CAR-T LYMPHOCYTES ENGINEERED TO HOME TO LYMPH NODE B CELL ZONE, SKIN, OR GASTROINTESTINAL TRACT

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/036,447, filed August 12, 2014, the disclosure of which is incorporated by reference herein in its entirety.

1. FIELD

[0002] The disclosure herein relates to the field of immunology, and more specifically, to the modification of T lymphocytes or other immune cells.

2. BACKGROUND

[0003] T lymphocytes recognize and interact with specific antigens, including tumor-associated or tumor-specific antigens. Because T lymphocytes are able to kill tumor cells, the last 25 years has seen a great deal of interest in targeting tumor cells with T lymphocytes, either antigen-specific T lymphocytes, or T lymphocytes genetically modified to express one or more chimeric antigen receptors (CARs; *see*, *e.g.*, Eshhar, U.S. Patent No. 7,741,465; Eshhar, U.S. Patent Application Publication No. 2012/0093842). However, given the difficulty of targeting CAR T cells to the necessary areas of the body, it is desirable to find new methods to enhance the homing of CAR T cells.

3. SUMMARY

[0004] Provided herein are genetically modified cells, for example immune cells, such as T lymphocytes, e.g., human T lymphocytes, that comprise a receptor that causes a cell expressing said receptor to home to a particular anatomical zone, a particular tissue, or a particular type of cell, e.g., the B cell zone of the lymph nodes, gastrointestinal tract, or skin. In a specific embodiment, the genetically modified cells provided herein are T lymphocytes, for example, primary T lymphocytes. In certain embodiments, the genetically modified cells express a chimeric antigen receptor (CAR). Without wishing to be bound by any particular mechanism or theory, it is thought that when the genetically modified cells herein express receptors that cause a cell expressing said receptors to home to a particular zone, they are more likely to be exposed to

native antigen, where the cells, for example, cells expressing a CAR, are capable of being activated.

[0005] In a first aspect, provided herein is a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or a population of such cells, that comprises, e.g., has been engineered to express, a homing receptor and a CAR. In certain embodiments, the homing receptor is not normally or endogenously expressed in the T lymphocyte. In certain embodiments, the homing receptor is a B cell zone homing receptor. In a specific embodiment, the B cell zone homing receptor is CXCR5. In a more specific embodiment, the cell, or population of cells comprising the homing receptor, e.g., the B cell zone homing receptor, additionally lacks expression of a T cell zone homing receptor, e.g., CXCR7, or has reduced expression of said T cell zone homing receptor as compared to normal T cells, e.g., the cell, or population of cells, is engineered to express a T cell homing receptor at a lower level than normal T cells.

[0006] In certain embodiments, the homing receptor is a gastrointestinal homing receptor. In a specific embodiment, the gastrointestinal homing receptor is integrin α4β7 (also known as lymphocyte Peyer patch adhesion molecule). In other specific embodiments, the gastrointestinal homing receptor is CCR9 (C-C chemokines receptor type 9). In certain embodiments, the cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprises, e.g., has been engineered to express more than one, e.g., a second, gastrointestinal homing receptor, e.g., the primary T lymphocyte comprises CCR9 and integrin α4β7.

[0007] In one embodiment, the cell, e.g., the T lymphocyte, or a population of such cells, that comprises, e.g., has been engineered to express, a gastrointestinal homing receptor has been activated, expanded, or both activated and expanded in the presence of a Vitamin A metabolite. In specific embodiments, the Vitamin A metabolite is retinoic acid.

[0008] In certain embodiments, the homing receptor is a skin homing receptor. In a specific embodiment, the skin homing receptor is CLA (cutaneous lymphocyte-associated antigen receptor). In other specific embodiments, the skin homing receptor is CCR4, CCR8, or CCR10. In certain embodiments, the cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells comprises, e.g., has been engineered to express, second skin homing receptor. In yet other embodiments, the cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprises, e.g., expresses, a third skin homing receptor.

In yet other embodiments, the cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprises, e.g., expresses, a fourth skin homing receptor. In other embodiments, the cell or population of cells comprises, e.g., expresses, two or more skin homing receptors, e.g., two or more of CLA, CCR4, CCR8, and/or CCR10.

[0009] In one embodiment, the cell, e.g., the T lymphocyte, for example, the primary T lymphocyte, or population of such cells comprising, e.g., expressing, a skin-homing receptor has been activated, expanded, or both activated and expanded in the presence of a Vitamin D metabolite. In specific embodiments, the Vitamin D metabolite is 1,26-dihydroxycholecalciferol ($1,25(OH)_2D_3$). In some embodiments, the cell, e.g., the T lymphocyte, for example, the primary T lymphocyte, or population of such cells has been activated, expanded, or both activated and expanded in the presence of IL-12. In specific embodiments, the cell , e.g., the T lymphocyte, for example, the primary T lymphocyte, or population of such cells, have been activated, expanded, or activated and expanded in the presence of both IL-12 and a vitamin D metabolite.

[0010] In some embodiments, the cell, e.g., the T lymphocyte, for example, the primary T lymphocyte, or population of such cells, comprises, e.g., has been engineered to express, either a gastrointestinal homing receptor or a skin homing receptor, and additionally comprises a B cell homing receptor. In specific embodiments, the B cell homing receptor is CXCR5.

[0011] In another aspect, provided herein are methods of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, which expresses a homing receptor. In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, that homes to the B cell zone of a lymph node, comprising engineering the cell or population of cells to express a B cell zone homing receptor in an amount or at a level sufficient to cause the cell or population of cells to home to the B cell zone of the lymph node. In a specific embodiment, the B cell zone homing receptor is CXCR5.

[0012] In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, that homes to the gastrointestinal tract, comprising engineering the cell or population of cells to express a gastrointestinal homing receptor in an amount or at a level sufficient to cause the cell or population of cells to home to the gastrointestinal tract. In a specific embodiment, the

gastrointestinal homing receptor is integrin α4β7. In other specific embodiments, the gastrointestinal homing receptor is CCR9. In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprising engineering the cell or population of cells to express an additional gastrointestinal homing receptor, e.g., additionally express a second gastrointestinal homing receptor. In certain embodiments, the methods provided herein additionally comprise a step wherein the cell or population of cells is activated, expanded, or both activated and expanded in the presence of a Vitamin A metabolite. In specific embodiments, the Vitamin A metabolite is retinoic acid.

[0013] In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, that homes to the skin, comprising engineering the cell or population of cells to express a skin homing receptor in an amount or at a level sufficient to cause the cell or population of cells to home to the skin. In a specific embodiment, the skin homing receptor is CLA. In other specific embodiments, the skin homing receptor is CCR4, CCR8, or CCR10. In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprising engineering the cell or population of cells to express an additional skin homing receptor, e.g., additionally express a second skin homing receptor. In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or population of such cells, comprising engineering the cell or population of cells to additionally express a third skin homing receptor. In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or a population of such cells, comprising engineering the cell or population of cells to additionally express a fourth skin homing receptor. In certain embodiments, the methods provided herein additionally comprise a step wherein the cell or population of cells is activated, expanded, or both activated and expanded in the presence of a Vitamin D metabolite. In specific embodiments, the Vitamin D metabolite is 1,26-dihydroxycholecalciferol ($1,25(OH)_2D_3$). In certain embodiments, the methods provided herein additionally comprise a step wherein the cell or population of cells is activated, expanded, or both activated and expanded in the presence of IL-12.

[0014] In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or a population of such cells, that is engineered to express a gastrointestinal homing receptor or a skin homing receptor, and additionally is engineered to express a B cell zone homing receptor. In specific embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or a population of such cells, that is engineered to express a gastrointestinal homing receptor or a skin homing receptor, and additionally is engineered to express CXCR5.

[0015] In certain embodiments, provided herein is a method of generating a cell, e.g., a T lymphocyte, for example, a primary T lymphocyte, or a population of such cells, that is engineered to express a gastrointestinal homing receptor or a skin homing receptor, which method comprises a step of administering to the T lymphocyte a lentiviral vector encoding a chimeric antigen receptor (CAR).

[0016] In another aspect, provided herein are methods of treating a cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a B cell zone homing receptor; and (ii) a CAR. In certain embodiments, the B cell zone homing receptor is CXCR5.

[0017] In certain embodiments, provided herein are methods of treating a gastrointestinal cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising, e.g., expressing, (i) a gastrointestinal homing receptor; and (ii) a CAR. In specific embodiments, the gastrointestinal homing receptor is integrin $\alpha 4\beta 7$. In other specific embodiments, the gastrointestinal homing receptor is CCR9. In certain embodiments, provided herein are methods of treating a gastrointestinal cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of Ty lymphocytes, additionally comprising, e.g., expressing, a second gastrointestinal homing receptor.

[0018] In certain embodiments, provided herein are methods of treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a skin homing receptor; and (ii) a CAR. In specific embodiments, the skin homing receptor is CLA. In other specific embodiments, the skin homing receptor is CCR4, CCR8, or CCR10. In certain embodiments, provided herein are methods of

treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, additionally comprising a second skin homing receptor. In certain embodiments, provided herein are methods of treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, additionally comprising a third skin homing receptor. In certain embodiments, provided herein are methods of treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, additionally comprising a fourth skin homing receptor.

[0019] In certain embodiments, provided herein are methods of treating a gastrointestinal cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a gastrointestinal homing receptor; and (ii) a CAR, wherein the T lymphocyte, or a population of T lymphocytes, further comprises a B cell zone homing receptor. In specific embodiments, the B cell zone homing receptor is CXCR5. In certain embodiments, the T lymphocytes provided herein are for use in methods of treating a gastrointestinal cancer or tumor.

[0020] In certain embodiments, provided herein are methods of treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a skin homing receptor; and (ii) a CAR, wherein the T lymphocyte, or a population of T lymphocytes, further comprises a B cell zone homing receptor. In specific embodiments, the B cell zone homing receptor is CXCR5. In certain embodiments, the T lymphocytes provided herein are for use in methods of treating a skin cancer or tumor.

[0021] In specific embodiments, provided herein are methods of treating a cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a homing receptor; and (ii) a CAR, wherein the extracellular domain of the CAR binds an antigen selected from the group consisting of Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD19, CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP),

gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, high molecular weight melanoma-associated antigen (HMW-MAA), protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysis, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), an abnormal ras protein, an abnormal p53 protein, fuc-GM1, GM2 (oncofetal antigen-immunogenic-1; OFA-I-1); GD2 (OFA-I-2), GM3, GD3, alpha-actinin-4, Bage-1, BCR-ABL, Bcr-Abl fusion protein, beta-catenin, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, Casp-8, cdc27, cdk4, cdkn2a, coa-1, dek-can fusion protein, EBNA, EF2, Epstein Barr virus antigens, ETV6-AML1 fusion protein, HLA-A2, HLA-A11, hsp70-2, KIAAO205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RARα fusion protein, PTPRK, triosephosphate isomerase, Gage 3,4,5,6,7, GnTV, Herv-K-mel, Lage-1, NA-88, NY-Eso-1/Lage-2, SP17, SSX-2, TRP2-Int2, , gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, RAGE, GAGE-1, GAGE-2, p15(58), RAGE, , SCP-1, Hom/Mel-40, PRAME, HER-2/neu, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, human papillomavirus (HPV) antigens E6 and E7, TSP-180, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, 13-Catenin, Mum-1, p16, TAGE, PSMA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, , CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS, CD19, CD22, CD27, CD30, CD70, EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), integrin αvβ3 (CD61), galactin, and Ral-B. In specific embodiments, provided herein are methods of treating a gastrointestinal cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a gastrointestinal homing receptor; and (ii) a CAR, wherein the extracellular domain of the CAR binds an antigen associated with, e.g., expressed by, a gastrointestinal tumor or cancer. In specific embodiments, the antigen associated with, e.g., expressed by, a gastrointestinal tumor or cancer is CEA, Her2, CA242, MUC1, CA125, or CA19-9. In specific embodiments, the T lymphocytes provided herein are for use in methods of treating a cancer or tumor.

[0022] In other specific embodiments, provided herein are methods of treating a skin cancer or tumor in an individual, comprising administering to an individual in need thereof a T lymphocyte, or a population of T lymphocytes, comprising (i) a skin homing receptor; and (ii) a CAR, wherein the extracellular domain of the CAR binds an antigen associated with a skin tumor or cancer. In specific embodiments, the antigen associated with, e.g., expressed by, a skin tumor or cancer is HMW-MAA, Her2, GD2, GD3, CEA, or SPAG9. In other specific embodiments, the T lymphocytes provided herein are for use in methods of treating a skin cancer or tumor.

4. DETAILED DESCRIPTION

[0023] Adaptive immune responses are initiated in secondary lymphoid organs, including the lymph nodes. B cells and T cells are sequestered in distinct regions of the lymph nodes, termed the "B cell zone," located in the outer cortex of the lymph node, or follicles, and the "T cell zone," which is more diffusely distributed in the area surrounding the follicles (also known as the paracortex) respectively. B cells and T cells express receptors that allow them to home to these respective zones so that they can be exposed to antigen. Intact antigens are present in the B cell zone, whereas in the T cell zone, antigens are presented by antigen-presenting cells, such as dendritic cells. Intact antigens, such as tumor antigens, are also present at the site of the tumor.

[0024] Provided herein are genetically modified cells, for example immune cells, such as T lymphocytes, e.g., human T lymphocytes, that comprise a receptor that causes a cell expressing said receptor to home to a particular anatomical zone, a particular tissue, or a particular type of cell, e.g., B cell zone of the lymph nodes, gastrointestinal tract, or skin. In a specific embodiment, the genetically modified cells provided herein are T lymphocytes. In certain embodiments, the genetically modified cells express a chimeric antigen receptor (CAR), as described in Section 4.4. In certain embodiments, the genetically modified cells express a CAR and endogenously express one or more homing receptors, e.g., receptors that that cause a cell expressing the receptors to home to the B cell zone of the lymph nodes, gastrointestinal tract, or skin. Without wishing to be bound by any particular mechanism or theory, it is thought that when the genetically modified cells herein express receptors that cause a cell expressing said receptors to home to a particular zone, they are more likely to be exposed to native antigen, where the cells, for example, cells expressing a CAR, are capable of being activated.

4.1 Cells Comprising B-cell Zone Homing Receptors, Methods of Making, and Uses Thereof

[0025] In one embodiment, provided herein are genetically modified cells, for example immune cells, such as T lymphocytes, e.g., human T lymphocytes, that comprise, e.g., have been engineered to express, a receptor that causes the cells to home to the B cell zone of the lymph nodes, e.g., the follicles of the lymph node. Such a receptor is referred to herein as a "B cell zone homing receptor." In specific embodiments, the B cell zone homing receptor is CXCR5, for example, human CXCR5. GenBank™ accession numbers NM_001716.4 and NM_032966.2 provide exemplary nucleotide sequences for human CXCR5. GenBank™ accession numbers NP_116743.1 and NP_001707.1 provide exemplary amino acid sequences for human CXCR5. Exemplary nucleotide and amino acid sequences for human homing receptors can be found in Table 1. In a specific embodiment, the genetically modified cells provided herein are T lymphocytes. In certain embodiments, the genetically modified cells express a B cell zone homing receptor and also express a CAR, as described in Section 4.4. In certain embodiments, the genetically modified cells express a CAR and endogenously express one or more B cell zone homing receptors.

[0026] Also provided herein is a method of generating genetically engineered T lymphocytes that home to the B cell zone of a lymph node, e.g., the follicles of a lymph node, comprising a step of engineering a T lymphocyte to express a B cell zone homing receptor, e.g., CXCR5, wherein said B cell zone homing receptor is expressed by the cell at a sufficient level or sufficient amount to cause the cell to home to the B cell zone of the lymph node. In some embodiments, the step of engineering a T cell to express a B cell zone homing receptor comprises a step of introducing to the cells one or more vectors comprising the receptor nucleic acid sequence(s), i.e., the nucleic acid sequence (s) encoding the receptor(s). In specific embodiments, the vector comprises the nucleic acid sequence for human CXCR5. In a certain embodiment, the step of engineering a T cell to express a B cell zone homing receptor is performed by any method known to one of skill in the art.

[0027] Exemplary nucleic acids useful for engineering a T lymphocyte to express a B cell zone homing receptor are disclosed, for example, in Section 4.5.

[0028] Also provided herein are methods of treating a cancer or tumor in an individual comprising administering to the individual a therapeutically effective amount of genetically modified cells, e.g. human T lymphocytes, that comprise (i) a receptor that causes a cell expressing said receptor to home to a B cell zone of the lymph nodes, e.g., the follicles of the lymph node, and (ii) a CAR. In specific embodiments, the B cell zone homing receptor is CXCR5. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) a receptor that causes a cell expressing said receptor to home to a B cell zone of the lymph nodes, e.g., the follicles of the lymph node, and (ii) a CAR, suppress the proliferation of tumor cells. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) a receptor that causes a cell expressing said receptor to home to a B cell zone of the lymph nodes, e.g., the follicles of the lymph node, and (ii) a CAR, inhibit growth of the tumor. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) a receptor that causes a cell expressing said receptor to home to a B cell zone of the lymph nodes, e.g., the follicles of the lymph node, and (ii) a CAR, kill tumor cells. In specific embodiments, the extracellular domain of the CAR binds an antigen binds an antigen selected from the group consisting of Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD19, CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, high molecular weight melanoma-associated antigen (HMW-MAA), protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysis, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), an abnormal ras protein, an abnormal p53 protein, fuc-GM1, GM2 (oncofetal antigen-immunogenic-1; OFA-I-1); GD2 (OFA-I-2), GM3, GD3, alpha-actinin-4, Bage-1, BCR-ABL, Bcr-Abl fusion protein, beta-catenin, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, Casp-8, cdc27, cdk4, cdkn2a, coa-1, dek-can fusion protein, EBNA, EF2, Epstein Barr virus antigens, ETV6-AML1 fusion protein, HLA-A2, HLA-A11, hsp70-2, KIAAO205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RARα fusion protein, PTPRK, triosephosphate isomerase, Gage 3,4,5,6,7, GnTV, Herv-K-mel,

Lage-1, NA-88, NY-Eso-1/Lage-2, SP17, SSX-2, TRP2-Int2, , gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, RAGE, GAGE-1, GAGE-2, p15(58), RAGE, , SCP-1, Hom/Mel-40, PRAME, HER-2/neu, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, human papillomavirus (HPV) antigens E6 and E7, TSP-180, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, 13-Catenin, Mum-1, p16, TAGE, PSMA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, , CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS, CD19, CD22, CD27, CD30, CD70, EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), integrin αvβ3 (CD61), galactin, and Ral-B. Also provided herein are genetically modified cells for use in methods of treating a cancer or tumor.

4.2. Cells Comprising Gastrointestinal Homing Receptors, Methods of Making, and Uses Thereof

[0029] In one embodiment, provided herein are genetically modified cells, for example immune cells, such as T lymphocytes, e.g., human T lymphocytes, that comprise, e.g., have been engineered to express, a receptor that causes a cell expressing said receptor to home to the gastrointestinal tract, e.g., gastrointestinal organs, tissues, or cells. Such a receptor that causes a cell to home to the gastrointestinal tract is referred to herein as a "gastrointestinal homing receptor." In a specific embodiment, the genetically modified cells provided herein are T lymphocytes. In certain embodiments, the gastrointestinal homing receptor is CCR9 or integrin α4β7, for example, human CCR9 or human integrin α4β7. GenBank™ accession numbers NM_031200.2 and NM001256369.1 provide exemplary nucleotide sequences for human CCR9. GenBank™ accession numbers NP_112477.1 and NP_001243298.1 provide exemplary amino acid sequences for human CCR9. GenBank™ accession numbers NM_000885.4 and NM_000889.2 provide exemplary nucleotide sequences for human α4 and human β7, respectively. GenBank™ accession numbers NP_000876.3 and NP_000880.1 provide exemplary amino acid sequences for human α4 and human β7, respectively. Exemplary nucleotide and amino acid sequences for human homing receptors can be found in Table 1. In some embodiments, the genetically modified cells further comprise a second gastrointestinal

homing receptor. In some embodiments, the genetically modified cells comprise a first gastrointestinal homing receptor, wherein the first gastrointestinal homing receptor is CCR9, and further comprise a second gastrointestinal homing receptor, wherein the second gastrointestinal homing receptor is integrin α4β7. In other specific embodiments, the genetically modified cells comprise the gastrointestinal-homing receptor CXCR3.

[0030] In certain embodiments, the genetically modified cells containing one or more gastrointestinal homing receptors are expanded, activated, or both expanded and activated in the presence of a Vitamin A metabolite. In specific embodiments, the expansion, activation, or both expansion and activation occurs *in vivo*, *in vitro*, or *ex vivo*. In specific embodiments, the Vitamin A metabolite is retinoic acid. In certain embodiments, the genetically modified cells containing one or more gastrointestinal homing receptors additionally comprise a B cell zone homing receptor. In specific embodiments, the B cell zone homing receptor is CXCR5. In certain embodiments, the genetically modified cells express a gastrointestinal homing receptor and also express a CAR, as described in Section 4.4. In certain embodiments, the genetically modified cells express a CAR and endogenously express one or more gastrointestinal homing receptors.

[0031] Also provided herein are methods of generating genetically modified cells, e.g. human T lymphocytes, which comprise one or more receptors that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, e.g., gastrointestinal organs, skin, or tissue. In certain embodiments, T lymphocytes comprising one or more receptors that that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, e.g., CCR9 or integrin α4β7, are generated by a method comprising a step of engineering a T lymphocyte to express one or more gastrointestinal homing receptors. In some embodiments, the step of engineering a T cell to express one or more gastrointestinal homing receptors comprises introducing to the cells one or more vectors comprising a nucleic acid sequence encoding the receptor. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR9, the nucleic acid sequence for human integrin α4β7, or both.

[0032] In certain embodiments, T lymphocytes that home to the gastrointestinal tract are generated by a method comprising a step of treating the cells with a molecule that induces the

expression of one or more gastrointestinal homing receptors, e.g., CCR9 or α4β7. In specific embodiments, the molecule is Vitamin A.

[0033] In certain embodiments, the method for generating the genetically modified T lymphocytes that comprise one or more receptors that that cause a cell expressing the one or more receptors to home to the gastrointestinal tract comprises a step of expanding the cells, which step is carried out in the presence of a vitamin A metabolite. In certain embodiments, the method for generating the genetically modified T lymphocytes that comprise one or more receptors homing to the gastrointestinal tract comprises a step of activating the cells, which step is carried out in the presence of a vitamin A metabolite. In certain embodiments, both the expanding and activating steps are carried out in the presence of a vitamin A metabolite. In certain embodiments the vitamin A metabolite is retinoic acid. In a certain embodiment, the step of engineering a T cell to express a gastrointestinal homing receptor is performed by any method known to one of skill in the art.

[0034] Exemplary nucleic acids useful for engineering a T lymphocyte to express a gastrointestinal homing receptor are discussed, for example, in Section 4.5.

[0035] Also provided herein are methods of treating a gastrointestinal cancer or tumor in an individual comprising administering to the individual a therapeutically effective amount of genetically modified cells, e.g. human T lymphocytes that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, and (ii) a CAR. In certain embodiments, the gastrointestinal homing receptor is CCR9 or α4β7. In some embodiments, the genetically modified cells further comprise a second gastrointestinal homing receptor. In some embodiments, the genetically modified cells comprise a first gastrointestinal homing receptor, wherein the first gastrointestinal homing receptor is CCR9, and further comprise a second gastrointestinal homing receptor, wherein the second gastrointestinal homing receptor is α4β7. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, and (ii) a CAR, suppress the proliferation of tumor cells. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, and (ii) a CAR, inhibit growth of the tumor. In certain embodiments,

the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, and (ii) a CAR, kill tumor cells. In specific embodiments, the gastrointestinal cancer or tumor is liver cancer, stomach cancer, esophageal cancer, gallbladder cancer, colorectal cancer, anal cancer, or pancreatic cancer. In certain embodiments, the extracellular domain of the CAR binds an antigen associated with a gastrointestinal cancer or tumor. Also provided herein are genetically modified cells for use in methods of treating a gastrointestinal cancer or tumor.

4.3. Cells Comprising Skin Homing Receptors, Methods of Making, and Uses Thereof

[0036] In one embodiment, provided herein are genetically modified cells, for example immune cells, such as T lymphocytes, e.g., human T lymphocytes, that comprise a receptor that causes a cell expressing said receptor to home to the skin, e.g., skin tissue, or skin cells. In a specific embodiment, the genetically modified cells provided herein are T lymphocytes. In certain embodiments, the skin homing receptor is CCR10, CCR8, CCR4, or CLA, for example, human CCR10, human CCR8, human CCR4, or human CLA. GenBank™ accession numbers NM_016602.2 and AF215981.1 provide exemplary nucleotide sequences for human CCR10. GenBank™ accession numbers NP_057686.2 and P46092.3 provide exemplary amino acid sequences for human CCR10. GenBank™ accession numbers NM_005201.3 and BC107159.1 provide exemplary nucleotide sequences for human CCR8. GenBank™ accession numbers NP_005192.1 and AAI07160.1 provide exemplary amino acid sequences for human CCR8. GenBank™ accession number NM_005508.4 provides an exemplary nucleotide sequence for human CCR4. GenBank™ accession number P51679.1 provides an exemplary amino acid sequence for human CCR4. GenBank™ accession numbers NM_001206609.1 and NM_003006.4 provide exemplary nucleotide sequences for human CLA. GenBank™ accession numbers NP_001193538.1 and NP_002997.2 provide exemplary amino acid sequences for human CLA. Exemplary nucleotide and amino acid sequences for human homing receptors can be found in Table 1. In some embodiments, the genetically modified cells further comprise a second skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, and further comprise a second skin homing receptor,

wherein the second skin homing receptor is CCR4. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR4, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA. In some embodiments, the genetically modified cells further comprise a third skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, and further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR8, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA, CCR4, or CCR10. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR8, further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA, CCR4, or CCR10, and further comprise a third skin homing receptor, wherein the third skin homing receptor is distinct from the second skin homing receptor, and is selected from the group consisting of CLA, CCR4, and CCR10. In some embodiments, the genetically modified cells further comprise a third skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA, and further comprise a fourth skin homing receptor, wherein the fourth skin homing receptor is CCR8. In certain embodiments, the genetically modified cells comprise one or more skin homing receptors. In other specific embodiments, the genetically modified cells comprise the skin-homing receptor CCR6.

[0037] In certain embodiments, the genetically modified cells containing one or more skin homing receptors are expanded, activated, or both expanded and activated in the presence of a Vitamin D metabolite. In specific embodiments, the expansion, activation, or both expansion and activation occurs *in vivo*, *in vitro*, or *ex vivo*. In specific embodiments, the Vitamin D metabolite is 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$). In certain embodiments, the genetically modified cells containing one or more skin homing receptors are expanded, activated, or both expanded and activated in the presence of IL-12. In specific embodiments, the expansion,

activation, or both expansion and activation occurs *in vivo*, *in vitro*, or *ex vivo*. In more specific embodiments, the genetically modified cells containing one or more skin homing receptors are expanded, activated, or both expanded and activated in the presence of a Vitamin D metabolite and IL-12. In specific embodiments, the expansion, activation, or both expansion and activation occurs *in vivo*, *in vitro*, or *ex vivo*. In certain embodiments, the genetically modified cells containing one or more skin homing receptors additionally comprise a B cell zone homing receptor. In specific embodiments, the B cell zone homing receptor is CXCR5. In certain embodiments, the genetically modified cells express a skin homing receptor and also express a CAR, as described in Section 4.4. In certain embodiments, the genetically modified cells express a CAR and endogenously express one or more skin homing receptors.

[0038] Also provided herein are methods of generating genetically modified cells, e.g. human T lymphocytes, that comprise one or more receptors homing to the skin, e.g., skin tissue or cells. In certain embodiments, T lymphocytes that home to the skin are generated by a method comprising a step of engineering the T lymphocytes to express a skin homing receptor, e.g., CCR4, CCR8, CCR10, or CLA. In some embodiments, the step of engineering the T lymphocytes to express a skin homing receptor comprises introducing into the cells one or more vectors comprising the receptor nucleic acid sequence(s), i.e., the nucleic acid sequence(s) encoding the receptor(s). In specific embodiments, the vector comprises the nucleic acid sequence for human CCR10, the nucleic acid sequence for human CLA, or both. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR4, and optionally the nucleic acid sequence for human CLA. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR4 and the nucleic acid sequence for human CCR10. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR10, the nucleic acid sequence for human CCR4, and the nucleic acid sequence for human CLA. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8, and optionally the nucleic acid sequence for human CLA. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8 and the nucleic acid sequence for human CCR10. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8, the nucleic acid sequence for human CCR4, and the nucleic acid sequence for human CLA. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8,

the nucleic acid sequence for human CCR10, and the nucleic acid sequence for human CLA. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8, the nucleic acid sequence for human CCR4, and the nucleic acid sequence for human CCR10. In specific embodiments, the vector comprises the nucleic acid sequence for human CCR8, the nucleic acid sequence for human CCR4, the nucleic acid for CCR10, and the nucleic acid sequence for human CLA.

[0039] In certain embodiments, cells, e.g., T lymphocytes, that home to the skin are generated by a method comprising a step of treating the cells, e.g., T lymphocytes, with a molecule that induces, e.g., increases, the expression of one or more skin homing receptors, e.g., CCR4, CCR10, CCR8, or CLA. In specific embodiments, the molecule is Vitamin D. In certain embodiments, the induction of expression of skin homing receptors is aided by treating the cells, e.g., T lymphocytes, with IL-12, e.g., contacting the cells with IL-12 in an amount and for a time sufficient to increase expression of one or more of CCR4, CCR8, CCR10, or CLA by said cells.

[0040] In certain embodiments, the method for generating the genetically modified T lymphocytes that comprise one or more receptors that cause a cell expressing the one or more receptors to home to the skin, comprises a step of expanding the cells, which step is carried out in the presence of a vitamin D metabolite and, optionally, IL-12. In certain embodiments, the method for generating the genetically modified T lymphocytes that comprise one or more receptors that that cause a cell expressing the one or more receptors to home to the gastrointestinal tract, comprises a step of activating the cells, which step is carried out in the presence of a vitamin D metabolite, and, optionally, IL-12. In certain embodiments, both the expanding and activating steps are carried out in the presence of a vitamin D metabolite, and, optionally, IL-12. In certain embodiments the vitamin D metabolite is $1,25(OH)_2D_3$. In a certain embodiment, the step of engineering a T cell to express a skin homing receptor is performed by any method known to one of skill in the art.

[0041] Exemplary nucleic acids useful for engineering a T lymphocyte to express a skin homing receptor are discussed, for example, in Section 4.5.

[0042] Also provided herein are methods of treating a skin cancer or tumor in an individual comprising administering to the individual a therapeutically effective amount of genetically modified cells, e.g. human T lymphocytes that comprise (i) one or more receptors that that cause

a cell expressing the one or more receptors to home to the skin, and (ii) a CAR. In certain embodiments, the skin homing receptor is CCR10, CCR8, CCR4, or CLA. In some embodiments, the genetically modified cells further comprise a second skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR8. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR4, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CLA. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR4, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR8. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CLA, and further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR8. In some embodiments, the genetically modified cells further comprise a third skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, and further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, and further comprise a third skin homing receptor, wherein the third skin homing receptor is CCR8. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR8, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, and further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA. In some embodiments, the

genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR8, and further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA. In some embodiments, the genetically modified cells further comprise a fourth skin homing receptor. In some embodiments, the genetically modified cells comprise a first skin homing receptor, wherein the first skin homing receptor is CCR10, further comprise a second skin homing receptor, wherein the second skin homing receptor is CCR4, further comprise a third skin homing receptor, wherein the third skin homing receptor is CLA, and further comprise a fourth skin homing receptor, wherein the fourth skin homing receptor is CCR8. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the skin, and (ii) a CAR, suppress the proliferation of tumor cells. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the skin, and (ii) a CAR, inhibit growth of the tumor. In certain embodiments, the genetically modified cells, e.g. human T lymphocytes, that comprise (i) one or more receptors that cause a cell expressing the one or more receptors to home to the skin, and (ii) a CAR, kill tumor cells. In specific embodiments, the skin cancer or tumor is melanoma, squamous cell carcinoma, or basal cell carcinoma. In certain embodiments, the extracellular domain of the CAR binds an antigen associated with a skin cancer or tumor. Also provided herein are genetically modified cells for use in methods of treating a skin cancer or tumor.

[0043] Table 1. Exemplary nucleotide and amino acid sequences for human homing receptors.

SEQ ID NO:	GenBank Accession Number and Description	Sequence
1	NM_001716.4 Exemplary nucleic acid sequence encoding human CXCR5	1 aaaaaaaaaa agtgatgagt tgtgaggcag gtcgcggccc tactgcctca ggagacgatg 61 cgcagctcat ttgcttaaat ttgcagctga cggctgccac ctctctagag gcacctggcg 121 gggagcctct caacataaga cagtgaccag tctggtgact cacagccggc acagccatga 181 actacccgct aacgctggaa atggacctcg agaacctgga ggacctgttc tgggaactgg 241 acagattgga caactataac gacacctccc tggtggaaaa tcatctctgc cctgccacag 301 aggggcccct catggcctcc ttcaaggccg tgttcgtgcc cgtggcctac agcctcatct 361 tcctcctggg cgtgatcggc aacgtcctgg tgctggtgat cctggagcgg caccggcaga 421 cacgcagttc cacggagacc ttcctgttcc acctggccgt ggccgacctc ctgctggtct

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		481 tcatcttgcc ctttgccgtg gccgagggct ctgtgggctg ggtcctgggg accttcctct 541 gcaaaactgt gattgccctg cacaaagtca acttctactg cagcagcctg ctcctggcct 601 gcatcgccgt ggaccgctac ctggccattg tccacgccgt ccatgcctac cgccaccgcc 661 gcctcctctc catccacatc acctgtggga ccatctggct ggtgggcttc ctccttgcct 721 tgccagagat tctcttcgcc aaagtcagcc aaggccatca caacaactcc ctgccacgtt 781 gcaccttctc ccaagagaac caagcagaaa cgcatgcctg gttcacctcc cgattcctct 841 accatgtggc gggattcctg ctgcccatgc tggtgatggg ctggtgctac gtgggggtag 901 tgcacaggtt gcgccaggcc cagcggcgcc ctcagcggca gaaggcagtc agggtggcca 961 tcctggtgac aagcatcttc ttcctctgct ggtcacccta ccacatcgtc atcttcctgg 1021 acaccctggc gaggctgaag gccgtggaca atacctgcaa gctgaatggc tctctccccg 1081 tggccatcac catgtgtgag ttcctgggcc tggcccactg ctgcctcaac cccatgctct 1141 acactttcgc cggcgtgaag ttccgcagtg acctgtcgcg gctcctgacg aagctgggct 1201 gtaccggccc tgcctccctg tgccagctct tccctagctg gcgcaggagc agtctctctg 1261 agtcagagaa tgccacctct ctcaccacgt tctaggtccc agtgtcccct tttattgctg 1321 cttttccttg gggcaggcag tgatgctgga tgctccttcc aacaggagct gggatcctaa 1381 gggctcaccg tggctaagag tgtcctagga gtatcctcat ttggggtagc tagaggaacc 1441 aacccccatt tctagaacat ccctgccagc tcttctgccg gccctggggc taggctggag 1501 cccagggagc ggaaagcagc tcaaaggcac agtgaaggct gtccttaccc atctgcaccc 1561 ccctgggctg agagaacctc acgcacctcc catcctaatc atccaatgct caagaaacaa 1621 cttctacttc tgcccttgcc aacggagagc gcctgcccct cccagaacac actccatcag 1681 cttaggggct gctgacctcc acagcttccc ctctctcctc ctgcccacct gtcaaacaaa 1741 gccagaagct gagcaccagg ggatgagtgg aggttaaggc tgaggaaagg ccagctggca 1801 gcagagtgtg gccttcggac aactcagtcc ctaaaaacac agacattctg ccaggccccc 1861 aagcctgcag tcatcttgac caagcaggaa gctcagactg gttgagttca ggtagctgcc 1921 cctggctctg accgaaacag cgctgggtcc accccatgtc accggatcct gggtggtctg 1981 caggcagggc tgactctagg tgcccttgga ggccagccag tgacctgagg aagcgtgaag 2041 gccgagaagc aagaaagaaa cccgacagag ggaagaaaag agctttcttc ccgaacccca 2101 aggagggaga tggatcaatc aaacccggcg gtcccctccg ccaggcgaga tggggtgggg 2161 tggagaactc ctagggtggc tgggtccagg ggatgggagg ttgtgggcat tgatggggaa 2221 ggaggctggc ttgtcccctc ctcactccct tcccataagc tatagacccg aggaaactca 2281 gagtcggaac ggagaaaggt ggactggaag gggcccgtgg gagtcatctc aaccatcccc 2341 tccgtggcat caccttaggc agggaagtgt aagaaacaca ctgaggcagg gaagtcccca 2401 ggccccagga agccgtgccc tgcccccgtg aggatgtcac tcagatggaa ccgcaggaag 2461 ctgctccgtg cttgtttgct cacctggggt gtgggaggcc cgtccggcag ttctgggtgc 2521 tccctaccac ctccccagcc tttgatcagg tggggagtca gggacccctg cccttgtccc 2581 actcaagcca agcagccaag ctccttggga ggccccactg gggaaataac agctgtggct 2641 cacgtgagag tgtcttcacg gcaggacaac gaggaagccc taagacgtcc ctttttttctc 2701 tgagtatctc ctcgcaagct gggtaatcga tgggggagtc tgaagcagat gcaaagaggc 2761 aagaggctgg attttgaatt ttctttttaa taaaaaggca cctataaaac aggtcaatac 2821 agtacaggca gcacagagac ccccggaaca agcctaaaaa ttgtttcaaa ataaaaacca 2881 agaagatgtc ttcacatatt gtaaaaaaaa aaaaaaaaa
2	NM_032966.2 Exemplary nucleic acid sequence encoding human	1 ccactctaag gaatgcggtc cctttgacag gcgaaaaact gaagttggaa aagacaaagt 61 gatttgttca aaattgaaat ttgaaacttg acatttggtc agtgggccct atgtaggaaa 121 aaacctccaa gagagctagg gttcctctca gagaggaaag acaggtcctt aggtcctcac 181 cctcccgtct ccttgcccttgcagttctgg gaactggaca gattggacaa ctataacgac 241 acctccctgg tggaaaatca tctctgccct gccacagagg ggcccctcat ggcctccttc

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	CXCR5	301 aaggccgtgt tcgtgcccgt ggcctacagc ctcatcttcc tcctgggcgt gatcggcaac 361 gtcctggtgc tggtgatcct ggagcggcac cggcagacac gcagttccac ggagaccttc 421 ctgttccacc tggccgtggc cgacctcctg ctggtcttca tcttgccctt tgccgtggcc 481 gagggctctg tgggctgggt cctggggacc ttcctctgca aaactgtgat tgccctgcac 541 aaagtcaact tctactgcag cagcctgctc ctggcctgca tcgccgtgga ccgctacctg 601 gccattgtcc acgccgtcca tgcctaccgc caccgccgcc tcctctccat ccacatcacc 661 tgtgggacca tctggctggt gggcttcctc cttgccttgc cagagattct cttcgccaaa 721 gtcagccaag gccatcacaa caactccctg ccacgttgca ccttctccca agagaaccaa 781 gcagaaacgc atgcctggtt cacctcccga ttcctctacc atgtggcggg attcctgctg 841 cccatgctgg tgatgggctg gtgctacgtg ggggtagtgc acaggttgcg ccaggcccag 901 cggcgccctc agcggcagaa ggcagtcagg gtggccatcc tggtgacaag catcttcttc 961 ctctgctggt caccctacca catcgtcatc ttcctggaca ccctggcgag gctgaaggcc 1021 gtggacaata cctgcaagct gaatggctct ctccccgtgg ccatcaccat gtgtgagttc 1081 ctgggcctgg cccactgctg cctcaacccc atgctctaca ctttcgccgg cgtgaagttc 1141 cgcagtgacc tgtcgcggct cctgacgaag ctgggctgta ccggccctgc ctccctgtgc 1201 cagctcttcc ctagctggcg caggagcagt ctctctgagt cagagaatgc cacctctctc 1261 accacgttct aggtcccagt gtccccttt attgctgctt ttccttgggg caggcagtga 1321 tgctggatgc tccttccaac aggagctggg atcctaaggg ctcaccgtgg ctaagagtgt 1381 cctaggagta tcctcatttg gggtagctag aggaaccaac ccccatttct agaacatccc 1441 tgccagctct tctgccggcc ctggggctag gctggagccc agggagcgga aagcagctca 1501 aaggcacagt gaaggctgtc cttacccatc tgcacccccc tgggctgaga gaacctcacg 1561 cacctcccat cctaatcatc caatgctcaa gaaacaactt ctacttctgc ccttgccaac 1621 ggagagcgcc tgcccctccc agaacacact ccatcagctt aggggctgct gacctccaca 1681 gcttcccctc tctcctcctg cccacctgtc aaacaaagcc agaagctgag caccagggga 1741 tgagtggagg ttaaggctga ggaaaggcca gctggcagca gagtgtggcc ttcggacaac 1801 tcagtcccta aaaacacaga cattctgcca ggcccccaag cctgcagtca tcttgaccaa 1861 gcaggaagct cagactggtt gagttcaggt agctgcccct ggctctgacc gaaacagcgc 1921 tgggtccacc ccatgtcacc ggatcctggg tggtctgcag gcagggctga ctctaggtgc 1981 ccttggaggc cagccagtga cctgaggaag cgtgaaggcc gagaagcaag aaagaaaccc 2041 gacagaggga agaaaagagc tttcttcccg aaccccaagg agggagatgg atcaatcaaa 2101 cccggcggtc ccctccgcca ggcgagatgg ggtggggtgg agaactccta gggtggctgg 2161 gtccagggga tgggaggttg tgggcattga tggggaagga ggctggcttg tcccctcctc 2221 actcccttcc cataagctat agacccgagg aaactcagag tcggaacgga gaaaggtgga 2281 ctggaagggg cccgtgggag tcatctcaac catcccctcc gtggcatcac cttaggcagg 2341 gaagtgtaag aaacacactg aggcagggaa gtccccaggc cccaggaagc cgtgccctgc 2401 ccccgtgagg atgtcactca gatggaaccg caggaagctg ctccgtgctt gtttgctcac 2461 ctggggtgtg ggaggcccgt ccggcagttc tgggtgctcc ctaccacctc cccagccttt 2521 gatcaggtgg ggagtcaggg acccctgccc ttgtcccact caagccaagc agccaagctc 2581 cttgggaggc cccactgggg aaataacagc tgtggctcac gtgagagtgt cttcacggca 2641 ggacaacgag gaagccctaa gacgtccctt ttttctctga gtatctcctc gcaagctggg 2701 taatcgatgg gggagtctga agcagatgca aagaggcaag aggctggatt ttgaattttc 2761 tttttaataa aaaggcacct ataaaacagg tcaatacagt acaggcagca cagagacccc 2821 cggaacaagc ctaaaaattg tttcaaaata aaaaccaaga agatgtcttc acatattgta 2881 aaaaaaaaaa aaaaaa
3	NP_116743.1	1 masfkavfvp vayslifllg vignvlvlvi lerhrqtrss tetflfhlav adlllvfilp 61 favaegsvgw vlgtflcktv ialhkvnfyc sslllaciav drylaivhav hayrhrrlls

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	Exemplary amino acid sequence for human CXCR5 precursor	121 ihitcgtiwl vgfllalpei lfakvsqghh nnslprctfs qenqaethaw ftsrflyhva 181 gfllpmlvmg wcyvgvvhrl rqaqrrpqrq kavrvailvt siifflcwspy hivifldtla 241 rlkavdntck lngslpvait mceflglahc clnpmlytfa gvkfrsdlsr lltklgctgp 301 aslcqlfpsw rrsslsesen atslttf
4	NP_001707.1 Exemplary amino acid sequence for human CXCR5 precursor	1 mnypltlemd lenledlfwe ldrldnyndt slvenhlcpa tegplmasfk avfvpvaysl 61 ifllgvignv lvlvilerhr qtrsstetfl fhlavadlll vfilpfavae gsvgwvlgtf 121 lcktvialhk vnfycsslll aciavdryla ivhavhayrh rrllsihitc gtiwlvgfll 181 alpeilfakv sqghhnnslp rctfsqenqa ethawftsrf lyhvagfllp mlvmgwcyvg 241 vvhrlrqaqr rpqrqkavrv ailvtsiffl cwspyhivif ldtlarlkav dntcklngsl 301 pvaitmcefl glahcclnpm lytfagvkfr sdlsrlltkl gctgpaslcq lfpswrrssl 361 sesenatslt tf
5	NM_031200.2 Exemplary nucleic acid sequence encoding human CCR9	1 gcttccttte tcgtgttgtt atcgggtagc tgcctgctca gaacccacaa agcctgcccc 61 tcatcccagg cagagagcaa cccagctctt tccccagaca ctgagagctg gtggtgcctg 121 ctgtcccagg gagagttgca tcgccctcca cagagcaggc ttgcatctga ctgacccacc 181 atgacaccca cagacttcac aagccctatt cctaacatgg ctgatgacta tggctctgaa 241 tccacatctt ccatggaaga ctacgttaac ttcaacttca ctgacttcta ctgtgagaaa 301 aacaatgtca ggcagtttgc gagccatttc ctcccaccct tgtactggct cgtgttcatc 361 gtgggtgcct tgggcaacag tcttgttatc cttgtctact ggtactgcac aagagtgaag 421 accatgaccg acatgttcct tttgaatttg gcaattgctg acctcctctt tcttgtcact 481 cttcccttct gggccattgc tgctgctgac cagtggaagt tccagacctt catgtgcaag 541 gtggtcaaca gcatgtacaa gatgaacttc tacagctgtg tgttgctgat catgtgcatc 601 agcgtggaca ggtacattgc cattgcccag gccatgagag cacatacttg gagggagaaa 661 aggcttttgt acagcaaaat ggtttgcttt accatctggg tattggcagc tgctctctgc 721 atcccagaaa tcttatacag ccaaatcaag gaggaatccg gcattgctat ctgcaccatg 781 gtttacccta gcgatgagag caccaaactg aagtcagctg tcttgaccct gaaggtcatt 841 ctggggttct tccttccctt cgtggtcatg gcttgctgct ataccatcat cattcacacc 901 ctgatacaag ccaagaagtc ttccaagcac aaagccctaa aagtgaccat cactgtcctg 961 accgtctttg tcttgtctca gtttccctac aactgcattt tgttggtgca gaccattgac 1021 gcctatgcca tgttcatctc caactgtgcc gtttccacca acattgacat ctgcttccag 1081 gtcacccaga ccatcgcctt cttccacagt tgcctgaacc ctgttctcta tgtttttgtg 1141 ggtgagagat tccgccggga tctcgtgaaa accctgaaga acttgggttg catcagccag 1201 gcccagtggg tttcatttac aaggagagag ggaagcttga agctgtcgtc tatgttgctg 1261 gagacaacct caggagcact ctccctctga ggggtcttct ctgaggtgca tggttctttt 1321 ggaagaaatg agaaatacag aaacagtttc cccactgatg ggaccagaga gagtgaaaga 1381 gaaaagaaaa ctcagaaagg gatgaatctg aactatatga ttacttgtag tcagaatttg 1441 ccaaagcaaa tatttcaaaa tcaactgact agtgcaggag gctgttgatt ggctcttgac 1501 tgtgatgccc gcaattctca aaggaggact aaggaccggc actgtggagc accctggctt 1561 tgccactcgc cggagcatca atgccgctgc ctctggagga gcccttggat tttctccatg 1621 cactgtgaac ttctgtggct tcagttctca tgctgcctct tccaaaaggg gacacagaag 1681 cactggctgc tgctacagac cgcaaaagca gaaagtttcg tgaaaatgtc catctttggg 1741 aaatttttcta ccctgctctt gagcctgata acccatgcca ggtcttatag attcctgatc 1801 tagaaccttt ccaggcaatc tcagacctaa tttccttctg ttctccttgt tctgttctgg 1861 gccagtgaag gtccttgttc tgattttgaa acgatctgca ggtcttgcca gtgaacccct 1921 ggacaactga ccacacccac aaggcatcca aagtctgttg gcttccaatc catttctgtg 1981 tcctgctgga ggttttaacc tagacaagga ttccgcttat tccttggtat ggtgacagtg

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6	NM001256369.1 Exemplary nucleic acid sequence encoding human CCR9	1 gcttcctttc tcgtgttgtt atcgggtagc tgcctgctca gaacccacaa agcctgcccc 61 tcatcccagg cagagagcaa cccagctctt tccccagaca ctgagagctg gtggtgcctg 121 ctgtcccagg gagagttgca tcgccctcca cagagcaggc ttgcatctga ctgacccacc 181 atgacaccca cagacttcac atctcctcca ggccccgctc cagatcacct tccctcgctg 241 gcccaggaat ccatctcctt ccaggacctt agcccaggac taacacaagc cctattccta 301 acatggctga tgactatggc tctgaatcca catcttccat ggaagactac gttaacttca 361 acttcactga cttctactgt gagaaaaaca atgtcaggca gtttgcgagc catttcctcc 421 caccettgta ctggctcgtg ttcatcgtgg gtgccttggg caacagtctt gttatccttg 481 tctactggta ctgcacaaga gtgaagacca tgaccgacat gttccttttg aatttggcaa 541 ttgctgacct cctctttctt gtcactcttc ccttctgggc cattgctgct gctgaccagt 601 ggaagttcca gaccttcatg tgcaaggtgg tcaacagcat gtacaagatg aacttctaca 661 gctgtgtgtt gctgatcatg tgcatcagcg tggacaggta cattgccatt gcccaggcca 721 tgagagcaca tacttggagg gagaaaaggc ttttgtacag caaaatggtt tgctttacca 781 tctgggtatt ggcagctgct ctctgcatcc cagaaatctt atacagccaa atcaaggagg 841 aatccggcat tgctatctgc accatggttt accctagcga tgagagcacc aaactgaagt 901 cagctgtctt gaccctgaag gtcattctgg ggttcttcct tcccttcgtg gtcatggctt 961 gctgctatac catcatcatt cacaccctga tacaagccaa gaagtcttcc aagcacaaag 1021 ccctaaaagt gaccatcact gtcctgaccg tctttgtctt gtctcagttt ccctacaact 1081 gcattttgtt ggtgcagacc attgacgcct atgccatgtt catctccaac tgtgccgttt 1141 ccaccaacat tgacatctgc ttccaggtca cccagaccat cgccttcttc cacagttgcc 1201 tgaaccctgt tctctatgtt tttgtgggtg agagattccg ccgggatctc gtgaaaaccc 1261 tgaagaactt gggttgcatc agccaggccc agtgggtttc atttacaagg agagagggaa 1321 gcttgaagct gtcgtctatg ttgctggaga caacctcagg agcactctcc ctctgagggg 1381 tcttctctga ggtgcatggt tcttttggaa gaaatgagaa atacagaaac agtttcccca 1441 ctgatgggac cagagagagt gaaagagaaa agaaaactca gaaagggatg aatctgaact 1501 atatgattac ttgtagtcag aatttgccaa agcaaatatt tcaaaatcaa ctgactagtg 1561 caggaggctg ttgattggct cttgactgtg atgcccgcaa ttctcaaagg aggactaagg 1621 accggcactg tggagcaccc tggctttgcc actcgccgga gcatcaatgc cgctgcctct 1681 ggaggagccc ttggattttc tccatgcact gtgaacttct gtggcttcag ttctcatgct 1741 gcctcttcca aaaggggaca cagaagcact ggctgctgct acagaccgca aaagcagaaa 1801 gtttcgtgaa aatgtccatc tttgggaaat tttctaccct gctcttgagc ctgataaccc 1861 atgccaggtc ttatagattc ctgatctaga acctttccag gcaatctcag acctaatttc 1921 cttctgttct ccttgttctg ttctgggcca gtgaaggtcc ttgttctgat tttgaaacga 1981 tctgcaggtc ttgccagtga acccctggac aactgaccac acccacaagg catccaaagt 2041 ctgttggctt ccaatccatt tctgtgtcct gctggaggtt ttaacctaga caaggattcc 2101 gcttattcct tggtatggtg acagtgtctc tccatggcct gagcagggag attataacag 2161 ctgggttcgc aggagccagc cttggccctg ttgtaggctt gttctgttga gtggcacttg

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7	NP_112477.1 Exemplary amino acid sequence for human CCR9 precursor	1 mtptdftspi pnmaddygse stssmedyvn fnftdfycek nnvrqfashf lpplywlvfi 61 vgalgnslvi lvywyctrvk tmtdmfllnl aiadllflvt lpfwaiaaad qwkfqtfmck 121 vvnsmykmnf yscvllimci svdryiaiaq amrahtwrek rllyskmvcf tiwvlaaalc 181 ipeilysqik eesgiaictm vypsdestkl ksavltlkvi lgfflpfvvm accytiiiht 241 liqakksskh kalkvtitvl tvfvlsqfpy ncillvqtid ayamfisnca vstnidicfq 301 vtqtiaffhs clnpvlyvfv gerfrrdlvk tlknlgcisq aqwvsftrre gslklssmll 361 ettsgalsl
8	NP_001243298.1 Exemplary amino acid sequence for human CCR9 precursor	1 maddygsest ssmedyvnfn ftdfyceknn vrqfashflp plywlvfivg algnslvilv 61 ywyctrvktm tdmfllnlai adllflvtlp fwaiaaadqw kfqtfmckvv nsmykmnfys 121 cvllimcisv dryiaiaqam rahtwrekrl lyskmvcfti wvlaaalcip eilysqikee 181 sgiaictmvy psdestklks avltlkvilg fflpfvvmac cytiiihtli qakksskhka 241 lkvtitvltv fvlsqfpync illvqtiday amfisncavs tnidicfqvt qtiaffhscl 301 npvlyvfvge rfrrdlvktl knlgcisqaq wvsftrregs lklssmllet tsgalsl
9	NM_000885.4 Exemplary nucleic acid sequence encoding human α4	1 ataacgtctt tgtcactaaa atgttcccca ggggccttcg gcgagtcttt ttgtttggtt 61 ttttgttttt aatctgtggc tcttgataat ttatctagtg gttgcctaca cctgaaaaac 121 aagacacagt gtttaactat caacgaaaga actggacggc tccccgccgc agtcccactc 181 cccgagtttg tggctggcat ttgggccacg ccgggctggg cggtcacagc gaggggcgcg 241 cagtttgggg tcacacagct ccgcttctag gccccaacca ccgttaaaag gggaagcccg 301 tgccccatca ggtccgctct tgctgagccc agagccatcc cgcgctctgc gggctgggag 361 gcccgggcca ggacgcgagt cctgcgcagc cgaggttccc cagcgccccc tgcagccgcg 421 cgtaggcaga gacggagccc ggccctgcgc ctccgcacca cgcccgggac cccacccagc 481 ggcccgtacc cggagaagca gcgcgagcac ccgaagctcc cggctggcgg cagaaaccgg 541 gagtggggcc gggcgagtgc gcggcatccc aggccggccc gaacgctccg cccgcggtgg 601 gccgacttcc cctcctcttc cctctctcct tcctttagcc cgctggcgcc ggacacgctg 661 cgcctcatct cttggggcgt tcttccccgt tggccaaccg tcgcatcccg tgcaactttg 721 gggtagtggc cgtttagtgt tgaatgttcc ccaccgagag cgcatggctt gggaagcgag 781 gcgcgaaccc ggcccccgaa gggccgccgt ccgggagacg gtgatgctgt tgctgtgcct 841 gggggtcccg accggccgcc cctacaacgt ggacactgag agcgcgctgc tttaccaggg 901 cccccacaac acgctgttcg gctactcggt cgtgctgcac agccacgggg cgaaccgatg 961 gctcctagtg ggtgcgccca ctgccaactg gctcgccaac gcttcagtga tcaatcccgg 1021 ggcgatttac agatgcagga tcggaaagaa tcccggccag acgtgcgaac agctccagct 1081 gggtagccct aatggagaac cttgtggaaa gacttgtttg gaagagagag acaatcagtg 1141 gttgggggtc acactttcca gacagccagg agaaaatgga tccatcgtga cttgtgggca 1201 tagatggaaa aatatatttt acataaagaa tgaaaataag ctccccactg gtggttgcta 1261 tggagtgccc cctgatttac gaacagaact gagtaaaaga atagctccgt gttatcaaga 1321 ttatgtgaaa aaatttggag aaaattttgc atcatgtcaa gctggaatat ccagttttta

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10	NM_000889.2 Exemplary nucleic acid sequence encoding human β7	1 aaatcttccc caccctgggg agtgtcactt cctcctctgc cgtctcccag atcagtacac 61 aaaggctgct gctgccgcca gaggaaggac tgctctgcac gcacctatgt ggaaactaaa 121 gcccagagag aaagtctgac ttgccccaca gccagtgagt gactgcagca gcaccagaat 181 ctggtctgtt tcctgtttgg ctcttctacc actacggctt gggatctcgg gcatggtggc 241 tttgccaatg gtccttgttt tgctgctggt cctgagcaga ggtgagagtg aattggacgc 301 caagatccca tccacagggg atgccacaga atggcggaat cctcacctgt ccatgctggg 361 gtcctgccag ccagcccct cctgccagaa gtgcatcctc tcacacccca gctgtgcatg 421 gtgcaagcaa ctgaacttca ccgcgtcggg agaggcggag gcgcggcgct gcgcccgacg 481 agaggagctg ctggctcgag gctgcccgct ggaggagctg gaggagcccc gcggccagca 541 ggaggtgctg caggaccagc cgctcagcca gggcgcccgc ggagagggtg ccacccagct 601 ggcgccgcag cgggtccggg tcacgctgcg gcctggggag ccccagcagc tccaggtccg 661 cttccttcgt gctgagggat acccggtgga cctgtactac cttatggacc tgagctactc 721 catgaaggac gacctggaac gcgtgcgcca gctcgggcac gctctgctgg tccggctgca 781 ggaagtcacc cattctgtgc gcattggttt tggttccttt gtggacaaaa cggtgctgcc

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		841 ctttgtgagc acagtaccct ccaaactgcg ccacccctgc cccacccggc tggagcgctg 901 ccagtcacca ttcagctttc accatgtgct gtccctgacg ggggacgcac aagccttcga 961 gcgggaggtg gggcgccaga gtgtgtccgg caatctggac tcgcctgaag gtggcttcga 1021 tgccattctg caggctgcac tctgccagga gcagattggc tggagaaatg tgtcccggct 1081 gctggtgttc acttcagacg acacattcca tacagctggg gacgggaagt tgggcggcat 1141 tttcatgccc agtgatgggc actgccactt ggacagcaat ggcctctaca gtcgcagcac 1201 agagtttgac taccttctg tgggtcaggt agcccaggcc ctctctgcag caaatatcca 1261 gcccatcttt gctgtcacca gtgccgcact gcctgtctac caggagctga gtaaactgat 1321 tcctaagtct gcagttgggg agctgagtga ggactccagc aacgtggtac agctcatcat 1381 ggatgcttat aatagcctgt cttccaccgt gacccttgaa cactcttcac tccctcctgg 1441 ggtccacatt tcttacgaat cccagtgtga gggtcctgag aagagggagg gtaaggctga 1501 ggatcgagga cagtgcaacc acgtccgaat caaccagacg gtgactttct gggtttctct 1561 ccaagccacc cactgcctcc cagagcccca tctcctgagg ctccgggccc ttggcttctc 1621 agaggagctg attgtggagt tgcacacgct gtgtgactgt aattgcagtg acacccagcc 1681 ccaggctccc cactgcagtg atggccaggg acacctacaa tgtggtgtat gcagctgtgc 1741 ccctggccgc ctaggtcggc tctgtgagtg ctctgtggca gagctgtcct ccccagacct 1801 ggaatctggg tgccgggctc ccaatggcac agggcccctg tgcagtggaa agggtcactg 1861 tcaatgtgga cgctgcagct gcagtggaca gagctctggg catctgtgcg agtgtgacga 1921 tgccagctgt gagcgacatg agggcatcct ctgcggaggc tttggtcgct gccaatgtgg 1981 agtatgtcac tgtcatgcca accgcacggg cagagcatgc gaatgcagtg gggacatgga 2041 cagttgcatc agtcccgagg gagggctctg cagtgggcat ggacgctgca aatgcaaccg 2101 ctgccagtgc ttggacggct actatggtgc tctatgcgac caatgcccag gctgcaagac 2161 accatgcgag agacaccggg actgtgcaga gtgtggggcc ttcaggactg gcccactggc 2221 caccaactgc agtacagctt gtgcccatac caatgtgacc ctggccttgg cccctatctt 2281 ggatgatggc tggtgcaaag agcggaccct ggacaaccag ctgttcttct tcttggtgga 2341 ggatgacgcc agaggcacgg tcgtgctcag agtgagaccc caagaaaagg gagcagacca 2401 cacgcaggcc attgtgctgg gctgcgtagg gggcatcgtg gcagtggggc tggggctggt 2461 cctggcttac cggctctcgg tggaaatcta tgaccgccgg gaatacagtc gctttgagaa 2521 ggagcagcaa caactcaact ggaagcagga cagtaatcct ctctacaaaa gtgccatcac 2581 gaccaccatc aatcctcgct ttcaagaggc agacagtccc actctctgaa ggagggaggg 2641 acacttaccc aaggctcttc tccttggagg acagtgggaa ctggagggtg agaggaaggg 2701 tgggtctgta agaccttggt aggggactaa ttcactggcg aggtgcggcc accaccctac 2761 ttcattttca gagtgacacc caagagggct gcttcccatg cctgcaacct tgcatccatc 2821 tgggctaccc cacccaagta tacaataaag tcttacctca gaccacaaaa aaaaaaaa
11	NP_000876.3 Exemplary amino acid sequence for human α4 precursor	1 mawearrepg prraavretv mlllclgvpt grpynvdtes allyqgphnt lfgysvvlhs 61 hganrwllvg aptanwlana svinpgaiyr crigknpgqt ceqlqlgspn gepcgktcle 121 erdnqwlgvt lsrqpgengs ivtcghrwkn ifyiknenkl ptggcygvpp dlrtelskri 181 apcyqdyvkk fgenfascqa gissfytkdl ivmgapgssy wtgslfvyni ttnkykafld 241 kqnqvkfgsy lgysvgaghf rsqhttevvg gapqheqigk ayifsideke lnilhemkgk 301 klgsyfgasv cavdlnadgf sdllvgapmq stireegrvf vyinsgsgav mnametnlvg 361 sdkyaarfge sivnlgdidn dgfedvaiga pqeddlqgai yiyngradgi sstfsqrieg 421 lqiskslsmf gqsisgqida dnngyvdvav gafrsdsavl lrtrpvvivd aslshpesvn 481 rtkfdcveng wpsvcidltl cfsykgkevp gyivlfynms ldvnrkaesp prfyfssngt 541 sdvitgsiqv ssreancrth qafmrkdvrd iltpiqieaa yhlgphvisk rsteefpplq 601 pilqqkkekd imkktinfar fcahencsad lqvsakigfl kphenktyla vgsmktlmln 661 vslfnagdda yettlhvklp vglyfikile leekqincev tdnsgvvqld csigyiyvdh

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		721 lsridisfll dvsslsraee dlsitvhatc eneeemdnlk hsrvtvaipl kyevkltvhg 781 fvnptsfvyg sndenepetc mvekmnltfh vintgnsmap nvsveimvpn sfspqtdklf 841 nildvqtttg echfenyqrv caleqqksam qtlkgivrfl sktdkrllyc ikadphclnf 901 lcnfgkmesg keasvhiqle grpsilemde tsalkfeira tgfpepnprv ielnkdenva 961 hvlleglhhq rpkryftivi issslllgli vlllisyvmw kagffkrqyk silqeenrrd 1021 swsyinsksn dd
12	NP_000880.1 Exemplary amino acid sequence for human β7 precursor	1 mvalpmvlvl llvlsrgese ldakipstgd atewrnphls mlgscqpaps cqkcilshps 61 cawckqlnft asgeaearrc arreellarg cpleeleepr gqqevlqdqp lsqgargega 121 tqlapqrvrv tlrpgepqql qvrflraegy pvdlyylmdl sysmkddler vrqlghallv 181 rlqevthsvr igfgsfvdkt vlpfvstvps klrhpcptrl ercqspfsfh hvlsltgdaq 241 aferevgrqs vsgnldspeg gfdailqaal cqeqigwrnv srllvftsdd tfhtagdgkl 301 ggifmpsdgh chldsnglys rstefdypsv gqvaqalsaa niqpifavts aalpvyqels 361 klipksavge lsedssnvvq limdaynsls stvtlehssl ppgvhisyes qcegpekreg 421 kaedrgqcnh vringtvtfw vslqathclp ephllrlral gfseelivel htlcdcncsd 481 tqpqaphcsd gqghlqcgvc scapgrlgrl cecsvaelss pdlesgcrap ngtgplcsgk 541 ghcqcgrcsc sgqssghlce cddascerhe gilcggfgrc qcgvchchan rtgracecsg 601 dmdscispeg glcsghgrck cnrcqcldgy ygalcdqcpg cktpcerhrd caecgafrtg 661 platncstac ahtnvtlala pilddgwcke rtldnqlfff lveddargtv vlrvrpqekg 721 adhtqaivlg cvggivavgl glvlayrlsv eiydrreysr fekeqqqlnw kqdsnplyks 781 aitttinprf qeadsptl
13	NM_016602.2 Exemplary nucleic acid sequence encoding human CCR10	1 agagatgggg acggaggcca cagagcaggt ttcctggggc cattactctg gggatgaaga 61 ggacgcatac tcggctgagc cactgccgga gctttgctac aaggccgatg tccaggcctt 121 cagccgggcc ttccaaccca gtgtctccct gaccgtggct gcgctgggtc tggccggcaa 181 tggcctggtc ctggccaccc acctggcagc ccgacgcgca gcgcgctcgc ccacctctgc 241 ccacctgctc cagctggccc tggccgacct cttgctggcc ctgactctgc ccttcgcggc 301 agcaggggct cttcagggct ggagtctggg aagtgccacc tgccgcacca tctctggcct 361 ctactcggcc tccttccacg ccggcttcct cttcctggcc tgtatcagcg ccgaccgcta 421 cgtggccatc gcgcgagcgc tcccagccgg gccgcggccc tccactcccg gccgcgcaca 481 cttggtctcc gtcatcgtgt ggctgctgtc actgctcctg gcgctgcctg cgctgctctt 541 cagccaggat gggcagcggg aaggccaacg acgctgtcgc ctcatcttcc ccgagggcct 601 cacgcagacg gtgaaggggg cgagcgccgt ggcgcaggtg gccctgggct tcgcgctgcc 661 gctgggcgtc atggtagcct gctacgcgct tctgggccgc acgctgctgg ccgccagggg 721 gcccgagcgc cggcgtgcgc tgcgcgtcgt ggtggctctg gtggcggcct tcgtggtgct 781 gcagctgccc tacagcctcg ccctgctgct ggatactgcc gatctactgg ctgcgcgcga 841 gcggagctgc cctgccagca aacgcaagga tgtcgcactg ctggtgacca gcggcttggc 901 cctcgcccgc tgtggcctca atcccgttct ctacgccttc ctgggcctgc gcttccgcca 961 ggacctgcgg aggctgctac ggggtgggag ctgcccctca gggcctcaac cccgccgcgg 1021 ctgcccccgc cggccccgcc tttcttcctg ctcagctccc acggagaccc acagtctctc 1081 ctgggacaac tagggctgcg aatctagagg aggggcagg ctgagggtcg tgggaaaggg 1141 gagtaggtgg gggaacactg agaaagaggc agggacctaa agggactacc tctgtgcctt 1201 gccacattaa attgataaca tggaaatgag atgcaaccca acaa
14	AF215981.1 Exemplary nucleic	1 agagatgggg acggaggcca cagagcaggt ttcctggggc cattactctg gggatgaaga 61 ggacgcatac tcggctgagc cactgccgga gctttgctac aaggccgatg tccaggcctt 121 cagccgggcc ttccaaccca gtgtctccct gaccgtggct gcgctgggtc tggccggcaa

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	acid sequence encoding human CCR10	181 tggcctggtc ctggccaccc acctggcagc ccgacgcgca gcgcgctcgc ccacctctgc 241 ccacctgctc cagctggccc tggccgacct cttgctggcc ctgactctgc ccttcgcggc 301 agcaggggct cttcagggct ggagtctggg aagtgccacc tgccgcacca tctctggcct 361 ctactcggcc tccttccacg ccggcttcct cttcctggcc tgtatcagcg ccgaccgcta 421 cgtggccatc gcgcgagcgc tcccagccgg gccgcggccc tccactcccg gccgcgcaca 481 cttggtctcc gtcatcgtgt ggctgctgtc actgctcctg gcgctgcctg cgctgctctt 541 cagccaggat gggcagcggg aaggccaacg acgctgtcgc ctcatcttcc ccgagggcct 601 cacgcagacg gtgaaggggg cgagcgccgt ggcgcaggtg gccctgggct tcgcgctgcc 661 gctgggcgtc atggtagcct gctacgcgct tctgggccgc acgctgctgg ccgccagggg 721 gcccgagcgc cggcgtgcgc tgcgcgtcgt ggtggctctg gtggcggcct tcgtggtgct 781 gcagctgccc tacagcctcg ccctgctgct ggatactgcc gatctactgg ctgcgcgcga 841 gcggagctgc cctgccagca aacgcaagga tgtcgcactg ctggtgacca gcggcttggc 901 cctcgcccgc tgtggcctca atcccgttct ctacgccttc ctgggcctgc gcttccgcca 961 ggacctgcgg aggctgctac ggggtgggag ctcgccctca gggcctcaac cccgccgcgg 1021 ctgcccccgc cggccccgcc tttcttcctg ctcagctccc acggagaccc acagtctctc 1081 ctgggacaac tagggctgcg aatctagagg agggggcagg ctgagggtcg tgggaaaggg 1141 gagtaggtgg gggaacactg agaaagaggc agggacctaa agggactacc tctgtgcctt 1201 gccacattaa attgataaca tggaaatgaa aaaaaaaaaa aaaa
15	NP_057686.2 Exemplary amino acid sequence for human CCR10 precursor	1 mgteateqvs wghysgdeed aysaeplpel cykadvqafs rafqpsvslt vaalglagng 61 lvlathlaar raarsptsah llqlaladll laltlpfaaa galqgwslgs atcrtisgly 121 sasfhagflf lacisadryv aiaralpagp rpstpgrahl vsvivwllsl llalpallfs 181 qdgqregqrr crlifpeglt qtvkgasava qvalgfalpl gvmvacyall grtllaargp 241 errralrvvv alvaafvvlq lpyslalllld tadllaarer scpaskrkdv allvtsglal 301 arcglnpvly aflglrfrqd lrrllrggsc psgpqprrgc prrprlsscs aptethslsw 361 dn
16	P46092.3 Exemplary amino acid sequence for human CCR10 precursor	1 mgteateqvs wghysgdeed aysaeplpel cykadvqafs rafqpsvslt vaalglagng 61 lvlathlaar raarsptsah llqlaladll laltlpfaaa galqgwslgs atcrtisgly 121 sasfhagflf lacisadryv aiaralpagp rpstpgrahl vsvivwllsl llalpallfs 181 qdgqregqrr crlifpeglt qtvkgasava qvalgfalpl gvmvacyall grtllaargp 241 errralrvvv alvaafvvlq lpyslalllld tadllaarer scpaskrkdv allvtsglal 301 arcglnpvly aflglrfrqd lrrllrggsc psgpqprrgc prrprlsscs aptethslsw 361 dn
17	NM_005201.3 Exemplary nucleic acid sequence encoding human CCR8	1 tttgtagtgg gaggatacct ccagagaggc tgctgctcat tgagctgcac tcacatgagg 61 atacagactt tgtgaagaag gaattggcaa cactgaaacc tccagaacaa aggctgtcac 121 taaggtcccg ctgccttgat ggattataca cttgacctca gtgtgacaac agtgaccgac 181 tactactacc ctgatatctt ctcaagcccc tgtgatgcgg aacttattca gacaaatggc 241 aagttgctcc ttgctgtctt ttattgcctc ctgtttgtat tcagtcttct gggaaacagc 301 ctggtcatcc tggtccttgt ggtctgcaag aagctgagga gcatcacaga tgtatacctc 361 ttgaacctgg ccctgtctga cctgcttttt gtcttctcct tcccctttca gacctactat 421 ctgctggacc agtgggtgtt tgggactgta atgtgcaaag tggtgtctgg cttttattac 481 attggcttct acagcagcat gtttttcatc accctcatga gtgtggacag gtacctggct 541 gttgtccatg ccgtgtatgc cctaaaggtg aggacgatca ggatgggcac aacgctgtgc 601 ctggcagtat ggctaaccgc cattatggct accatcccat tgctagtgtt ttaccaagtg 661 gcctctgaag atggtgttct acagtgttat tcattttaca atcaacagac tttgaagtgg

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		721 aagatcttca ccaacttcaa aatgaacatt ttaggcttgt tgatcccatt caccatcttt 781 atgttctgct acattaaaat cctgcaccag ctgaagaggt gtcaaaacca caacaagacc 841 aaggccatca ggttggtgct cattgtggtc attgcatctt tacttttctg ggtcccattc 901 aacgtggttc ttttcctcac ttccttgcac agtatgcaca tcttggatgg atgtagcata 961 agccaacagc tgacttatgc cacccatgtc acagaaatca tttcctttac tcactgctgt 1021 gtgaaccctg ttatctatgc ttttgttggg gagaagttca agaaacacct ctcagaaata 1081 tttcagaaaa gttgcagcca aatcttcaac tacctaggaa gacaaatgcc tagggagagc 1141 tgtgaaaagt catcatcctg ccagcagcac tcctcccgtt cctccagcgt agactacatt 1201 ttgtgaggat caatgaagac taaatataaa aaacattttc ttgaatggca tgctagtagc 1261 agtgagcaaa ggtgtgggtg tgaaaggttt ccaaaaaaag ttcagcatga aggatgccat 1321 atatgttgtt gccaacactt ggaacacaat gactaaagac atagttgtgc atgcctggca 1381 caacatcaag cctgtgattg tgtttattga tgatgttgaa caagtggtaa ctttaaagga 1441 ttctgtatgc caagtgaaaa aaaaagatgt ctgacctcct tacatat
18	BC107159.1 Exemplary nucleic acid sequence encoding human CCR8	1 ctttgtgaag aaggaattgg caacactgaa acctccagaa caaaggctgt cactaaggtc 61 ccgctgcctt gatggattat acacttgacc tcagtgtgac aacagtgacc gactactact 121 accctgatat cttctcaagc ccctgtgatg cggaacttat tcagacaaat ggcaagttgc 181 tccttgctgt cttttattgc ctcctgtttg tattcagtct tctgggaaac agcctggtca 241 tcctggtcct tgtggtctgc aagaagctga ggagcatcac agatgtatac ctcttgaacc 301 tggccctgtc tgacctgctt tttgtcttct ccttcccctt tcagacctac tatctgctgg 361 accagtgggt gtttgggact gtaatgtgca aagtggtgtc tggcttttat tacattggct 421 tctacagcag catgtttttc atcaccctca tgagtgtgga caggtacctg gctgttgtcc 481 atgccgtgta tgccctaaag gtgaggacga tcaggatggg cacaacgctg tgcctggcag 541 tatggctaac cgccattatg gctaccatcc cattgctagt gttttaccaa gtggcctctg 601 aagatggtgt tctacagtgt tattcatttt acaatcaaca gactttgaag tggaagatct 661 tcaccaactt caaaatgaac attttaggct tgttgatccc attcaccatc tttatgttct 721 gctacattaa aatcctgcac cagctgaaga ggtgtcaaaa ccacaacaag accaaggcca 781 tcaggttggt gctcattgtg gtcattgcat ctttactttt ctgggtccca ttcaacgtgg 841 ttcttttcct cacttccttg cacagtatgc acatcttgga tggatgtagc ataagccaac 901 agctgactta tgccacccat gtcacagaaa tcatttcctt tactcactgc tgtgtgaacc 961 ctgttatcta tgcttttgtt ggggagaagt tcaagaaaca cctctcagaa atatttcaga 1021 aaagttgcag ccaaatcttc aactacctag gaagacaaat gcctagggag agctgtgaaa 1081 agtcatcatc ctgccagcag cactcctccc gttcctccag cgtagactac attttgtgag 1141 gatcaatgaa gactaaatat aaaaaacatt ttcttgaatg gcatgctagt agcagtgagc 1201 aaaggtgtgg gtgtgaaagg tttccaaaaa aagttcagca tgaaggatgc cgtgtgtgtt 1261 gttgccaaca cttggaacac gatgactggg gacgtggttg tgcatgcctg gcacaacatc 1321 aagcctgtga ttgtgtttat tgatgatgtt gaacaagtgg tggctttgga ggattctgta 1381 tgccaagtga aaggggagat gtctgacctc cttcatatag
19	NP_005192.1 Exemplary amino acid sequence for human CCR8 precursor	1 mdytldlsvt tvtdyyypdi fsspcdaeli qtngklllav fycllfvfsl lgnslvilvl 61 vvckklrsit dvyllnlals dllfvfsfpf qtyylldqwv fgtvmckvvs gfyyigfyss 121 mffitlmsvd rylavvhavy alkvrtirmg ttlclavwlt aimatipllv fyqvasedgv 181 lqcysfynqq tlkwkiftnf kmnilgllip ftifmfcyik ilhqlkrcqn hnktkairlv 241 livviasllf wvpfnvvlfl tslhsmhild gcsisqqlty athvteiisf thccvnpviy 301 afvgekfkkh lseifqkscs qifnylgrqm presceksss cqqhssrsss vdyil
20	AAI07160.1	1 mdytldlsvt tvtdyyypdi fsspcdaeli qtngklllav fycllfvfsl lgnslvilvl

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	Exemplary amino acid sequence for human CCR8 precursor	61 vvckklrsit dvyllnlals dllfvfsfpf qtyylldqwv fgtvmckvvs gfyyigfyss 121 mffitlmsvd rylavvhavy alkvrtirmg ttlclavwlt aimatipllv fyqvasedgv 181 lqcysfynqq tlkwkiftnf kmnilglllip ftifmfcyik ilhqlkrcqn hnktkairlv 241 livviasllf wvpfnvvlfl tslhsmhild gcsisqqlty athvteiisf thccvnpviy 301 afvgekfkkh lseifqkscs qifnylgrqm presceksss cqqhssrsss vdyil
21	NM_005508.4 Exemplary nucleic acid sequence encoding human CCR4	1 gctcacagga agccacgcac ccttgaaagg caccgggtcc ttcttagcat cgtgcttcct 61 gagcaagcct ggcattgcct cacagacctt cctcagagcc gctttcagaa aagcaagctg 121 cttctggttg ggcccagacc tgccttgagg agcctgtaga gttaaaaaat gaaccccacg 181 gatatagcag acaccaccct cgatgaaagc atatacagca attactatct gtatgaaagt 241 atccccaagc cttgcaccaa agaaggcatc aaggcatttg gggagctctt cctgccccca 301 ctgtattcct tggtttttgt atttggtctg cttggaaatt ctgtggtggt tctggtcctg 361 ttcaaataca agcggctcag gtccatgact gatgtgtacc tgctcaacct tgccatctcg 421 gatctgctct tcgtgttttc cctccctttt tggggctact atgcagcaga ccagtgggtt 481 tttgggctag gtctgtgcaa gatgatttcc tggatgtact tggtgggctt ttacagtggc 541 atattctttg tcatgctcat gagcattgat agatacctgg caattgtgca cgcggtgttt 601 tccttgaggg caaggacctt gacttatggg gtcatcacca gtttggctac atggtcagtg 661 gctgtgttcg cctcccttcc tggctttctg ttcagcactt gttatactga gcgcaaccat 721 acctactgca aaaccaagta ctctctcaac tccacgacgt ggaaggttct cagctccctg 781 gaaatcaaca ttctcggatt ggtgatcccc ttagggatca tgctgttttg ctactccatg 841 atcatcagga ccttgcagca ttgtaaaaat gagaagaaga acaaggcggt gaagatgatc 901 tttgccgtgg tggtcctctt ccttgggttc tggacacctt acaacatagt gctcttccta 961 gagaccctgg tggagctaga agtccttcag gactgcacct ttgaaagata cttggactat 1021 gccatccagg ccacagaaac tctggctttt gttcactgct gccttaatcc catcatctac 1081 ttttttctgg gggagaaatt tcgcaagtac atcctacagc tcttcaaaac ctgcaggggc 1141 ctttttgtgc tctgccaata ctgtgggctc ctccaaattt actctgctga cacccccagc 1201 tcatcttaca cgcagtccac catggatcat gatctccatg atgctctgta gaaaaatgaa 1261 atggtgaaat gcagagtcaa tgaactttcc acattcagag cttacttaaa attgtatttt 1321 agtaagagat tcctgagcca gtgtcaggag gaaggcttac acccacagtg gaaagacagc 1381 ttctcatcct gcaggcagct ttttctctcc cactagacaa gtccagcctg gcaagggttc 1441 acctgggctg aggcatcctt cctcacacca ggcttgcctg caggcatgag tcagtctgat 1501 gagaactctg agcagtgctt gaatgaagtt gtaggtaata ttgcaaggca aagactattc 1561 ccttctaacc tgaactgatg ggtttctcca gagggaattg cagagtactg gctgatggag 1621 taaatcgcta ccttttgctg tggcaaatgg gccctct
22	P51679.1 Exemplary amino acid sequence for human CCR4 precursor	1 mnptdiadtt ldesiysnyy lyesipkpct kegikafgel flpplyslvf vfgllgnsvv 61 vlvlfkykrl rsmtdvylln laisdllfvf slpfwgyyaa dqwvfglglc kmiswmylvg 121 fysgiffvml msidrylaiv havfslrart ltygvitsla twsvavfasl pgflfstcyt 181 ernhtycktk yslnsttwkv lssleinilg lviplgimlf cysmiirtlq hcknekknka 241 vkmifavvvl flgfwtpyni vlfletlvel evlqdctfer yldyaiqate tlafvhccln 301 piiyfflgek frkyilqlfk tcrglfvlcq ycgllqiysa dtpsssytqs tmdhdlhdal
23	NM_001206609.1 Exemplary nucleic acid sequence encoding human	1 aatcatccga gaaccttgga gggtggacag tgccccttt acagatgaga aaactgaggc 61 ttgaaggga gaagcagctg cctctggcgg catggcttct ggctgcagga tgcccatgga 121 gttcgtggtg accctaggcc tgtgtctcgg cttcctttgc tgaacttgaa caggaagatg 181 gcagtggggg ccagtggtct agaaggagat aagatggctg gtgccatgcc tctgcaactc 241 ctcctgttgc tgatcctact gggccctggc aacagcttgc agctgtggga cacctgggca

SEQ ID NO:	GenBank Accession Number and Description	Sequence
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24	NM_003006.4 Exemplary nucleic acid sequence encoding human CLA	1 acacacagcc attgggggtt gctcggatcc gggactgccg caggggtgc cacagcagtg 61 cctggcagcg tgggctggga ccttgtcact aaagcagaga agccacttct tctgggccca 121 cgaggcagct gtcccatgct ctgctgagca cggtggtgcc atgcctctgc aactcctcct 181 gttgctgatc ctactgggcc ctggcaacag cttgcagctg tgggacacct gggcagatga 241 agccgagaaa gccttgggtc ccctgcttgc ccgggaccgg agacaggcca ccgaatatga 301 gtacctagat tatgatttcc tgccagaaac ggagcctcca gaaatgctga ggaacagcac 361 tgacaccact cctctgactg ggcctggaac ccctgagtct accactgtgg agcctgctgc

SEQ ID NO:	GenBank Accession Number and Description	Sequence
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25	NP_001193538.1 Exemplary amino acid sequence for human CLA precursor	1 mavgasgleg dkmagamplq lllllillgp gnslqlwdtw adeaekalgp llardrrqat 61 eyeyldydfl peteppemlr nstdttpltg pgtpesttve paarrstgld aggavteltt 121 elanmgnlst dsaameiqtt qpaateaqtt qpvpteaqtt plaateaqtt rltateaqtt 181 plaateaqtt ppaateaqtt qptgleaqtt apaameaqtt apaameaqtt ppaameaqtt 241 qttameaqtt apeateaqtt qptateaqtt plaamealst epsatealsm epttkrglfi 301 pfsvssvthk gipmaasnls vnypvgapdh isvkqcllai lilalvatif fvctvvlavr 361 lsrkghmypv rnysptemvc issllpdgge gpsatanggl skakspgltp epredregdd 421 ltlhsflp
26	NP_002997.2	1 mplqllllli llgpgnslql wdtwadeaek algpllardr rqateyeyld ydflpetepp

SEQ ID NO:	GenBank Accession Number and Description	Sequence
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4.4. Chimeric Antigen Receptors

[0044] When the cells provided herein are T lymphocytes which comprise homing receptors, as described above, such T lymphocytes can, in certain embodiments, comprise chimeric antigen receptors (CARs), which are artificial membrane-bound proteins that direct a T lymphocyte to an antigen, and stimulate the T lymphocyte to kill a cell displaying the antigen. See, e.g., Eshhar, U.S. Patent No. 7,741,465. At a minimum, the CAR comprises an extracellular domain that binds to an antigen, e.g., an antigen on a cell, a transmembrane domain, and an intracellular (cytoplasmic) signaling domain that transmits a primary activation signal to an immune cell. All other conditions being satisfied, when the CAR is expressed on the surface of, e.g., a T lymphocyte, for example, a primary T lymphocyte, and the extracellular domain of the CAR binds to an antigen, the intracellular signaling domain transmits a signal to the T lymphocyte to activate and/or proliferate, and, if the antigen is present on a cell surface, to kill the cell expressing the antigen. Because T lymphocytes require two signals, a primary activation signal and a costimulatory signal, in order to maximally activate, typically CARs also comprise a costimulatory domain such that binding of the antigen to the extracellular domain results in transmission of both a primary activation signal and a costimulatory signal.

4.4.1. General CAR Structure Intracellular Domain

[0045] In certain embodiments, the intracellular domain of the CAR is or comprises an intracellular domain or motif of a protein that is expressed on the surface of T lymphocytes and triggers activation and/or proliferation of said T lymphocytes. Such a domain or motif is able to transmit a primary antigen-binding signal that is necessary for the activation of a T lymphocyte

in response to the antigen's binding to the CAR's extracellular portion. Typically, this domain or motif comprises, or is, an ITAM (immunoreceptor tyrosine-based activation motif). ITAM-containing polypeptides suitable for CARs include, for example, the zeta CD3 chain (CD3ζ) or ITAM-containing portions thereof. In a specific embodiment, the intracellular domain is a CD3ζ intracellular signaling domain. In other specific embodiments, the intracellular domain is from a lymphocyte receptor chain, a TCR/CD3 complex protein, an Fc receptor subunit or an IL-2 receptor subunit.

[0046] In certain embodiments, the CAR additionally comprises one or more co-stimulatory domains or motifs, e.g., as part of the intracellular domain of the polypeptide. The one or more co-stimulatory domains or motifs can be, or comprise, one or more of a co-stimulatory CD27 polypeptide sequence, a co-stimulatory CD28 polypeptide sequence, a co-stimulatory OX40 (CD134) polypeptide sequence, a co-stimulatory 4-1BB (CD137) polypeptide sequence, or a co-stimulatory inducible T-cell costimulatory (ICOS) polypeptide sequence, or other costimulatory domain or motif.

[0047] The transmembrane region can be any transmembrane region that can be incorporated into a functional CAR, typically a transmembrane region from a CD4 or a CD8 molecule.

4.4.2. CAR Extracellular Domain

[0048] The extracellular domain of the polypeptide binds to an antigen of interest. In certain embodiments of any of the polypeptides described herein, the extracellular domain comprises a receptor, or a portion of a receptor, that binds to said antigen. The extracellular domain may be, e.g., a receptor, or a portion of a receptor, that binds to said antigen. In certain embodiments, the extracellular domain comprises, or is, an antibody or an antigen-binding portion thereof. In specific embodiments, the extracellular domain comprises, or is, a single-chain Fv domain. The single-chain Fv domain can comprise, for example, a V_L linked to V_H by a flexible linker, wherein said V_L and V_H are from an antibody that binds said antigen.

[0049] The antigen to which the extracellular domain of the polypeptide binds can be any antigen of interest, e.g., can be an antigen on a tumor cell. The tumor cell may be, e.g., a cell in a solid tumor, or a cell of a blood cancer. The antigen can be any antigen that is expressed on a cell of any tumor or cancer type, e.g., cells of a lymphoma, a lung cancer, a breast cancer, a prostate cancer, an adrenocortical carcinoma, a thyroid carcinoma, a nasopharyngeal carcinoma,

a melanoma, e.g., a malignant melanoma, a skin carcinoma, a colorectal carcinoma, a desmoid tumor, a desmoplastic small round cell tumor, an endocrine tumor, an Ewing sarcoma, a peripheral primitive neuroectodermal tumor, a solid germ cell tumor, a hepatoblastoma, a neuroblastoma, a non-rhabdomyosarcoma soft tissue sarcoma, an osteosarcoma, a retinoblastoma, a rhabdomyosarcoma, a Wilms tumor, a glioblastoma, a myxoma, a fibroma, a lipoma, or the like. In more specific embodiments, said lymphoma can be chronic lymphocytic leukemia (small lymphocytic lymphoma), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, MALT lymphoma, nodal marginal zone B cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt's lymphoma, T lymphocyte prolymphocytic leukemia, T lymphocyte large granular lymphocytic leukemia, aggressive NK cell leukemia, adult T lymphocyte leukemia/lymphoma, extranodal NK/T lymphocyte lymphoma, nasal type, enteropathy-type T lymphocyte lymphoma, hepatosplenic T lymphocyte lymphoma, blastic NK cell lymphoma, mycosis fungoides, Sezary syndrome, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, angioimmunoblastic T lymphocyte lymphoma, peripheral T lymphocyte lymphoma (unspecified), anaplastic large cell lymphoma, Hodgkin lymphoma, or a non-Hodgkin lymphoma.

[0050] In certain embodiments, the antigen is a tumor-associated antigen or a tumor-specific antigen. In various specific embodiments, without limitation, the tumor-associated antigen or tumor-specific antigen is Her2, prostate stem cell antigen (PSCA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, calretinin, MUC-1, epithelial membrane protein (EMA), epithelial tumor antigen (ETA), tyrosinase, melanoma-associated antigen (MAGE), CD19, CD34, CD45, CD99, CD117, chromogranin, cytokeratin, desmin, glial fibrillary acidic protein (GFAP), gross cystic disease fluid protein (GCDFP-15), HMB-45 antigen, high molecular weight melanoma-associated antigen (HMW-MAA), protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), myo-D1, muscle-specific actin (MSA), neurofilament, neuron-specific enolase (NSE), placental alkaline phosphatase, synaptophysis, thyroglobulin, thyroid transcription factor-1, the dimeric form of the pyruvate kinase isoenzyme type M2 (tumor M2-PK), an abnormal ras protein, or an abnormal p53 protein.

[0051] In certain embodiments, the TAA or TSA is a cancer/testis (CT) antigen, e.g., BAGE, CAGE, CTAGE, FATE, GAGE, HCA661, HOM-TES-85, MAGEA, MAGEB, MAGEC, NA88, NY-ESO-1, NY-SAR-35, OY-TES-1, SPANXB1, SPA17, SSX, SYCP1, or TPTE.

[0052] In certain other embodiments, the TAA or TSA is a carbohydrate or ganglioside, e.g., fuc-GM1, GM2 (oncofetal antigen-immunogenic-1; OFA-I-1); GD2 (OFA-I-2), GM3, GD3, and the like.

[0053] In certain other embodiments, the TAA or TSA is alpha-actinin-4, Bage-1, BCR-ABL, Bcr-Abl fusion protein, beta-catenin, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, Casp-8, cdc27, cdk4, cdkn2a, CEA, coa-1, dek-can fusion protein, EBNA, EF2, Epstein Barr virus antigens, ETV6-AML1 fusion protein, HLA-A2, HLA-A11, hsp70-2, KIAAO205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RARα fusion protein, PTPRK, K-ras, N-ras, triosephosphate isomerase, Gage 3,4,5,6,7, GnTV, Herv-K-mel, Lage-1, NA-88, NY-Eso-1/Lage-2, SP17, SSX-2, TRP2-Int2, gp100 (Pmel 17), tyrosinase, TRP-1, TRP-2, MAGE-1, MAGE-3, RAGE, GAGE-1, GAGE-2, p15(58), RAGE, , SCP-1, Hom/Mel-40, PRAME, p53, H-Ras, HER-2/neu, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, 13-Catenin, Mum-1, p16, TAGE, PSMA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, 13HCG, BCA225, BTAA, CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB\70K, NY-CO-1, RCAS1, SDCCAG16, TA-90, TAAL6, TAG72, TLP, TPS, CD19, CD22, CD27, CD30, CD70, GD2 (ganglioside G2), EGFRvIII (epidermal growth factor variant III), sperm protein 17 (Sp17), mesothelin, PAP (prostatic acid phosphatase), prostein, TARP (T cell receptor gamma alternate reading frame protein), Trp-p8, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), an abnormal ras protein, or an abnormal p53 protein. In another specific embodiment, said tumor-associated antigen or tumor-specific antigen is integrin αvβ3 (CD61), galactin, K-Ras (V-Ki-ras2 Kirsten rat sarcoma viral oncogene), or Ral-B. Other tumor-associated and tumor-specific antigens are known to those in the art.

[0054] Antibodies, and scFvs, that bind to TSAs and TAAs are known in the art, as are nucleotide sequences that encode them.

[0055] In certain specific embodiments, the antigen is an antigen not considered to be a TSA or a TAA, but which is nevertheless associated with tumor cells, or damage caused by a tumor. In certain embodiments, for example, the antigen is, e.g., a growth factor, cytokine or interleukin, e.g., a growth factor, cytokine, or interleukin associated with angiogenesis or vasculogenesis. Such growth factors, cytokines, or interleukins can include, e.g., vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), or interleukin-8 (IL-8). Tumors can also create a hypoxic environment local to the tumor. As such, in other specific embodiments, the antigen is a hypoxia-associated factor, e.g., HIF-1α, HIF-1β, HIF-2α, HIF-2β, HIF-3α, or HIF-3β. Tumors can also cause localized damage to normal tissue, causing the release of molecules known as damage associated molecular pattern molecules (DAMPs; also known as alarmins). In certain other specific embodiments, therefore, the antigen is a DAMP, e.g., a heat shock protein, chromatin-associated protein high mobility group box 1 (HMGB1), S100A8 (MRP8, calgranulin A), S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), or can be a deoxyribonucleic acid, adenosine triphosphate, uric acid, or heparin sulfate.

[0056] In a specific embodiment, in which the cancer a gastrointestinal cancer, for example, liver cancer, stomach cancer, esophageal cancer, gallbladder cancer, colorectal cancer, anal cancer, or pancreatic cancer, the antigen is an antigen specific for or associated with a gastrointestinal cancer. In a specific embodiment, T lymphocytes provided herein express a gastrointestinal homing receptor and also express a CAR with an extracellular domain that binds to an antigen associated with a gastrointestinal cancer. In a specific embodiment, the extracellular domain of the CAR binds CEA. In other specific embodiments, the extracellular domain of the CAR binds Her2, CA242, MUC1, CA125, or CA19-9.

[0057] In a specific embodiment, in which the cancer is a skin cancer, for example, melanoma, squamous cell carcinoma, or basal cell carcinoma, the antigen is an antigen specific for or associated with a skin cancer. In a specific embodiment, T lymphocytes provided herein express a skin homing receptor and also express a CAR with an extracellular domain that binds to an antigen associated with a skin cancer. In a specific embodiment, the extracellular domain of the CAR binds HMW-MAA. In other specific embodiments, the extracellular domain of the CAR binds Her2, GD2, GD3, CEA, or SPAG9.

[0058] In certain embodiments of the polypeptides described herein, the extracellular domain is joined to said transmembrane domain by a linker, spacer or hinge polypeptide sequence, e.g., a sequence from CD28.

4.5. Isolated Nucleic Acids

[0059] In one embodiment, provided herein are polynucleotide sequences that encode the polypeptides provided herein (e.g., chimeric receptors and homing receptors). The polynucleotides may be contained within any polynucleotide vector suitable for the transformation of immune cells, e.g., T lymphocytes. For example, T lymphocytes may be transformed using synthetic vectors, lentiviral or retroviral vectors, autonomously replicating plasmids, a virus (e.g., a retrovirus, lentivirus, adenovirus, or herpes virus), or the like, containing polynucleotides encoding the first and second polypeptides (e.g., chimeric receptors). Lentiviral vectors suitable for transformation of T lymphocytes include, but are not limited to, e.g., the lentiviral vectors described in U.S. Patent Nos. 5,994,136; 6,165,782; 6,428,953; 7,083,981; and 7,250,299, the disclosures of which are hereby incorporated by reference in their entireties. HIV vectors suitable for transformation of T lymphocytes include, but are not limited to, e.g., the vectors described in U.S. Patent No. 5,665,577, the disclosure of which is hereby incorporated by reference in its entirety.

[0060] Nucleic acids useful in the production of the polypeptides provided herein, e.g., within a T lymphocyte, include DNA, RNA, or nucleic acid analogs. Nucleic acid analogs can be modified at the base moiety, sugar moiety, or phosphate backbone, and can include deoxyuridine substitution for deoxythymidine, 5-methyl-2'-deoxycytidine or 5-bromo-2'-deoxycytidine substitution for deoxycytidine. Modifications of the sugar moiety can include modification of the 2' hydroxyl of the ribose sugar to form 2'-O-methyl or 2'-O-allyl sugars. The deoxyribose phosphate backbone can be modified to produce morpholino nucleic acids, in which each base moiety is linked to a six membered, morpholino ring, or peptide nucleic acids, in which the deoxyphosphate backbone is replaced by a pseudopeptide backbone and the four bases are retained. See, for example, Summerton and Weller (1997) Antisense Nucleic Acid Drug Dev. 7:187-195; and Hyrup et al. (1996) Bioorgan. Med. Chain. 4:5-23. In addition, the deoxyphosphate backbone can be replaced with, for example, a phosphorothioate or phosphorodithioate backbone, a phosphoroamidite, or an alkyl phosphotriester backbone.

[0061] A nucleic acid encoding a polypeptide provided herein may be introduced into host cells as part of a vector, such as, *e.g.*, an expression vector. In addition, a polypeptide provided herein may be produced by transfecting a host cell with a nucleic acid encoding such a polypeptide, and such nucleic acid may be part of a vector. In a specific embodiment, the vector is an expression vector that is capable of directing the expression of a nucleic acid encoding a polypeptide provided herein. Non-limiting examples of expression vectors include, but are not limited to, plasmids and viral vectors, such as replication defective retroviruses, adenoviruses, adeno-associated viruses, Newcastle disease virus, vaccinia virus and baculoviruses. Standard molecular biology techniques may be used to introduce a nucleic acid encoding a polypeptide provided herein into an expression vector.

[0062] An expression vector comprises a nucleic acid encoding a polypeptide provided herein in a form suitable for expression of the nucleic acid in a host cell or non-human subject. In a specific embodiment, an expression vector includes one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid to be expressed. Within an expression vector, "operably linked" is intended to mean that a nucleic acid of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleic acid (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). Regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Regulatory sequences include those which direct constitutive expression of a nucleic acid in many types of host cells, those which direct expression of the nucleic acid only in certain host cells (*e.g.*, tissue-specific regulatory sequences), and those which direct the expression of the nucleic acid upon stimulation with a particular agent (e.g., inducible regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as, *e.g.*, the choice of the host cell to be transformed, the level of expression of protein desired, etc.

[0063] An expression vector can be introduced into host cells via conventional transformation or transfection techniques. Such techniques include, but are not limited to, calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, and electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook et al., 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, New York, and other laboratory manuals. In certain embodiments, a host cell is

transiently transfected with an expression vector containing a nucleic acid encoding a polypeptide provided herein. In other embodiments, a host cell is stably transfected with an expression vector containing a nucleic acid encoding a polypeptide provided herein.

4.6. Cells

[0064] Non-limiting examples of cells in which the homing receptors may be used include, but are not limited to, natural killer (NK) cells, dendritic cells (DC), placental stem cells (e.g., the placental stem cells disclosed in U.S. Patent Nos. 7,468,276; 8,057,788 and 8,202,703, the disclosures of which are hereby incorporated by reference in their entireties), mesenchymal-like stem cells from umbilical cord blood, placental blood, peripheral blood, bone marrow, dental pulp, adipose tissue, osteochondral tissue, and the like; embryonic stem cells, embryonic germ cells, neural crest stem cells, neural stem cells, and differentiated cells (e.g., fibroblasts, etc.). The homing receptors may also be used in tumor cell lines, e.g., for animal model experimental purposes.

[0065] In a specific embodiment, the cells comprising the polypeptides provided herein are T lymphocytes. The T lymphocytes comprising the polypeptides provided herein may be naive T lymphocytes or MHC-restricted T lymphocytes. In certain embodiments, the T lymphocytes are tumor infiltrating lymphocytes (TILs). In certain embodiments, the T lymphocytes have been isolated from a tumor biopsy, or have been expanded from T lymphocytes isolated from a tumor biopsy. In certain other embodiments, the T lymphocytes have been isolated from, or are expanded from T lymphocytes expanded from, peripheral blood, cord blood, or lymph.

[0066] In certain embodiments, the immune cells, e.g., T lymphocytes, used in the present methods are autologous to an individual to whom the T lymphocytes are to be administered. In certain embodiments, the T lymphocytes are allogeneic to an individual to whom the T lymphocytes are to be administered. Where allogeneic T lymphocytes are used to prepare T lymphocytes, it is preferable to select T lymphocytes that will reduce the possibility of graft-versus-host disease (GVHD) in the individual. For example, in certain embodiments, virus-specific T lymphocytes are selected for preparation of T lymphocytes; such lymphocytes will be expected to have a greatly reduced native capacity to bind to, and thus become activated by, any recipient antigens. In certain embodiments, recipient-mediated rejection of allogeneic T

lymphocytes can be reduced by co-administration to the host of one or more immunosuppressive agents, e.g., cyclosporine, tacrolimus, sirolimus, cyclophosphamide, or the like.

[0067] In one embodiment, T lymphocytes are obtained from an individual, optionally then expanded, and then transformed with a polynucleotide encoding one or more homing receptors, and optionally one or more polynucleotides encoding one or more CAR(s), and optionally then expanded. In another embodiment, T lymphocytes are obtained from an individual, optionally then expanded, and then transformed with a polynucleotide encoding one or more homing receptors, and optionally one or more polynucleotides encoding one or more CAR(s), and optionally then expanded. Cells containing any of the polynucleotide may be selected using one or more selectable markers.

[0068] In certain embodiments, any of the T lymphocytes provided herein express or comprise native TCR proteins, e.g., TCR-α and TCR-β that are capable of forming native TCR complexes. In certain other embodiments, either or both of the native genes encoding TCR-α and TCR-β in the T lymphocytes are modified to be non-functional, e.g., a portion or all are deleted, a mutation is inserted, etc.

[0069] In certain embodiments, any of the T lymphocytes provided herein are isolated from a tumor lesion, e.g., are tumor-infiltrating lymphocytes; such T lymphocytes are expected to be specific for a TSA or TAA.

[0070] T lymphocytes, and T lymphocytes comprising a polypeptide comprising a CD3ζ signaling domain and a CD28 co-stimulatory domain can be expanded using antibodies to CD3 and CD28, e.g., antibodies attached to beads, or to the surface of a cell culture plate; see, e.g., U.S. Patent Nos. 5,948,893; 6,534,055; 6,352,694; 6,692,964; 6,887,466; and 6,905,681.

[0071] In certain embodiments, the antigen and/or antibody can exist free in the medium in which the T lymphocytes are cultured, or either or both can be attached to a solid support, e.g., tissue culture plastic surface, beads, or the like.

4.7. Methods of Using Cells Comprising Homing Receptors

[0072] In one aspect, the cells, e.g., T lymphocytes, provided herein that comprise one or more homing receptors and optionally one or more CARs, as described elsewhere herein, are used to treat an individual having one or more types of cells desired to be targeted by the cells described

herein, e.g., one or more types of cells to be killed. In certain embodiments, the cells to be killed are cancer cells, e.g., tumor cells. In specific embodiments, the cancer cells are cells of a solid tumor. In specific embodiments, the cells are cells of a lymphoma, a lung cancer, a breast cancer, a prostate cancer, an adrenocortical carcinoma, a thyroid carcinoma, a nasopharyngeal carcinoma, a melanoma, e.g., a malignant melanoma, a skin carcinoma, a colorectal carcinoma, a desmoid tumor, a desmoplastic small round cell tumor, an endocrine tumor, an Ewing sarcoma, a peripheral primitive neuroectodermal tumor, a solid germ cell tumor, a hepatoblastoma, a neuroblastoma, a non-rhabdomyosarcoma soft tissue sarcoma, an osteosarcoma, a retinoblastoma, a rhabdomyosarcoma, a Wilms tumor, a glioblastoma, a myxoma, a fibroma, a lipoma, or the like. In more specific embodiments, said lymphoma can be chronic lymphocytic leukemia (small lymphocytic lymphoma), B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, MALT lymphoma, nodal marginal zone B cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt's lymphoma, T lymphocyte prolymphocytic leukemia, T lymphocyte large granular lymphocytic leukemia, aggressive NK cell leukemia, adult T lymphocyte leukemia/lymphoma, extranodal NK/T lymphocyte lymphoma, nasal type, enteropathy-type T lymphocyte lymphoma, hepatosplenic T lymphocyte lymphoma, blastic NK cell lymphoma, mycosis fungoides, Sezary syndrome, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, angioimmunoblastic T lymphocyte lymphoma, peripheral T lymphocyte lymphoma (unspecified), anaplastic large cell lymphoma, Hodgkin lymphoma, or a non-Hodgkin lymphoma.

[0073] In certain embodiments, the modified cells, e.g., modified T lymphocytes described herein are administered to a subject in need thereof, such that the combination of homing receptors selected is compatible with the patient population (or subpopulation) in which the cells, e.g., T lymphocytes, have been administered. For example, the combination of homing receptors is chosen based on the type of tumor or cancer present in the patient.

[0074] In specific embodiments, T lymphocytes expressing gastrointestinal homing receptors are administered to patients having a gastrointestinal tumor or cancer. In certain embodiments, the gastrointestinal tumor or cancer is esophageal cancer, stomach cancer, liver cancer,

gallbladder cancer, pancreatic cancer, colorectal cancer, or anal cancer. In a specific embodiment, said T cells further comprise a CAR with an extracellular domain that binds to an antigen associated with a gastrointestinal tumor or cancer.

[0075] In other specific embodiments, T lymphocytes expressing skin homing receptors are administered to patients having a skin tumor or cancer. In certain embodiments, the skin tumor or cancer is melanoma, basal cell carcinoma, or squamous cell carcinoma. In a specific embodiment, said T cells further comprise a CAR with an extracellular domain that binds to an antigen associated with a skin tumor or cancer. In specific embodiments, the T lymphocytes comprising a homing receptor also comprise a CAR with an extracellular domain that binds to an antigen expressed in the tumor or cancer cells of the patient.

[0076] Efficacy of the cells, e.g., T lymphocytes, after administration to an individual having a disease or disorder remediable by such cells, e.g., T lymphocytes, e.g., an individual having cancer, can be assessed by one or more criteria, specific to the particular disease or disorder, known to those of ordinary skill in the art, to be indicative of progress of the disease or disorder. Generally, administration of the cells to such an individual is effective when one or more of said criteria detectably, e.g., significantly, moves from a disease state value or range to, or towards, a normal value or range.

[0077] In certain embodiments, the cells, e.g., T lymphocytes, are formulated in a pharmaceutically-acceptable solution. In preferred embodiments, the pharmaceutically-acceptable solution is suitable for the delivery of living cells. In specific embodiments, the pharmaceutically-acceptable solution is, for example, saline solution (such as Ringer's solution), gelatins, carbohydrates (e.g., lactose, amylose, starch, or the like), fatty acid esters, hydroxymethylcellulose, or polyvinyl pyrolidine. In more specific embodiments, the pharmaceutically-acceptable solution is sterilized prior to addition of the cells. In other more specific embodiments, the pharmaceutically-acceptable solution may be mixed with auxiliary agents such as lubricants, preservatives, stabilizers, emulsifiers, salts for influencing osmotic pressure, buffers, and coloring. Pharmaceutical carriers suitable for use in formulating the cells are known in the art and are described, for example, in WO 96/05309.

[0078] In certain embodiments, the cells, e.g., T lymphocytes, are formulated into individual doses, wherein said individual doses comprise at least, at most, or about 1×10^4, 5×10^4, 1×10^5,

5×10^5, 1×10^6, 5×10^6, 1×10^7, 5×10^7, 1×10^8, 5×10^8, 1×10^9, 5×10^9, 1×10^{10}, 5×10^{10}, or 1×10^{11} T lymphocytes. In certain embodiments, the cells, e.g., T lymphocytes, are formulated into individual doses, wherein said individual does comprise a range from 1×10^4 to 5×10^4, 5×10^4 to 1×10^5, 1×10^5 to 5×10^5, 5×10^5 to 1×10^6, 1×10^6 to 5×10^6, 5×10^6 to 1×10^7, 1×10^7 to 5×10^7, 5×10^7 to 1×10^8, 1×10^8 to 5×10^8, 5×10^8 to 1×10^9, 1×10^9 to 5×10^9, 5×10^9 to 1×10^{10}, 1×10^{10} to 5×10^{10}, or 5×10^{10} to 1×10^{11} T lymphocytes. In certain embodiments, the cells are formulated for intravenous, intra-arterial, parenteral, intramuscular, subcutaneous, intrathecal, or intraocular administration, or administration within a particular organ or tissue.

5. EXAMPLES

5.1. Example 1: Generation of Murine CXCR5$^+$ CAR T Cells and *in vivo* Study

[0079] T lymphocytes are obtained from the spleen of B6 Thy 1.1 mice. A lentiviral construct comprising a chimeric antigen receptor (CAR) comprising humanized mouse anti-human CEA-scFv or anti-human HER2-scFv and mouse co-stimulation intracellular domain and CD3ζ is generated. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a mouse CXCL13 chemotaxis assay.

[0080] For the *in vivo* assay, the activities of murine CXCR5+ CAR T cells are compared to the activities of CXCR5- CAR T cells and non-transduced T cells. Human CEA (or HER2)-transgenic mice that can spontaneously develop CEA+ gastrointestinal tumors (or HER2+ mammary tumors) are used as subjects. Adoptive transfer of the cells is accomplished with one or more doses by intravenous administration.

[0081] To examine the location of adoptively transferred CAR T cells in draining lymph nodes, (mesenteric lymph nodes for CEA transgenic mice or axillary lymph nodes for HER2 transgenic mice), a readout assay is done via draining lymph node immunohistochemistry. Animals are sacrificed and the draining lymph nodes are identified. Lymph nodes are grasped with curved forceps and pulled free of attached tissue. Lymph nodes are embedded in optimal cutting temperature compound and frozen on dry ice, and then stored at -80˚C. Cryosections are cut, air-dried, and fixed in acetone. Sections are pre-incubated with rabbit (or goat) serum at room temperature, and subsequently incubated with primary antibodies (rat anti-mouse CD3, CD8, CD4, biotinylated mouse anti-mouse Thy-1.1, biotinylated goat-anti-human IgG (H+L)), and biotinylated rabbit (or goat) anti-rat IgG (mouse adsorbed) followed by avidin-peroxidase (or

fluorochrome) conjugate. Then sections are incubated with substrate of peroxidase for color development. The images of immunohistochemistry staining results are acquired using confocal microscopy. Donor T cells are identified via anti-mouse Thy1.1 and CAR T cells are identified with anti-human IgG.

[0082] To examine the antigen-specific immune response establishment in the draining lymph nodes, a readout assay is done via flow cytometry of CAR T cells isolated from draining lymph nodes. Phenotypic characterization of surface markers Thy 1.1, anti-human IgG, CXCR5, CD69, and HLA-DR is performed. CD69 is a marker for activated T cells. HLA-DR is a marker for antigen-presenting cells. Functional evaluation is done to assay proliferation, Ki67 expression, and numerization of CAR T cells. Cytokine production is evaluated by intracellular cytokine staining upon stimulation.

[0083] To examine tumor killing activity of CAR T cells in a tumor site, tumor volume and survival are assayed. Volumes of tumors are determined *in vivo* by external caliper. The greatest longitudinal diameter (length) and the greatest transverse diameter (width) are determined. Tumor volume based on caliper measurements are calculated by the modified ellipsoidal formula: tumor volume = ½(length × width^2).

5.2. Example 2: Generation of Human CXCR5$^+$ CAR T Cells

[0084] T lymphocytes are obtained from human PBMCs. A lentiviral construct comprising a chimeric antigen receptor (CAR) composed of humanized mouse anti-human CEA-scFv or anti-human HER2-scFv and human co-stimulation intracellular domain and CD3ζ is generated and used to transduce the T cells to create a population of CEA-specific CAR T cells. The CAR T cells are further transduced with lentiviral vectors containing nucleic acid sequences encoding human CXCR5; CAR T cells expressing CXCR5 are selected for further study. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a human CXCL13 chemotaxis assay.

5.3. Example 3: Generation of Murine Gastrointestinal Homing CAR T Cells and *in vivo* Study

[0085] T lymphocytes are obtained from the spleen of mice. CAR T cells are generated using a lentiviral construct, as described above, containing a nucleotide sequence encoding a CAR

comprising a humanized mouse anti-human CEA-scFv and mouse co-stimulation intracellular domain and CD3ζ. The gastrointestinal homing receptors are introduced via lentiviral transduction of mouse CCR9 and α4β7 nucleic acid sequences. Retinoic acid treatment is performed during T cell activation. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a mouse TECK (thymus expressed chemokine, or CCL25) chemotaxis assay (Binger, et al., 2009, *Experimental Cell Research* 315:1468-79). The chemotactic response to TECK is assessed using 5 μm pore-size polycarbonate membranes in 96-multiwell format chemotaxis plates. Lower wells containing TECK in deprivation medium are separated from the upper wells by the membrane. The T cells, in deprivation medium, are seeded into the upper wells and incubated at 37°C for 20 hours. Non-migrated cells left on top of the membrane are removed. Migrated cells are fixed, stained, and enumerated microscopically or are enumerated via flow cytometry with counting beads. Negative controls are performed with deprivation medium without chemokine, and positive controls are performed with medium for cell culturing containing 10% FBS.

[0086] For an *in vivo* assay, human CEA-transgenic mice that can spontaneously develop CEA+ gastrointestinal tumors are used as subjects. Adoptive transfer of the cells is accomplished with one or more doses by intravenous administration.

[0087] To examine the location of adoptively transferred CAR T cells in established gastrointestinal tract tumors, a readout assay is done via gastrointestinal tract immunohistochemistry. Animals are sacrificed and the gastrointestinal tracts are removed. The small intestine is sectioned into 4-5 parts before immersion fixation. Sections are pre-incubated with rabbit (or goat) serum at room temperature, and subsequently incubated with primary antibodies (rat anti-mouse CD3, biotinylated mouse anti-mouse Thy-1.1, biotinylated goat-anti-human IgG (H+L)), and biotinylated rabbit (or goat) anti-rat IgG (mouse adsorbed) followed by avidin-peroxidase (or fluorochrome) conjugate. Then sections are incubated with substrate of peroxidase for color development. The images of immunohistochemistry staining results are acquired using microscopy. Donor T cells are identified via anti-mouse Thy1.1 and CAR T cells are identified with anti-human IgG. qRT-PCR or PCR of gastrointestinal tract for detection of migrated CAR T cells in the tissue is also performed.

[0088] To examine the antigen-specific immune response establishment in the gastrointestinal tract, a readout assay is done via flow cytometry of CAR T cells isolated from the gastrointestinal tract. Phenotypic characterization of surface markers Thy 1.1, anti-human IgG, CCR9, α4β7, CD69, and HLA-DR is performed. Functional evaluation is done to assay proliferation, Ki67 expression, and numerization of CAR T cells. Cytokine production is evaluated by intracellular cytokine staining upon stimulation.

[0089] To examine tumor killing activity of CAR T cells in a tumor site, tumor volume and survival are assayed.

5.4. Example 4: Generation of Human Gastrointestinal Homing CAR T Cells

[0090] T lymphocytes are obtained from human PBMCs. Generation of CAR T cells is performed using a CAR comprising humanized mouse anti-human CEA-scFv and mouse co-stimulation intracellular domain and CD3ζ. The CAR T cells are further transduced with lentiviral vectors containing nucleic acid sequences encoding human CCR9 and α4β7; CAR T cells expressing both of these proteins are selected for further study. During subsequent T cell activation, the CAR T cells are contacted with retinoic acid such that the level of the CCR9 and α4β7 are increased as compared to CAR T cells expressing these two proteins, but not contacted with retinoic acid. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a human TECK chemotaxis assay.

5.5. Example 5: Generation of Mouse Skin Homing CAR T cells and *in vivo* Study

[0091] T lymphocytes are obtained from mouse spleen. Generation of CAR T cells is performed using a CAR comprising humanized mouse anti-human HMW-MAA-scFv and mouse co-stimulation intracellular domain and CD3ζ. The CAR T cell s are further transduced with lentiviral vectors containing nucleic acid sequences encoding human CCR10 or CCR4, and/or CLA; CAR T cells expressing both of these proteins are selected for further study. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a mouse CCL27 chemotaxis assay. The chemotactic response to CCL27 is assessed using 5 μm pore-size polycarbonate membranes in 96-multiwell format chemotaxis plates. Lower wells containing CCL27 in deprivation medium are separated from the upper wells by the membrane. The T cells, in deprivation medium, are seeded into the upper wells and incubated at 37°C for 20 hours. Non-migrated cells left on top of the membrane are removed. Migrated cells are fixed, stained,

and enumerated microscopically or are enumerated via flow cytometry with counting beads. Negative controls are performed with deprivation medium without chemokine, and positive controls are performed with medium for cell culturing containing 10% FBS.

[0092] For the *in vivo* assay, immunodeficient mice engrafted with human melanoma cell line that expresses HMW-MAA are used as subjects. Cells are administered through adoptive transfer with multiple doses of intravenous administration.

[0093] To examine the location of adoptively transferred CAR T cells in established melanoma, a readout assay is done via immunohistochemistry. Donor T cells are identified via anti-CD3 and CAR T cells are identified with anti-mouse IgG. qRT-PCR or PCR for detection of migrated CAR T cells in the tissue is also performed.

[0094] To examine the antigen-specific immune response establishment in the melanoma, a readout assay is done via flow cytometry of CAR T cells isolated from the melanoma. Phenotypic characterization of surface markers CD3, anti-mouse IgG, CCR10 (or CCR4), CLA, CD69, and HLA-DR is performed. Functional evaluation is done to assay proliferation, Ki67 expression, and numerization of CAR T cells. Cytokine production is evaluated by intracellular cytokine staining upon stimulation.

[0095] To examine tumor killing activity of CAR T cells in a tumor site, tumor volume and survival are assayed.

5.6. Example 6: Generation of Human Skin Homing CAR T cells

[0096] T lymphocytes are obtained from human PBMCs. CAR T cells generation is performed using a CAR composed of humanized mouse anti-human HMW-MAA-scFv and human co-stimulation intracellular domain and CD3ζ. The gastrointestinal homing receptors are introduced via lentiviral transduction of human CCR10 or CCR4, and CLA nucleic acid sequences. Treatment with $1,25(OH)_2VD_3$ and IL-12 is performed during T cell activation. Validation of the CAR T cells is done via phenotypic characterization and functional evaluation via a human CCL27 chemotaxis assay, as in Example 5.

5.7. Example 7: Treatment of Gastrointestinal Tumor

[0097] An individual presents with a gastrointestinal tumor, for example, adenomatous polyposis coli. Testing of tumor cells from the individual determines that the tumor cells express

CEA. T lymphocytes are obtained from the individual, transfected with a lentiviral vector comprising a nucleotide sequence that encodes a chimeric antigen receptor (CAR), and transfected with a second lentiviral vector comprising a nucleotide sequence encoding human CCR9 and/or α4β7 nucleic acid sequences. The T lymphocytes are expanded using CD3+CD28-coated beads in the presence of retinoic acid to sufficient numbers for administration. The chimeric receptor comprises an extracellular antigen-binding region that binds to CEA; a transmembrane domain; an intracellular co-stimulatory domain from CD28; and an intracellular CD3ζ domain. The individual is administered between 10^9 and 10^{10} of the T lymphocytes in 200 mL saline solution by intravenous infusion over 30 minutes. The individual is re-assessed for the gastrointestinal tumor stage and spread to lymph nodes, and histology of biopsied gastrointestinal tissue is performed at 30, 60, and 90 days post-administration.

5.8. Example 8: Treatment of Melanoma

[0098] An individual presents with melanoma. Testing of tumor cells from the individual determines that the tumor cells express HMW-MAA. T lymphocytes are obtained from the individual, transfected with a lentiviral vector comprising a nucleotide sequence that encodes a chimeric antigen receptor (CAR), and transfected with a second lentiviral vector comprising a nucleotide sequence encoding human CCR10 (or CCR4) and CLA nucleic acid sequences. The T lymphocytes are expanded using CD3+CD28-coated beads in the presence of $1,25(OH)_2VD_3$ and IL-12 to sufficient numbers for administration. The chimeric receptor comprises an extracellular antigen-binding region that binds to HMW-MAA; a transmembrane domain; an intracellular co-stimulatory domain from CD28; and an intracellular CD3ζ domain. The individual is administered between 10^9 and 10^{10} of the T lymphocytes in 200 mL saline solution by intravenous infusion over 30 minutes. The individual is re-assessed for the melanoma stage and spread to lymph nodes, and histology of biopsied skin tissue is performed at 30, 60, and 90 days post-administration.

EQUIVALENTS

[0099] The present disclosure is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the subject matter provided herein, in addition to those described, will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[00100] Various publications, patents and patent applications are cited herein, the disclosures of which are incorporated by reference in their entireties.

[00101] The T lymphocytes of the invention are for use in the methods disclosed herein

CLAIMS

1. A T lymphocyte expressing: (i) a B cell zone homing receptor not normally expressed by the T lymphocyte, (ii) a skin homing receptor or a gastrointestinal homing receptor, and (iii) a chimeric antigen receptor (CAR).

2. The T lymphocyte of claim 1, wherein the B cell zone homing receptor is CXCR5.

3. The T lymphocyte of claim 1, wherein the B cell homing receptor is encoded by the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:2, or comprises the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:4.

4. The T lymphocyte of any one of claims 1-3, wherein the T lymphocyte comprises a skin homing receptor.

5. The T lymphocyte of claim 4, wherein the skin homing receptor is CLA, CCR4, or CCR10.

6. The T lymphocyte of any one of claims 1-3, wherein the T lymphocyte comprises a gastrointestinal homing receptor.

7. The T lymphocyte of claim 6, wherein said gastrointestinal homing receptor is integrin α4β7 or CCR9.

8. A T lymphocyte comprising: (i) a B cell zone homing receptor not normally expressed by the T lymphocyte, (ii) a skin homing receptor or a gastrointestinal homing receptor, and (iii) a CAR; wherein said T lymphocyte is for use in the treatment of cancer or a tumor in an individual; wherein said T lymphocyte is to be administered to the individual; and wherein the cancer is a skin cancer, melanoma, squamous cell carcinoma, basal cell carcinoma, splenic marginal zone lymphoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, colorectal cancer, stomach cancer, liver cancer, or pancreatic cancer.

9. The T lymphocyte for use according to claim 8, wherein the B cell zone homing receptor is CXCR5.

10. The T lymphocyte for use according to claim 8, wherein the B cell zone homing receptor is encoded by the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:2, or comprises the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:4.

11. The T lymphocyte for use according to claim 8, wherein the T lymphocyte comprises a skin homing receptor.

12. The T lymphocyte for use according to claim 11, wherein said skin homing receptor is CLA, CCR4, or CCR10.

13. The T lymphocyte for use according to claim 8, wherein the T lymphocyte comprises a gastrointestinal homing receptor.

14. The T lymphocyte for use according to claim 13, wherein said gastrointestinal homing receptor is integrin α4β7 or CCR9.

15. The T lymphocyte of any one of claims 1-3, or the T lymphocyte for use according to any one of claims 8-10, wherein said CAR comprises an extracellular domain, and said extracellular domain binds an antigen selected from the group consisting of: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen-125 (CA-125), CA19-9, tyrosinase, melanoma-associated antigen (MAGE), CD19, CD117, protein melan-A (melanoma antigen recognized by T lymphocytes; MART-1), hsp70-2, gp100 (Pmel 17), CA 72-4, and CD22.

16. The T lymphocyte of any one of claims 1, 4, and 5, or the T lymphocyte for use according to any one of claims 8, 11, and 12, wherein said CAR comprises an extracellular domain, and said extracellular domain binds CEA.

17. The T lymphocyte of any one of claims 1, 6, and 7, or the T lymphocyte for use according to any one of claims 8, 13, and 14, wherein said CAR comprises an extracellular domain, and said extracellular domain binds an antigen selected from the group consisting of: CEA, CA125, and CA19-9.

18. The T lymphocyte of claim 17, wherein said extracellular domain binds CEA.