportunity for benefit in parts of the world beyond the US. Indeed, with a collection of blockers directed at 6-8 of the most common HLA-I alleles in the world, it should be possible to cover the large majority of solid tumors that harbor LOH at the HLA locus—estimated to be >15% of solid-tumor mortality at present [22, 30]. In addition we have shown in a parallel line of work that the HLA-A*02 blocker can be paired effectively with other activators including a CAR directed at another well-known tumor-associated antigen, CEA (Sandberg et al., in preparation; 31).

[0723] The modular Tmod system leverages the capacity of cells—unique among therapeutic modalities—to integrate multiple signals into a coordinated response and thus offers a means to address the fundamental obstacles of solid-tumor therapy [18, 21, 22]. Therapeutics must access the tumor and overcome barriers that do not exist for blood cancers where cell therapies have proven effective [23]. T cells have an advantage over most other modalities, including antibodies, in that they possess a natural mechanism for active extravasation and biodistribution (see for review Mastrogiovanni et al. [24]). Furthermore, the Tmod approach described here that exploits LOH mitigates the key constraint on solid-tumor therapeutics posed by normal tissue expression of most targets. Though notoriously non-homogeneous, a large proportion of genetic alterations arise in the founding cell of the neoplasm and are present in all its descendants [25]. Such homogeneous mutations include LOH and, if such clonal LOH can be distinguished via a diagnostic test from later alterations present in tumors, LOH heterogeneity at the HLA locus should not constitute a source of resistance [26]. Unlike single nucleotide substitutions that generate most neoantigens, LOH is an irreversible event and should be stable even after strong selective pressure is applied via therapy. Finally, as use of checkpoint inhibitors becomes more prevalent, rates of HLA-I loss will likely increase, further expanding the pool of patients who may benefit from MSLN Tmod therapeutics [34].

MATERIALS AND METHODS

Cell line culture

[0724] Cell lines were purchased from ATCC (American Type Culture Collection) and handled according to manufacturer's instructions: T2, Shp77, Raji, MS751, A-375, A-498, SW982, SW480, HeLa, NIH-OVCAR-3, HepG2, NCI-H508, LNCaP clone FGC, K562, U2OS, BB7.1 and GAP A3 hybridomas. Jurkat cells encoding an NFAT luciferase reporter gene were obtained from BPS Bioscience and maintained in RPMI supplemented with 10% heat-inactivated (HIA) FBS (inactivated at 56 °C for 1 h), 1% penicillin and streptomycin (pen/strep), and 0.4 mg/ml Geneticin. Human peripheral blood mononuclear cells (PBMCs) were obtained from Stem Cell Technologies and thawed in X-VIVO 15 (Lonza) supplemented with 5% HIA human AB serum and activated with T Cell TransAct (Miltenyi Biotec) as recommended by manufacturer. Lentiviral transductions of CAR or CAR Tmod single vector constructs (see Fig. 1b, unless otherwise noted) were done at 24 h post-activation and cultures were maintained in LymphoONE T cell Expansion Medium (Takara Bio) supplemented with 1% HIA human AB serum and 300 IU/mL IL-2.

Molecular cloning and mRNA in vitro transcription

[0725] Activating and blocking CAR constructs were designed and constructed as previously described[9]. Briefly, activating CARs were created by fusing the anti-MSLN scFv LBDs to the CD8α hinge, CD28 transmembrane (TM), and CD28, 4-1BB and CD3ζ intracellular domains (ICD). Blocking CARs were generated by fusing the anti-HLA-A*02, A*03 or B*07 scFv LBDs derived from monoclonal antibodies PA2.1 [32], GAP A3 [36] or BB7.1 [37], respectively, to the hinge, TM and ICD domains of LIR-1. Gene segments were combined using Golden Gate cloning and inserted downstream of a human EF1α promoter in a lentiviral expression vector.

[0726] For messenger RNA (mRNA) preparation, PCR was used to generate the DNA template used for in vitro synthesis mRNA. Briefly, T7 promoter was introduced via N-terminal primer and common overhang regions were used for both N- and C-terminal primers. The PCR product was used as a template for in vitro transcription (IVT) using the T7 ARCA mRNA kit (New England Biolabs, E2060S). The IVT reaction comprised 1x ARCA/NTP mix, 1.25 mM Ψ-UTP (TriLink), 25 ug PCR product template, and 1x T7 RNA polymerase. The IVT reaction was incubated at 37 ºC for 2 h, then 2 uL of DNase I (New

England Biolabs, M0303S) was added to each reaction and incubated at 37 ºC for 15 min. To the IVT reaction, 65 uL water, 10 uL 10x poly-adenylation reaction buffer (NEB M0276S) and 5 uL of poly-adenylation enzyme (NEB M0276S) was added to a total volume of ~100 uL. The reaction was incubated at 37 ºC for 30 min. The resulting product was cleaned using the Monarch RNA cleanup kit (T2040L) according to the manufacturer's protocol.

MSLN and HLA-A*11 binder generation using mammalian display

[0727] Binder generation using the HuTARG mammalian display technology has been previously described (Patent No: US 8,012,714 B2; Wang et al., *in press*). For the MSLN binder generation, soluble MSLN (catalog #MSN-H82E9) and irrelevant, off-target proteins, EGFR and CEA, were purchased from Acro Biosystems. The HuTARG library was subjected to serial rounds of on-target enrichment and off-target depletion using fluorescence-activated cell sorting (FACS). The HLA-A*11 binder generation campaign was similarly conducted. The HuTARG library was subjected to on-target enrichment using HLA-A*11:01 tetramer and off-target depletion using a pool of 4 unrelated HLA class I tetramers. In the final round of both campaigns, on- and off-target binding cells were collected, and RNA was reverse transcribed into cDNA. Fragments containing the complementarity determining regions (CDRs) were amplified using polymerase chain reaction (PCR) and sequenced by next-generation sequencing (NGS). Binders of interest were selected by comparing the input and output NGS counts.

MSLN surface quantification

[0728] To quantify surface mesothelin molecules, adherent cells were first washed once with DPBS then once with Versene. Cells were coated with Versene and incubated at 37 ºC for ~15 min. After incubation, flasks were tapped vigorously to promote complete detachment. The cells were then diluted with DBPS at 1:2 ratio (Versene:DPBS) and counted. 300,000 cells were centrifuged at 500 xg for 5 min. Cells were resuspended in 300 uL 1x FACS buffer (DPBS + 1% BSA). 100 uL of aliquot was divided into 2 v-bottom wells. Cells were washed one more time with 100 uL FACS buffer, then stained with 100 uL of anti-MSLN antibody at 10 ug/mL (R&D Systems, clone 618923) on ice for 30 min. After the primary stain, 50 uL of calibration beads from the QIFIKIT (Agilent) were added for washing. The mixture was washed with 100 uL FACS buffer twice, then stained with 100 uL of anti-mouse F(ab')2-Goat Alexa Fluor 647 (Invitrogen) antibody diluted 2000x in FACS buffer for 45 min on ice. The stained cells and beads were washed 2x with 100 uL FACS

buffer, then resuspended in 100 uL FACS buffer to measure fluorescence. The calibration curve plotting median fluorescence intensity of each bead population vs. number of molecules was plotted according to manufacturer's protocol provided by the QIFIKIT (Agilent). The number of endogenous MSLN molecules was determined by fitting the cell's median fluorescence intensity onto the calibration curve generated with the QIFIKIT beads.

MSLN activator and various blocker sensitivity determination

[0729] To determine activator or blocker sensitivities, antigen was titrated into antigen(-) cell lines at various concentrations. Flow cytometry and QIFIKIT methodology [17] using standard curves could then be used to calculate absolute molecules/cell. The EC_{50} or IC_{50} value of activators or blockers, respectively, expressed in Jurkat cells was then measured by luminescence. Specifically, HEK293T or HeLa cell transfection with antigen mRNA was performed using the 4D nucleofection kit (Lonza). For single-antigen titrations (i.e., MSLN, HLA-A*02, HLA-A*11, HLA-A*03, HLA-B*07), mRNA was diluted to 1000 ng/uL in SE or SF buffer supplemented with Supplement solution (complete buffer) for HEK293T or HeLa cells respectively. The diluted mRNA was serially diluted 2x by adding stock mRNA to equal volumes of complete buffer 13 times, with the 15^{th} well lacking any added mRNA. Target cells were detached from the flask using TrypLE Express (Gibco). Appropriate number of cells were harvested then resuspended in complete buffer at 11.1e6 viable cells/mL. 22.5 uL of resuspended cells were added to 2.5 uL of serially-diluted mRNA to a final volume of 25 uL cell and mRNA mix. 20 uL of this sample was zapped using the 4D nucleofector using the CM-130 program for HEK293T cells or CN-114 program for HeLa cells. The cells were transferred into 280 uL of MEM + 10% FBS + 0.1% P/S. 15 uL of the diluted cells were transferred into 384-well plate and incubated 18-24 h at 37 °C, 5% CO_2. The remaining diluted cells were transferred to a 96-well plate and kept for next day analysis of surface antigen expression using the QIFIKIT as described above. In parallel, Jurkat-NFAT luciferase effector cells were transfected with appropriate CAR DNA at 1 ug per 1e6 cells or CAR Tmod DNA (single vector construct, unless otherwise noted) at 4 ug per 1e6 cells using the Neon electroporation system using the following parameters: 1500 V, 10 ms, 3 pulses. Transfected cells were immediately transferred to pre-warmed RPMI supplemented with 20% heat-inactivated (HIA) FBS and 0.1% pen/strep and incubated for 18-24 h at 37 °C, 5% CO_2. Next, Jurkat cells were counted and resuspended in RPMI + 10% HIA FBS and 0.1% pen/strep at 0.67e6 cells per mL. 1e4 resuspended Jurkat cells in 15 uL

were then co-cultured with transfected cells in the 384-well plate for 6 h. Luciferase activity was measured using ONE-Step Luciferase Assay System (BPS Bioscience).

[0730] For target cell co-transfections including MSLN and HLA-A*02 the protocol above was used except for minor adjustments to the mRNA dilutions step. mRNA encoding HLA-A*02 and MSLN were prepared by Aldevron and TriLink respectively. Briefly, to generate EC_{50} curves, a 14-point 2x serial dilution was performed with MSLN mRNA. This serial dilution was combined with each of four dilutions of various constant amounts of A*02 mRNA so that the top concentration of MSLN mRNA was 500 ng/ul and the A*02 mRNA concentrations were as follows: 500 ng/uL, 25 ng/ul, 1.25 ng/uL, and 0 ng/uL. To generate IC_{50} curves, a 14-point 2x serial dilution was performed with A*02 mRNA. This serial dilution was combined with each of four dilutions of various constant amounts of MSLN mRNA so that the top concentration of A*02 mRNA was 500 ng/uL and the MSLN mRNA concentrations were as follows: 125 ng/uL, 25 ng/ul, 5 ng/uL, and 1 ng/uL.

Primary T cell in vitro cytotoxicity assays

[0731] Killing of MSLN(+)A*02(-)RFP(+) tumor or MSLN(+)A*02(+)GFP(+) normal target cells by primary T cells transduced with Gen2 M5 CAR, MSLN CAR3 or CAR3 Tmod single vector constructs was assessed as previously described[9]. Briefly, 2,000 target cells were plated in 25 uL complete LymphoOne media (containing 1% HIA human AB serum) per well in a black, clear-bottom 384-well plate and allowed to adhere overnight at 37 ºC with 5% CO_2. For mixed culture assays, target cells were pre-mixed at the desired ratios prior to seeding. ~16-18 h after target cell plating, T cells were counted, spun down at 300 xg for 10 min and resuspended at 2,000 CAR(+) or Tmod(+) T cells in 25 uL complete LymphoOne media (in the absence of additional cytokines) for an effective effector:target (E:T) = 1:1 (or more or less concentrated depending on the desired E:T) and gently plated on top of the target cells. For experiments including sMSLN, T cells were resuspended in LymphoOne media containing 1000 ng/mL (2x) soluble, monomeric MSLN (Acro Biosystems) for a final concentration of 500 ng/mL upon plating with target cells. Each sample was tested in triplicate wells. Within 30 min of co-culture, the plate was imaged for GFP(+) or RFP(+) target cell expression using an Incucyte imager and serial images were obtained every 2-4 h thereafter for up to 48 h. Quantification of target cell area (i.e., GFP(+) or RFP(+) total area per image) was done using Incucyte imaging software. Plating variability was accounted for by normalizing to area at time = 0 per well. Killing was then quantified as the difference in area between CAR or Tmod T cell wells to corresponding untransduced T cell wells,

normalized to the untrasduced T cell well (% Killing = ($A_{untransduced} - A_{CAR\ or\ Tmod}$)/$A_{untransduced}$).

[0732] For HLA-A*11 blocker evaluation in primary T cells, cytotoxicity assays were performed as described above, using HeLa target cells that express native levels of MSLN and transgenic HLA-A*11 antigen.

[0733] To further assess cytokine secretion and relative T cell activation post-48 h co-culture, the T cell containing media in each well was mixed and transferred to a v-bottom plate and spun down at 400 xg for 5 min. Supernatants were collected and frozen until further analysis for secreted IFN-γ using a BD Human IFN-γ flex kit as per manufacturer's instructions. Remaining T cells were then stained for human CD3, washed, and characterized for forward and side scatter by flow cytometry [35].

Repeat antigen-challenge assay (RACA) and reversibility assays

[0734] The RACA and reversibility assays were performed as previously described (Wang et al., *in press* [18]) with some modifications. Briefly, CAR or Tmod transduced primary T cells were co-cultured with MSLN(+)A*02(-) RFP(+) tumor or MSLN(+)A*02(+) GFP(+) normal target cells similarly as described above with effective E:T = 1.2:1. Round 1 images were taken over the course of 48 h in a 384-well plate format. Parallel 6-well plates with 250,000 target cells and 300,000 CAR3(+) or CAR3 Tmod(+) T cells were also set up to allow for bulk T cell isolation and transfer between rounds. After 48 h, T cell containing media was gently mixed and transferred to conical tubes. Remaining T cells engaged with live target cells were further dissociated by a single 1-min rinse with 10mM EDTA + 0.5% BSA in PBS and combined with the bulk T cell fraction. These cells (along with target cell debris and lifted target cells) were then spun down, washed, and stained with a cocktail of anti-MSLN, anti-EGFR, and anti-N-cadherin PE-conjugated antibodies to stain undesirable target cells. These target cells were then conjugated to anti-PE MACS beads followed by depletion through LS columns, resulting in clean T cell fractions. T cells were then counted and re-seeded for round 2 (similarly to round 1) onto fresh tumor or normal target cells. Imaging and quantification then proceeded exactly as was done in round 1.

MSLN knockout cell line generation

[0735] To develop MSLN(-) cell line controls for endogenous MSLN(+) cell lines, a CRISPR strategy to target full-length MSLN was utilized. Two Alt-R CRISPR-Cas9 sgRNAs targeting different exons of mesothelin were obtained from Integrated DNA Technologies

(IDT), with sgRNA_1 targeting exon 2, and sgRNA_2 targeting exon 16. The sgRNAs were rehydrated in nuclease-free water and combined with Alt-R® S.p. HiFi Cas9 Nuclease V3 (IDT) to yield a 9:1 sgRNA:Cas9 mole ratio. Both RNP solutions were incubated at room temperature for 10-20 min separately to allow each of the guides to complex with Cas9 independently. The RNP complexes of both guides were subsequently combined, added to the desired cells as per the manufacturer's instructions, and electroporated. After CRISPR, cells were scaled up and sorted on the MSLN(-) population (R&D, anti-MSLN pAb or clone #618923). Bulk-sorted MSLN(-) cells were then screened against MSLN binders in Jurkat cell-based assays.

Selectivity screening using Jurkat cells

[0736] To explore off-target reactivity of MSLN CAR3 Tmod cells, Jurkat cell activation was tested against a diverse panel of target cell lines chosen to encompass the large majority of adult gene expression similarly as described elsewhere (Wang et al., *in preparation*). Positive controls were used to confirm that effector cells could be activated by MSLN(+) cell lines, and negative controls to set a baseline for response (see FIGs. 26B and 28A for cell line characterization). Briefly, Jurkat-NFAT-Luciferase cells were transiently transfected to express either CARs or CAR3 Tmod exactly as described above. In parallel, endogenous MSLN(+) target cells, along with their respective MSLN(-) control target cells generated using CRISPR as described above, were plated at 1e4 target cells in 15 uL complete RPMI (containing 10% FBS and 1% P/S) per well in a 384-well plate format. Approximately 18 h post-transfection, 1e4 Jurkat cells were co-cultured with each target cell and activity compared to Gen2 M5 CAR was assessed via luminescence after 6 h. Luciferase activity was measured using ONE-Step Luciferase Assay System (BPS Bioscience).

Mouse xenograft study

[0737] Blinded in vivo experiments were conducted by Explora BioLabs under Institutional Animal Care and Use Committee (IACUC)-approved protocols. 5–6 week old female NOD.Cg-Prkdcscid Il2rgtm1Wjl Tg(HLA-A/H2-D/B2M)1Dvs/SzJ (NSG-HLA-A2/HHD) mice were purchased from The Jackson Labs. Animals were acclimated to the housing environment prior to the initiation of the study. Animals (10/cohort) were implanted subcutaneously with 5e6 MS751 firefly luciferase(+) HLA-A KO tumor or renilla luciferase(+) A*02 transgenic normal cells mixed 1:1 with Matrigel in 100 uL on their right and left flanks, respectively, in half of the mice in each cohort, and vice versa in the other

half to control for flank growth variation. When tumors reached an average of 100-150 mm^3 each (V=L x W x W/2), animals were randomized into 5 groups (n = 10) and 2e7 T cells, or saline control, were administered via the tail vein. Prior to injection, T cells were ~60% CAR(+) or Tmod(+). Post T cell injection, graft measurements by calipers were performed 3x times per week and BLI 1x time per week for the duration of the study. At each BLI session, RediJect Coelenterazine h substrate (PerkinElmer) was first injected to visualize renilla luciferase(+) normal cells, followed by injection of XenoLight D-Luciferin Potassium Salt (PerkinElmer) 6 h later to visualize firefly luciferase(+) tumor cells on the reverse flank.

CRISPR knockout of B2M in primary T cells

[0738] Frozen PBMCs were thawed and activated as described above. Transductions were performed 24 h post-activation using lentivirus (Alstem) at MOI 10. 24 h post-transduction, primary T cells were transfected with CRISPR-Cas9:sgRNA complexes. Briefly, cells were collected and washed with PBS before resuspending in supplemented P3 nucleofection buffer (Lonza). 20 pmol of Cas9 (Synthego) was combined with 130 pmol B2M-targeting sgRNA (Synthego) and incubated in P3 nucleofection buffer before addition to cells. 20 uL of the cell and ribonucleoprotein (RNP) mixture was transferred to a 16-well Nucleocuvette Strip and electroporated with the 4D nucleofector using the stimulated T cell program (EO-115). The cells were recovered in 100 uL of prewarmed media, X-VIVO 15 (Lonza) supplemented with 5% HIA human AB serum and 300 IU/mL IL-2. PBMCs were cultured and expanded in LymphoONE Tcell Expansion Medium (Takara Bio) supplemented with 1% HIA human AB serum and 300 IU/mL IL-2 for 6 days. Post expansion, positively transduced primary T cells were enriched using anti-PE microbeads (Miltenyi) according to manufacturer's instructions against Protein L-biotin:streptavidin-PE using LS column. Cytotoxicity of B2M KO primary T cells was then assessed exactly as described above.

Statistical analysis

[0739] Statistical analyses were performed using GraphPad Prism software. All Jurkat cell-based in vitro studies (including mRNA titration experiments) are shown as mean ± standard deviation (SD) of technical replicates, while primary T cell-based in vitro studies are shown as mean ± SD of technical triplicates. Where applicable, technical replicates are shown as individual data points, with bars denoting means. All data is representative of a minimum of n=2 experimental repeats, unless otherwise noted. Data for in vivo studies are shown as mean ± standard error of the mean (SEM). For mRNA titration studies, curves were

fit using a four-parameter non-linear regression analysis. EC_{50} and IC_{50} values were calculated directly from the curves. Direct comparisons were analyzed using unpaired, parametric t tests, unless otherwise noted.

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CLAIMS

What is claimed is:

1. An immune cell comprising:
    a. a first receptor, comprising an extracellular ligand binding domain specific to Mesothelin (MSLN); and
    b. a second receptor, comprising an extracellular ligand binding domain specific to a non-target antigen lost in a MSLN+ cancer cell,

wherein the first receptor is an activator receptor responsive to MSLN; and wherein the second receptor is an inhibitory receptor responsive to the non-target antigen, wherein the extracellular ligand binding domain of the second receptor specifically binds HLA-A*02, and wherein the extracellular ligand binding domain of the first receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOs: 535, 539, 542, 438, 454, and 533, and wherein the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs), wherein the CDR-L1 sequence is RSSQSIVHSNGNTYLE (SEQ ID NO: 42), the CDR-L2 sequence is KVSNRFSGVPAR, the CDR-L3 sequence is FQGSHVPRT (SEQ ID NO: 44), the CDR-H1 sequence is ASGYTFTSYHIH (SEQ ID NO: 45), the CDR-H2 sequence is WIYPGNVNTEYNEKFKGK (SEQ ID NO: 46), and the CDR-H3 sequence is EEITYAMDY (SEQ ID NO: 47), or wherein the extracellular ligand binding domain of the first receptor comprises complementarity determining regions (CDRs) CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, CDR-H3 of SEQ ID NOs: 535, 539, 542, 438, 454, and 488, and wherein the extracellular ligand binding domain of the second receptor comprises complementarity determining regions (CDRs), wherein the CDR-L1 sequence is RSSQSIVHSNGNTYLE (SEQ ID NO: 42), the CDR-L2 sequence is KVSNRFSGVPAR, the CDR-L3 sequence is FQGSHVPRT (SEQ ID NO: 44), the CDR-H1 sequence is ASGYTFTSYHIH (SEQ ID NO: 45), the CDR-H2 sequence is WIYPGNVNTEYNEKFKGK (SEQ ID NO: 46), and the CDR-H3 sequence is EEITYAMDY (SEQ ID NO: 47).

2. The immune cell of claim 1, wherein the extracellular ligand binding domain of the second receptor comprises SEQ ID NO: 34; or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto.

3. The immune cell of any one of claims 1 or 2, wherein the first receptor is a chimeric antigen receptor (CAR); and/or wherein the extracellular ligand binding domain of the first receptor comprises a variable heavy (VH) portion comprising SEQ ID NO: 233, or a sequence having at least 85%, at least 90%, or at least 95%, identity thereto, and a variable light (VL) portion comprising SEQ ID NO: 279, or a sequence having at least 85%, at least 90%, or at least 95% identity thereto; or wherein the extracellular ligand binding domain of the first receptor comprises the scFv sequence of SEQ ID NO: 171; or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto.

4. The immune cell of any one of claims 1-3, wherein the first receptor comprises a hinge domain, a transmembrane domain and an intracellular domain, optionally wherein the hinge domain comprises a CD8α hinge domain, optionally wherein the CD8α hinge domain comprises a sequence of SEQ ID NO: 7, or a sequence having at least 85%, at least 90%, at least 95%, at least 97% or at least 99% identity thereto, optionally wherein the transmembrane domain comprises a CD28 transmembrane domain, optionally wherein the CD28 transmembrane domain comprises the sequence of SEQ ID NO: 11, or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto, optionally wherein the intracellular domain comprises a CD28 co-stimulatory domain, a 4-1BB co-stimulatory domain, and a CD3ζ activation domain, optionally wherein the intracellular domain comprises the sequence of SEQ ID NO: 285, or a sequence having at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% identity thereto.

5. The immune cell of any one of claims 1-4, wherein the first receptor comprises the sequence of SEQ ID NO: 303, or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto; and/or

wherein the second receptor comprises a LILRB1 intracellular domain or a functional variant thereof, optionally

wherein the LILRB1 intracellular domain comprises a sequence at least 90%, at least 95%, at least 97%, at least 99%, or is identical to SEQ ID NO: 70;

wherein the second receptor comprises a LILRB1 transmembrane domain or a functional variant thereof, optionally

wherein the LILRB1 transmembrane domain or a functional variant thereof comprises a sequence at least 90%, at least 95%, at least 97%, at least 99%, or is identical to SEQ ID NO: 74; and/or

wherein the second receptor comprises a LILRB1 hinge domain or functional variant thereof, optionally

wherein the LILRB1 hinge domain comprises a sequence at least 90%, at least 95%, at least 97%, at least 99%, or is identical to SEQ ID NO: 73.

6. The immune cell of any one of claims 1-5, wherein the second receptor comprises a LILRB1 intracellular domain, a LILRB1 transmembrane domain, a LILRB1 hinge domain, a functional variant of any of these, or combinations thereof, optionally wherein the LILRB1 hinge domain, LILRB1 intracellular domain and LILRB1 transmembrane domain comprises SEQ ID NO: 71, or a sequence at least 90%, at least 95%, at least 97%, at least 99%, or is identical thereto; and/or wherein the second receptor comprises a sequence of SEQ ID NO: 348, or a sequence having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto.

7. The immune cell of any one of claims 1-6, wherein the immune cell is a T cell.

8. The immune cell of claim 7, wherein the T cell is a CD8+ CD4- T cell or a CD8- CD4+ T cell.

9. The immune cell of any one of claims 1-8, wherein expression and/or function of a MHC Class I gene has been reduced or eliminated, optionally

wherein the MHC Class I gene is beta-2-microglobulin (B2M); and/or

wherein the immune cell comprises a polynucleotide comprising an interfering RNA, the interfering RNA comprising a sequence complementary to a sequence of a B2M mRNA (SEQ ID NO: 769), optionally

wherein the interfering RNA is capable of inducing RNAi-mediated degradation of the B2M mRNA.

10. The immune cell of claim 9, wherein the interfering RNA is a short hairpin RNA (shRNA), and optionally

wherein the shRNA comprises:

a. a first sequence, having from 5′-end to 3′-end a sequence complementary to a sequence of the B2M mRNA; and

b. a second sequence, having from 5′-end to 3′-end a sequence complementary to the first sequence,

wherein the first sequence and the second sequence form the shRNA.

11. The immune cell of claim 10, comprising one or more modifications to a sequence encoding B2M (SEQ ID NO: 770), optionally wherein the one or more modifications comprise one or more inactivating mutations of the endogenous gene encoding B2M, optionally

wherein the one or more inactivating mutations are introduced with a nucleic acid guided endonuclease in a complex with at least one guide nucleic acid (gNA) that specifically targets a sequence of the endogenous gene encoding B2M (SEQ ID NO: 770).

12. The immune cell of any one of claims 1-11, wherein the first receptor comprises SEQ ID NO: 164, and the second receptor comprises SEQ ID NO: 52, or sequences having at least 90%, at least 95%, at least 97%, or at least 99% identity thereto; and/or

wherein the immune cell comprises an shRNA encoded by a sequence comprising GCACTCAAAGCTTGTTAAGATCGAAATCTTAACAAGCTTTGAGTGC (SEQ ID NO: 349) or GTTAACTTCCAATTTACATACCGAAGTATGTAAATTGGAAGTTAAC (SEQ ID NO: 350), or a sequence having at least 80%, at least 90%, or at least 95% identity thereto, optionally

wherein the immune cell is autologous, or

wherein the immune cell is allogeneic.

13. A pharmaceutical composition, comprising a therapeutically effective amount of the immune cells of any one of claims 1-12.

14. A polynucleotide or polynucleotide system, comprising one or more polynucleotides comprising polynucleotide sequences encoding the first receptor and the second receptor for generating the immune cells of any one of claims 1-12, or a vector, comprising the one or more polynucleotides.

15. The immune cell of any one of claims 1-12 for use in the treatment of MSLN+ cancer, optionally wherein the MSLN+ cancer is an MSLN+ tumor having loss of heterozygosity at a locus encoding a non-target antigen; and/or wherein the MSLN+ cancer comprises MSLN+ cancer cells having loss of heterozygosity at an MHC class I locus,

optionally wherein the cancer comprises mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma; and/or

wherein the cancer cells comprise MSLN+/HLA-A*02–cancer cells that do not express HLA-A*02; optionally

cancer cells derived from a MLSN+/HLA-A*02+ cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02.

16. Use of the immune cell of any one of claims 1-12 in the manufacture of a medicament for the treatment of MSLN+ cancer, optionally wherein the MSLN+ cancer is an MSLN+ tumor having loss of heterozygosity at a locus encoding a non-target antigen; and/or wherein the MSLN+ cancer comprises MSLN+ cancer cells having loss of heterozygosity at an MHC class I locus, optionally wherein the cancer comprises mesothelioma cancer, ovarian cancer, cervical cancer, colorectal cancer, esophageal cancer, head and neck cancer, kidney cancer, uterine cancer, gastric cancer, pancreatic cancer, lung cancer, colorectal cancer, or cholangiocarcinoma; and/or

wherein the cancer cells comprise MSLN+/HLA-A*02–cancer cells that do not express HLA-A*02; optionally

cancer cells derived from a MLSN+/HLA-A*02+ cell by loss of heterozygosity at HLA-A leading to loss of HLA-A*02.