



(43) International Publication Date
18 February 2016 (18.02.2016)

(51) International Patent Classification:

C12N 5/22 (2006.01) A61K 35/17 (2015.01)
C12N 5/0783 (2010.01)

(21) International Application Number:

PCT/US2015/044611

(22) International Filing Date:

11 August 2015 (11.08.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/036,447 12 August 2014 (12.08.2014) US

(71) Applicant: ANTHROGENESIS CORPORATION
[US/US]; 7 Powder Hom Drive, Warren, NJ 07059 (US).

(72) Inventors: LIANG, Bitao; 65 Bethany Circle, Closter, NJ 07624 (US). LIU, Wei; 392 Vanderveer Road, Bridgewater, NJ 08807 (US). LI, Tianjian; 19 Deer Run Drive, Belle Mead, NJ 08502 (US).

(74) Agents: GEORGE, Nikolaos, C. et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(88) Date of publication of the international search report:

7 April 2016



WO 2016/025454 A3

(54) Title: CAR-T LYMPHOCYTES ENGINEERED TO HOME TO LYMPH NODE B CELL ZONE, SKIN, OR GASTROINTESTINAL TRACT

(57) Abstract: In one embodiment, provided herein are cells, e.g., T cells expressing receptors that cause a cell expressing the receptors to home to specific anatomical regions, e.g., the B cell zone of lymph nodes, the gastrointestinal tract, or the skin. Also provided herein is use of such cells, e.g., T lymphocytes, to treat diseases such as cancer.

**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 $\alpha 4\beta 7$ (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 $\alpha 4\beta 7$.

[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)₂D₃). 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 $\alpha 4\beta 7$. 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 ($1,25(\text{OH})_2\text{D}_3$). 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 T 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, synaptophysin, 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, KIAA0205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α 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, NB70K, 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 $\alpha\beta$ 3 (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 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 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, synaptophysin, 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, KIAA0205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α 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 $\alpha v \beta 3$ (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 $\alpha 4 \beta 7$, for example, human CCR9 or human integrin $\alpha 4 \beta 7$. 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 $\alpha 4$ and human $\beta 7$, respectively. GenBank™ accession numbers NP_000876.3 and NP_000880.1 provide exemplary amino acid sequences for human $\alpha 4$ and human $\beta 7$, 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 $\alpha 4\beta 7$. 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 $\alpha 4\beta 7$, 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 $\alpha 4\beta 7$, 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 $\alpha 4\beta 7$. 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 $\alpha 4\beta 7$. 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 $\alpha 4\beta 7$. 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. GenBankTM accession numbers NM_016602.2 and AF215981.1 provide exemplary nucleotide sequences for human CCR10. GenBankTM accession numbers NP_057686.2 and P46092.3 provide exemplary amino acid sequences for human CCR10. GenBankTM accession numbers NM_005201.3 and BC107159.1 provide exemplary nucleotide sequences for human CCR8. GenBankTM accession numbers NP_005192.1 and AAI07160.1 provide exemplary amino acid sequences for human CCR8. GenBankTM accession number NM_005508.4 provides an exemplary nucleotide sequence for human CCR4. GenBankTM accession number P51679.1 provides an exemplary amino acid sequence for human CCR4. GenBankTM accession numbers NM_001206609.1 and NM_003006.4 provide exemplary nucleotide sequences for human CLA. GenBankTM 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)₂D₃). 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)₂D₃. 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 ttgetttaat ttgcagctga cggctgccac ctctctagag gcacctggcg 121 gggagcctct caacataaga cagtgaccag tctggtgact cacagccggc acagccatga 181 actaccoget aacgctggaa atggacctcg agaacctgga ggacctgttc tgggaactgg 241 acagattgga caactataac gacacctccc tggggaaaa tcatctctgc cctgccacag 301 aggggccctt catggcctcc ttcaaggccg tgttcgtgcc cgtggcctac agcctcatct 361 tctcctggg cgtgatcgcc aacgtcctgg tgctggtgat cctggagcgg caccggcaga 421 cacgcagttc cacggagacc ttctgttcc acctggccgt ggccgacctc ctgctggtct

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>481 tcatcttgcc ctttgccgtg gccgagggt ctgtgggctg ggtcctgggg accttctct 541 gcaaaactgt gattgccctg cacaaagtca acttctactg cagcagcctg ctctctggcct 601 gcatcgccgt ggaccgctac ctggccattg tccacgccgt ccatgcctac cgccaccgcc 661 gcctcctctc catccacatc acctgtggga ccatctggct ggtgggcttc ctctctgct 721 tgccagagat tctcttcgcc aaagttagcc aaggccatca caacaactcc ctgcccactt 781 gcaccttctc ccaagagaac caagcagaaa cgcatgcctg gttcacctcc cgattcctct 841 accatgtggc gggattcctg ctgcccactg tggatgatgg ctggtgctac gtgggggtag 901 tgccagagtt gcgccaggcc cagcggcgcc ctccagcgga gaaggcagtc aggggtggca 961 tcttggtgac aagcatcttc ttcctctgct ggtcacctca ccacatcgtc atcttctctg 1021 acaccctggc gaggtgaag gccgtggaca atacctgcaa gctgaatggc tctctccccg 1081 tggccatcac catgtgtgag ttcctgggcc tggcccactg ctgcctcaac cccatgctct 1141 acactttcgc cggcgtgaag ttccgagtg acctgtcgcg gctcctgacg aagctgggct 1201 gtaccggccc tgcctcctg tgccagctct tccctagctg gcgcaggagc agtctctctg 1261 agtcagagaa tgcccactct ctcaccactg tctaggtccc agtgtcccct tttattgctg 1321 cttttccttg gggcaggcag tgatgtgga tgctccttcc aacaggagct gggatcctaa 1381 gggctcaccg tggctaagag tgtcctagga gtatcctcat ttggggtagc tagaggaacc 1441 aacccccatt tctagaacat ccttgcagc tcttctgcc gccctggggc taggctggag 1501 cccaggagc ggaaagcagc tcaaaggcac agtgaaggct gtccttacc atctgcacc 1561 ccttggctg agagaacctc acgcacctcc catcctaac atccaatgct caagaaacaa 1621 cttctacttc tgccttgc aacggagagc gcctgcccct cccagaacac actccatcag 1681 cttaggggct gctgacctcc acagcttccc ctctctctc ctgcccact gtcaaaaaa 1741 gccagaagct gagcaccagg ggatgagtgg aggttaaggc tgaggaaagg ccagctggca 1801 gcagagtgtg gccttcggac aactcagtcc ctaaaaacac agacattctg ccaggcccc 1861 aagcctgcag tcatcttgac caagcaggaa gctcagactg gttgagttca ggtagctgcc 1921 cctggctctg accgaaacag cgctgggtcc acccctatgc accggatcct ggggtggtctg 1981 caggcagggc tgactctagg tgcccttggg gccagccag tgacctgagg aagcgtgaag 2041 gccgagaagc aagaaagaaa cccgacagag ggaagaaaag agctttcttc ccgaaccca 2101 aggagggaga tggatcaatc aaaccggcg gtcccctccg ccaggcgaga tgggtgggg 2161 tggagaactc ctagggtggc tgggtccagg ggatgggagg ttgtgggcat tgatggggaa 2221 ggaggctggc ttgtcccctc ctactccct tcccataagc tatagaccg aggaactca 2281 gagtcggaac ggagaaaggt ggactggaag gggcccgtgg gactcatctc aaccatcccc 2341 tccgtggcat caccttaggc agggaaagtgt aagaaacaca ctgaggcagg gaagtcccc 2401 ggccccagga agcctgccc tgccccctg aggatgtcac tcagatggaa ccgagggaag 2461 ctgctccgtg cttgtttgct cacctggggt gtgggaggcc cgtccggcag ttctgggtgc 2521 tccctaccac ctcccagcc tttgatcagg tggggagtca gggaccctg ccctgtctcc 2581 actcaagcca agcagccaag ctcttggga ggcccactg gggaaataac agctgtggct 2641 cacgtgagag tgtcttcacg gcaggacaac gaggaagccc taagacgtcc ctttttctc 2701 tgagtatctc ctgcgaagct gggtaacga tgggggagtc tgaagcagat gcaagaggc 2761 aagaggctgg attttgaatt ttctttttaa taaaaaggca cctataaac aggtcaatac 2821 agtacaggca gcacagagac ccccggaaca agcctaaaaa ttgtttcaaa ataaaaacca 2881 agaagatgct ttcacatatt gtaaaaaaaa aaaaaaaaa</p>
2	<p>NM_032966.2 Exemplary nucleic acid sequence encoding human</p>	<p>1 ccaactaag gaatgcggtc cctttgacag gcgaaaaact gaagttggaa aagacaaagt 61 gatttgttca aaattgaaat ttgaaacttg acatttggct agtgggccc atgtaggaaa 121 aaacctcaa gagagctagg gttcctctca gagaggaaa acaggtcctt aggtcctcac 181 cctcccgtct ccttgccctt gcagttctgg gaactggaca gattggacaa ctataacgac 241 acctccctgg tggaaaaatca tctctgccct gccacagagg ggcccctcat ggcctcctc</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	CXCR5	<p>301 aaggccgtgt tCGTgcccgt ggcctacagc ctcAtcttcc tcctgggCGt gatcggcaac 361 gtCctggTgc tggTgatCct ggagcggcac cggcagacac gcagttccac ggagaccttC 421 ctgttccacc tggccgtggc cgacctcctg ctggcttcca tcttgccctt tgccgtggcc 481 gagggctctg tgggctgggt cctggggacc ttcctctgca aaactgtgat tgcctgcac 541 aaagtcaact tctactgcag cagcctgctc ctggcctgca tcgccgtgga ccgctacctg 601 gccattgtcc acgccgtcca tgcctaccgc caccgcccgc tcctctccat ccacatcacc 661 tgtgggacca tctggctggT gggcttctc cttgcttgc cagagattct cttcgccaaa 721 gtCagccaag gccatcacia caactccctg ccacgttgca ccttctcca agagaaccaa 781 gcagaaacgc atgcctggtt cacctcccga ttcctctacc atgtggcggg attcctgctg 841 cccatgctgg tgatgggctg gtgctacgtg ggggtagtgc acagttgctg ccaggcccag 901 cggcgcctc agcggcagaa ggcagtCagg gtggccatcc tggTgacaag catcttcttC 961 ctctgctggT caccctacca catcgtcatc ttcctggaca ccctggcgag gctgaaggcc 1021 tgggacaata cctgcaagct gaatggctct ctcCCcgtgg ccatcaccat gtgtgagttC 1081 ctgggcctgg cccactgctg cctcaacccc atgctctaca ctttgcccg cgtgaagttc 1141 cgCagtgacc tgtcgcggct cctgacgaag ctgggctgta ccggccctgc ctcctgtgc 1201 cagctcttcc ctagctggcg caggagcagt ctctctgagt cagagaatgc cacctctctC 1261 accacgttct aggtcccagt gtcccctttt attgctgctt ttcctgggg caggcagtga 1321 tgttgatgc tcctccaac aggagctggg atcctaaggg ctcaccgtgg ctaagagtgt 1381 ctaggagta tcctcatTTg gggtagctag aggaaccaac cccatttct agaacatccc 1441 tgccagctct tctgccggcc ctggggctag gctggagccc agggagcggg aagcagctca 1501 aaggcacagt gaaggctgtc cttaccatc tgcaccccc tgggctgaga gaacctcacg 1561 cacctcccat cctaatac cAatgtcaa gaaacaact ctacttctgc cctgccaac 1621 ggagagcgc tgcCCctccc agaacacact ccatcagctt aggggctgct gacctccaca 1681 gcttccctc tctcctcctg cccactgtc aaacaagcc agaagctgag caccagggga 1741 tgagtggagg ttaaggctga ggaaaggcca gctggcagca gagtgtggcc ttcggacaac 1801 tcagtcccta aaaacacaga cattctgcca ggcccccaag cctgcagtca tctgaccaa 1861 gcaggaagct cagactgggt gagttcaggt agctgcccct ggctctgacc gaaacagcgc 1921 tgggtccacc ccatgtcacc ggatcctggg tggctgCag gcagggtga ctctaggtgc 1981 ccttgaggc cagccagtga cctgaggaag cgtgaaggcc gagaagcaag aaagaaaccc 2041 gacagaggga agaaaagagc tttcttccc aacccaag agggagatgg atcaatcaaa 2101 cccggcggtc ccctccgcca ggcgagatgg ggtggggtg agaactccta gggTggctg 2161 gtccagggga tgggaggtt tgggcattga tggggaagga ggctggctt tcccctcctC 2221 actccctcc cataagctat agacccgagg aaactcagag tcggaacgga gaaaggtgga 2281 ctggaagggg ccctgggg tcatctcaac catcccctc gtggcatcac cttaggcagg 2341 gaagtgtAag aaacacactg aggcaggga gtccccagg cccaggaagc cgtgccctgc 2401 ccccgtagg atgtcactca gatggaaccg caggaagctg ctccgtgctt gttgtctcAc 2461 ctgggggtgt ggaggccgt cggcagttc tgggtgctcc ctaccacct cccagccttt 2521 gatcaggtg ggagtcaggg acccctgccc ttgtcccact caagccaagc agccaagctc 2581 cttgggaggc cccactggg aaataacagc tgtggctcac gtgagagtgt cttcacggca 2641 ggacaacgag gaagccctaa gacgtccctt tttctctga gtatctcctc gcaagctggg 2701 taatcgatg gggagtctga agcagatgca aagaggcaag aggtggatt ttgaattttC 2761 tttttaataa aaaggcacct ataaaacagg tcaatacagt acaggcagca cagagacccc 2821 cggaacaagc ctaaaaattg tttcaaaata aaaaccaaga agatgtcttc acatattgta 2881 aaaaaaaaa aaaaaa</p>
3	NP_116743.1	<p>1 masfkavfvp vayslifllg vignvlvlvi lerhrqtrss tetflfhlav adlllvfilp 61 favaegsvgw vlgtfllcktv ialhkvnfyc sllllaciav drylaihvhav hayrhrlls</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	Exemplary amino acid sequence for human CXCR5 precursor	121 ihitcgtiwl vgfllalpei lfakvsqghh nnsldrctfs qenqaethaw ftsrfllyhva 181 gfillpmlvmg wcyvgvvhrl rqaqrrpqrq kavrvailvt sifflwspy hivifldtla 241 rlkavdntck lngslpvait mceflglahc clnplytfa gvkfrsdlr lltklgctgp 301 aslcqlfsw rrsllsesen atslttf
4	NP_001707.1 Exemplary amino acid sequence for human CXCR5 precursor	1 mnypltlemd lenledlfe ldrlndyndt slvenhlcpa tegplmasfk avfvpvaysl 61 ifllgvignv lvlvilerhr qtrsstetfl fhlavadlll vfilpfavae gsvgwvlgtf 121 lcktvialhk vnfycslll aciavdryla ivhavhayrh rrlsihitc gtiwlvgfl 181 alpeilfakv sqghhnsllp rctfsqenqa ethawftrsf lyhvagflp mlvmgwcyyg 241 vvhrlrqaqr rpqrqkavrv ailvtsiffl cwspyhivif ldtlarlkav dntcklngsl 301 pvaitmcefl glahcclnpm lytfagvkfr sdlsrlltkl gctgpaslq lfpwrrssl 361 sesenatslt tf
5	NM_031200.2 Exemplary nucleic acid sequence encoding human CCR9	1 gcttccttcc tegtgtgtgt atcgggtagc tgccctgctca gaaccacaca agcctgcccc 61 tcatcccagg cagagagcaa cccagctctt tcccagaca ctgagagctg gtgggtgctg 121 ctgtcccagg gagagtgcga tgcctctcca cagagcaggc ttgcatctga ctgaccacc 181 atgacacca cagacttccac aagccctatt cctaactatg ctgatgacta tggctctgaa 241 tccacatctt ccatggaaga ctacgttaac ttcaacttca ctgacttcta ctgtgagaaa 301 aacaatgtca ggcagtttg gagccatttc ctcccacct tgtactggct cgtgttcac 361 gtgggtgctt tgggcaacag tcttgttata cttgtctact ggtactgcac aagagtgaag 421 accatgaccg acatgttctt tttgaatttg gcaattgctg acctcctctt tctgtcact 481 ctccctctct gggccattgc tgctgctgac cagtgaagt tccagacct catgtgcaag 541 gtgggtcaaca gcatgtacaa gatgaacttc tacagctgtg tttgtctgat catgtgcatc 601 agcgtggaca ggtacattgc cattgcccag gccatgagag cacatacttg gagggagaaa 661 aggcctttgt acagcaaaa ggtttgcttt accatctggg tattggcagc tgctctctgc 721 atcccagaaa tcttatacag ccaaatcaag gaggaatccg gcattgctat ctgaccatg 781 gtttaccta gcgatgagag caccaaactg aagtcagctg tcttgaccct gaaggtcatt 841 ctgggggtct tccttccctt cgttgctcat gcttgctgct ataccatcat cattcacacc 901 ctgatacaag ccaagaagtc ttccaagcac aaagccctaa aagtgacct cactgtcctg 961 accgtctttg tcttgtctca gtttccttac aactgcattt tggttggtgca gaccattgac 1021 gcctatgcca tgttcatctc caactgtgcc gtttccacca acattgacat ctgcttccag 1081 gtcaccagca ccatgcctt cttccacagt tgccgaacc ctgttctcta tgtttttgtg 1141 ggtgagagat tccgcccagg tctctgaaa accctgaaga acttgggttg catcagccag 1201 gccagtgagg ttctatttac aaggagagag ggaagcttga agctgtcgtc tatgttgctg 1261 gagacaacct caggagcact ctccctctga ggggtcttct ctgaggtgca tggttctttt 1321 ggaagaaatg agaaatacag aaacagtttc cccactgatg ggaccagaga gagtgaaga 1381 gaaaagaaaa ctcaaaagg gatgaatctg aactatatga ttactttag tagaatttg 1441 ccaagcaaaa tattcaaaa tcaactgact agtgaggag gctgttgatt ggctcttgac 1501 tgtgatgccc gcaattctca aaggaggact aaggaccggc actgtggagc accctggctt 1561 tgccactcgc cggagcatca atgcccctgc ctctggagga gcccttggat tttctccatg 1621 cactgtgaac ttctgtgget tcagttctca tgctgctct tccaaaagg gacacagaag 1681 cactggctgc tgctacagac cgcaaaagca gaaagtttcg tgaaaatgtc catctttggg 1741 aaattttcta ccctgctctt gagcctgata acccatgcca ggtcttatag attcctgatc 1801 tagaaccttt ccaggcaatc tcagacctaa tttcctctg ttctccttgt tctgttctgg 1861 gccagtgaag gtccttgttc tgattttgaa acgatctgca ggtcttgcga gtgaacctc 1921 ggacaactga ccacaccac aaggcatcca aagtctgtt gcttccaatc catttctgtg 1981 tctgtctgga ggttttaacc tagacaagga ttccgcttat tcttgggtat ggtgacagt

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		2041 tctctccatg gcctgagcag ggagattata acagctgggt tcgcaggagc cagccttggc 2101 cctggttag gcttgttctg ttgagtggca cttgctttgg gtccaccgtc tgtctgctcc 2161 ctagaaaatg ggctggttct tttggccctc ttctttctga ggcccacttt attctgagga 2221 atacagtgag cagatatggg cagcagccag gtagggcaaa ggggtgaagc gcaggccttg 2281 ctggaaggct atttacttcc atgcttctcc ttttcttact ctatagtggc aacattttaa 2341 aagcttttaa cttagagatt aggctgaaaa aaataagtaa tggaattcac ctttgcattc 2401 tttgtgtcct tcttatcatg atttggcaaa atgcatcacc tttgaaaata tttcacatat 2461 tggaaaagtg ctttttaaatg tgtatatgaa gcattaatta cttgtcactt tctttaccct 2521 gtctcaatat ttttaagtgtg tgcaattaaa gatcaaatag atacatt
6	NM001256369.1 Exemplary nucleic acid sequence encoding human CCR9	1 gcttccttcc tcgtgtgtgt atcgggtagc tgccctgctca gaaccacaa agcctgcccc 61 tcatcccagg cagagagcaa cccagctctt tccccagaca ctgagagctg gtggtgacctg 121 ctgtcccagg gagagtgtga tcgccctcca cagagcaggc ttgcatctga ctgaccacc 181 atgacacca cagacttccac atctctcca ggcccgcctc cagatcacct tccctcgctg 241 gccaggaat ccatctcctt ccaggacctt agcccaggac taacacaagc cctattccta 301 acatggctga tgactatggc tctgaatcca catcttccat ggaagactac gtttaactca 361 acttactga cttctactgt gagaaaaaca atgtcaggca gtttgcgagc catttcctcc 421 cacccttcta ctggctcgtg ttcactcgtg gtgccttggg caacagtctt gttatccttg 481 tctactgta ctgcacaaga gtgaagacca tgaccgacat gttccttttg aatttggcaa 541 ttgctgacct cctcttctt gtcactcttc ccttctgggc cattgctgct gctgaccagt 601 ggaagtcca gacctcatg tgcaagggtg tcaacagcat gtacaagatg aacttctaca 661 gctgtgtgtt gctgatcatg tgcatcagcg tggacaggta cattgccatt gccaggcca 721 tgagagcaca tacttgagg gagaaaaggc ttttgtacag caaaatggtt tgctttacca 781 tctgggtatt ggcagctgct ctctgcatcc cagaaatctt atacagccaa atcaaggagg 841 aatccgcat tgctatctgc accatggttt accctagcga tgagagcacc aaactgaagt 901 cagctgtcct gaccctgaag gtcattctgg ggttcttctt tcccttcgtg gtcattgctt 961 gctgctatac catcatcatt cacacctga tacaagccaa gaagtcttcc aagcacaag 1021 cctaaaagt gaccatcact gtcctgaccg tctttgtcct gtctcagttt cctacaact 1081 gcattttgtt ggtgcagacc attgacgctt atgccatgtt catctccaac tgtgccgttt 1141 ccaccaacat tgacatctgc ttccagggtca cccagaccat cgccttcttc cacagttgcc 1201 tgaacctgt tctctatggt tttgtgggtg agagattccg ccgggatctc gtgaaaacc 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 ttgtagttag aatttgccaa agcaaatatt tcaaatcaa ctgactagt 1561 caggaggctg ttgattggtt cttgactgtg atgcccgcaa ttctcaaagg aggactaagg 1621 accggcactg tggagcacc tggtcttggc actcgcggga gcatcaatgc cgctgcctct 1681 ggaggagccc ttggattttc tccatgcact gtgaacttct gtggttccag ttctcatgct 1741 gctcttcca aaaggggaca cagaagcact ggctgctgct acagaccgca aaagcagaaa 1801 gtttcgtgaa aatgtccatc tttgggaaat tttctaccct gctcttgagc ctgataacc 1861 atgccaggtc ttatagattc ctgatctaga accttccag gcaatctcag acctaatctc 1921 cttctgttct ccttgttctg ttctgggcca gtgaagggtc ttgttctgat tttgaaacga 1981 tctgcaggtc ttgccagtga acccctggac aactgaccac acccacaagg catccaaagt 2041 ctggttgctt ccaatccatt tctgtgtcct gctggagggt ttaacctaga caaggattcc 2101 gcttattcct tggatgggtg acagtgtctc tccatggcct gagcagggag attataacag 2161 ctgggttcgc aggagccagc cttggccctg ttgtaggctt gttctgttga gtggcacttg

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		2221 ctttgggtcc accgtetgtc tgctccctag aaaatgggct ggttcttttg gccctcttct 2281 ttctgaggcc cactttattc tgaggaatac agtgagcaga tatgggcagc agccaggtag 2341 ggcaaagggg tgaagcgcag gccttgctgg aaggctattht acttccatgc ttctcctttt 2401 cttactctat agtggcaaca ttttaaaagc ttttaactta gagattaggc tgaaaaaaat 2461 aagtaatgga attcaccttt gcatcttttg tgtctttctt atcatgattt ggcaaaatgc 2521 atcacctttg aaaatatctt acatattgga aaagtgcttt ttaatgtgta tatgaagcat 2581 taattacttg tcactttctt taccctgtct caatatttta agtgtgtgca attaaagatc 2641 aaatagatac att
7	NP_112477.1 Exemplary amino acid sequence for human CCR9 precursor	1 mtptdftspi pnmaddygse stssmedyvn fnftdfycekn nnvrfashf lpplywlvfi 61 vgalgnslvi lvywyctrvk tmdmflnl aiadllflvt lpfwaiaaad qwkfqtfmck 121 vnsmymkmnf yscvllimci svdryiaiaq amrahtwrek rllyskmvcf tiwvlaaalc 181 ipeilysqik eesgiaictm vypsdestkl ksavltlkvi lgfflpfvvm accyctiiht 241 liqakksskh kalkvtitvl tvfvlsgfpy ncillvqtid ayamfisnea vstnidicfq 301 vtqti affhs clnpvlyvfv gerfrrdlvk tlknlgcisq aqwvsftrre gsklssmll 361 ettsgalsl
8	NP_001243298.1 Exemplary amino acid sequence for human CCR9 precursor	1 maddygsest ssmedyvnfn ftdfycekn vrqfashflp plywlvfivg algnsilvilv 61 ywyctrvktm tdmflnlai adllflvtlp fwaiiaadqw kfqtfmckv nsmymkmfys 121 cvllimciv dryiaiaqam rahtwrekr lyskmvcfti wvlaaalcip eilysqiikee 181 sgiaictmvy psdestklks avltlkvilg fflpfvvmac cyctiihtli qakksskhka 241 lkvtitvltv fvlsqfpync illvqtiday amfisncavs tnidicfvqt qti affhscl 301 npvlyvfvge rfrddlvk tlnlgcisq wvsftrregs klssmlllet tsgalsl
9	NM_000885.4 Exemplary nucleic acid sequence encoding human $\alpha 4$	1 ataacgtctt tgctactaaa atgttcccga ggggccttcg gcgagtcttt ttgtttggtt 61 ttttgttttt aatctgtggc tcttgataat ttatctagtg gttgctaca cctgaaaaac 121 aagacacagt gtttaactat caacgaaaga actggacggc tcccgcgcgc agtcccactc 181 cccgagtttg tggtctggcat ttgggcccacg ccgggctggg cggctcacagc gaggggcccg 241 cagtttgagg tcacacagct ccgctctctag gcccacaacca ccgttaaaag ggggaagccc 301 tgccccatca ggtccgctct tgctgagccc agagccatcc cgcgctctgc gggctgggag 361 gcccgggcca ggacgcgagt cctgcgcagc cgaggttccc cagcgcctcc tgcagccgcg 421 cgtaggcaga gacggagccc ggccctgcgc ctccgcacca cgccggggac cccaccagc 481 gccccgtacc cggagaagca gcgcgagcac ccgaagctcc cggctggcgg cagaaccgg 541 gagtggggcc gggcgagtgc gcggcatccc agggccggcc gaacgctccg cccgcggtg 601 gccgacttcc cctcctcttc cctctctcct tccttagacc cgctggcgcc ggacacgctg 661 gcctcatct cttggggcgt tcttcccctg ttggccaaccg tcgcatcccg tgcaactttg 721 gggtagtggc cgtttagtgt tgaatgttcc ccaccgagag cgcatggctt ggggaagcag 781 gcgcgaaccc ggccccgaa gggcccgccg cgggagagac gtgatgctgt tgcgtgctc 841 gggggtccc accggccgc cctacaacgt ggacactgag agcgcgctgc tttaccaggg 901 cccccacaac acgctgttgc gctactcggc cgtgctgcac agccacgggg cgaaccgatg 961 gctcctagt ggtgcgcccc ctgccaaactg gctcgccaac gcttcagtga tcaatcccgg 1021 ggcgatttac agatgcagga tcgaaagaa tcccggccag acgtgcgaac agctccagct 1081 gggtagccct aatggagaac cttgtggaaa gacttgtttg gaagagagag acaatcagtg 1141 gttgggggtc acactttcca gacagccagg agaaaatgga tccatcgtga cttgtgggca 1201 tagatgaaa aatataattht acataaagaa tgaaaataag ctccccactg gtggttgcta 1261 tggagtccc cctgatttac gaacagaact gagtaaaaga atagctccgt gttatcaaga 1321 ttatgtgaaa aaatttgagg aaaattttgc atcatgtcaa gctggaatat ccagttttta

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		1381 cacaaaggat ttaattgtga tgggggcccc aggatcatct tactggactg gctctctttt 1441 tgtctacaat ataactacaa ataaatacaa ggctttttta gacaacaaaa atcaagtaaa 1501 atttggaagt tatttaggat attcagtcgg agctggcatc ttctggagcc agcatactac 1561 cgaagtagtc ggaggagctc ctcaacatga gcagattggt aaggcatata tattcagcat 1621 tgatgaaaaa gaactaaata tcttacatga aatgaaaggt aaaaagcttg gatcgtactt 1681 tggagcttct gtctgtgctg tggacctcaa tgcagatggc ttctcagatc tgctcgtggg 1741 agcaccatg cagagcacca tcagagagga aggaagagtg tttgtgtaca tcaactctgg 1801 ctogggagca gtaatgaatg caatggaaac aaacctcgtt ggaagtgaca aatagctgc 1861 aagatttggg gaatctatag ttaatcttgg cgacattgac aatgatggct ttgaagatgt 1921 tgctatcgga gctccacaag aagatgactt gcaaggtgct atttatattt acaatggccg 1981 tgcagatggg atctcgtcaa ccttctcaca gagaattgaa ggacttcaga tcagcaaatc 2041 gttaagtatg tttggacagt ctatatcagg acaaatgtat gcagataata atggctatgt 2101 agatgtagca gttggtgctt ttcggtctga ttctgctgct ttgctaagga caagacctgt 2161 agtaattggt gacgcttctt taagccaccc tgagtcagta aatagaacga aatttgactg 2221 tgttgaaaat ggatggcctt ctgtgtgcat agatctaaca ctttgtttct catataaggg 2281 caaggaagtt ccaggttaca ttgttttggg ttataacatg agtttggatg tgaacagaaa 2341 ggcagagtct ccaccaagat tctatttctc ttctaattga acttctgacg tgattacagg 2401 aagcatacag gtgtccagca gagaagctaa ctgtagaaca catcaagcat ttatgcgga 2461 agatgtgctg gacatcctca cccaattca gattgaagct gcttaccacc ttggtcctca 2521 tgtcatcagt aaacgaagta cagaggaatt cccaccactt cagccaattc ttcagcagaa 2581 gaaagaaaaa gacataatga aaaaaacaat aaactttgca aggtttttgtg cccatgaaaa 2641 ttgttctgct gatttacagg tttctgcaaa gattgggttt ttgaagcccc atgaaaataa 2701 aacatatctt gctgttggga gtatgaagac attgatggtt aatgtgtcct tgtttaatgc 2761 tggagatgat gcatatgaaa cgactctaca tgtcaacta cccgtgggtc tttatttcat 2821 taagatttta gagctggaag agaagcaaat aaactgtgaa gtcacagata actctggcgt 2881 ggtacaactt gactgcagta ttggctatat atatgtagat catctctcaa ggatagatat 2941 tagctttctc ctggatgtga gctcactcag cagagcggaa gaggacctca gtatcacagt 3001 gcatgctacc tgtgaaaatg aagaggaaat ggacaatcta aagcacagca gactgactgt 3061 agcaatacct ttaaaatgat aggttaagct gactgttcat gggtttgtaa acccaacttc 3121 atttgtgtat ggatcaaatg atgaaaatga gcctgaaacg tgcatggttg agaaaatgaa 3181 cttaactttc catgttatca acactggcaa tagtatggct cccaatgta gtgtggaat 3241 aatggtacca aattctttta gccccaaac tgataagctg ttcaacattt tggatgtcca 3301 gactactact ggagaatgcc actttgaaaa ttatcaaaga gtgtgtgcat tagagcagca 3361 aaagagtgca atgcagacct tgaaaggcat agtccgggtc ttgtccaaga ctgataagag 3421 gctattgtac tgcataaaag ctgatccaca ttgtttaa atctctgtgt attttgggaa 3481 aatggaaggt ggaaaagaag ccagtggtca tatccaactg gaaggccggc catccatttt 3541 agaaatggat gagacttcag cactcaagtt tgaaaataaga gcaacaggtt ttcagagacc 3601 aaatccaaga gtaattgaac taacaagga tgagaatggt gcgcatgttc tactggaagg 3661 actacatcat caaagaccca aacgttattt caccatagtg attatttcaa gtactttgct 3721 acttgactt attgtacttc tgttgatctc atatgttatg tggaggctg gcttctttaa 3781 aagacaatac aatctatcc tacaagaaga aaacagaaga gacagttgga gttatatcaa 3841 cagtaaaagc aatgatgatt aaggacttct ttcaaatgga gagaatggaa aacagactca 3901 ggtttagta aagaaattta aaagacactg tttacaagaa aaaaatgaat ttgtttggac 3961 ttcttttact catgatcttg tgacatatta tgtcttcag caaggggaaa atctcagcaa 4021 tgattactct ttgagataga agaactgcaa aggtaataat acagccaaag ataactcttc 4081 agctttttaa tgggtagaga aacactaaag cattcaattt attcaagaaa agtaagccct 4141 tgaagatata ttgaaatgaa agtataactg agttaaatta tactggagaa gtcttagact

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>4201 tgaataacta cttaccatat gtgcttgccct cagtaaaatg aacccccactg ggtgggcaga 4261 ggttcatttc aaatacatct ttgatacttg ttcaaaatat gttcctttaa aatataattt 4321 tttagagagc tgttcccaaa ttttctaacg agtggacatc tatcacttta aagcccttta 4381 tttataatac atttcctacg ggctgtgttc caacaacatc tttttttcag cagactatga 4441 atattatagt attataggcc aaactggcaa acttcagact gaacatgtac actggtttga 4501 gcttagtgaa attacttctg gataattatt tttttataat tatggatttc accatctttc 4561 tttctgtata tatacatgtg tttttatgta ggtatatatt taccattctt cctatctatt 4621 cttcctataa cacaccttta tcaagcatac ccaggagtaa tcttcaaatc tttgtttata 4681 ttctgaaaca aaagattgtg agtgttgccac tttacctgat acacgctgat ttgaaaaata 4741 cagaaacatc acctcactaa taactttaa atcaaagctg tgcaagactc agggggccta 4801 tacttcatat gtattatgta ctatgtaaaa tattgactat cacacaacta tttccttggg 4861 tgtaattctt tgttaccctt tacaagtata agtgttacct tacatggaaa cgaagaaaca 4921 aaattcataa atttaaattc ataaatttag ctgaaagata ctgattcaat ttgtatacag 4981 tgaatataaa tgagacgaca gcaaaatfff catgaaatgt aaaaatfff tatagtttgt 5041 tcatactata tgaggttcta ttttaaata ctttctggat tttaaaaaat ttctttaaata 5101 acaatcattt ttgtaataat tattttatgc ttatgatcta gataattgca gaatatcatt 5161 ttatctgact ctgccttcat aagagagctg tggccgaatt ttgaacatct gttatagggg 5221 gtgatcaaat tagaaggcaa tgtggaaaaa caattctggg aaagatttct ttatatgaag 5281 tccttgccac tagccagcca tcttaattga tgaaagttaa ctgttcacag gcctgcagtg 5341 atgggtgagga atgttctgag atttgcgaag gcatttgagt agtgaatgtc aagcacaata 5401 cctcctgaac ccagagtgtg tatacacagg aataaacttt atgacattta tgtattttta 5461 aaaaactttg tatcgttata aaaaggctag tcattctttc aggagaacat ctaggatcat 5521 agatgaaaaa tcaagccccg atttagaact gtcttctcca ggatgggtctc taaggaaatt 5581 tacatttggg tctttcctac tcagaactac tcagaacaaa ctatatattt caggttatct 5641 gagcacagtg aaagcagagt actatggttg tccaacacag gcctctcaga tacaggggga 5701 acacaattac atattgggct agattttgcc cagttcaaaa tagtatttgt tatcaactta 5761 ctttgttact tgtatcatga attttaaaac cctaccactt taagaagaca gggatgggtt 5821 attccttttt ggcaggtagg ctatataact atgtgatttt gaaatttaac tgctctggat 5881 tagggagcag tgaatcaagg cagacttatg aaatctgtat tatattttga acagaatata 5941 ggaaatttaa cataattgat gagctcaaat cctgaaaaat gaaagaatcc aaattatttc 6001 agaattatct aggttaaata ttgatgtatt atgatgggtg caaagttttt ttgtgtgtcc 6061 aataaacaca ttgtaaaaaa aa</p>
10	<p>NM_000889.2 Exemplary nucleic acid sequence encoding human β7</p>	<p>1 aaatcttccc caccctgggg agtgtcactt cctcctctgc cgtctcccag atcagtacac 61 aaaggctgct gctgccgcca gaggaaggac tgctctgcac gcacctatgt ggaactataa 121 gccagagag aaagtctgac ttgcccaca gccagtgagt gactgcagca gcaccagaat 181 ctggctctgt tctgttttgg ctcttctacc actacggctt gggatctcgg gcatgggtggc 241 tttgccaatg gtccttgttt tgetgtggt cctgagcaga ggtgagagtg aattggacgc 301 caagatccca tccacagggg atgccacaga atggcggaat cctcacctgt ccatgctggg 361 gtccctgccc ccagccccct cctgccagaa gtgcatcctc tcacacccca gctgtgcatg 421 tgcaagcaa ctgaacttca ccgcctcggg agaggcggag gcgcggcgct gcgcccagcg 481 agaggagctg ctggctcgag gctgccgct ggaggagctg gaggagcccc gcgcccagca 541 ggaggtgctg caggaccagc cgtcagcca gggcgcggcg ggagaggggtg ccaccagct 601 ggcgccgag cgggtcggg tcacgtgctg gcctggggag cccagcagc tccaggtcgg 661 cttcctctgt gctgagggat acccggtgga cctgtactac cttatggacc tgagctactc 721 catgaaggac gacctggaac gcgtgcgcca gctcgggcac gctctgctgg tccggctgca 781 ggaagtcacc cattctgtgc cattgggttt tggttccttt gtggacaaaa cgggtgctgc</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>841 ctttgtgagc acagtaccct caaaactgcg ccaccctgc cccaccggc tggagcgctg 901 ccagtcacca ttcagctttc accatgtgct gtcctgacg ggggacgcac aagccttcga 961 gcgggaggtg gggcgccaga gtgtgtccgg caatctggac tgcctgaag gtgcttcga 1021 tgccattctg caggctgcac tctgccagga gcagattggc tggagaaatg tgtcccggct 1081 gctgggtgtc acttcagacg acacattcca tacagctggg gacgggaagt tggcgggcat 1141 ttcatgccc agtgatgggc actgccactt ggacagcaat ggcctctaca gtcgcagcac 1201 agagtttgac tacccttctg tgggtcaggt agcccaggcc ctctctgcag caaatatcca 1261 gcccatcttt gctgtcacca gtgccgcaact gcctgtctac caggagctga gtaaactgat 1321 tctaagtct gcagttgggg agctgagtga ggactccagc aacgtggtac agctcatcat 1381 ggatgcttat aatagcctgt cttccaccgt gacccttgaa cactcttcac tccctcctgg 1441 ggtccacatt tcttacgaat cccagtgtga gggctctgag aagagggagg gtaaggctga 1501 ggatcgagga cagtgaacc acgtccgaat caaccagacg gtgactttct gggtttctct 1561 ccaagccacc cactgcctcc cagagcccca tctctgagg ctccggggcc ttggttctct 1621 agaggagctg attgtggagt tgcacacgct gtgtgactgt aattgcagtg acaccagcc 1681 ccaggctccc cactgcagtg atggccaggg acacctaca tgtggtgat gcagctgtgc 1741 cctggccgc ctaggtcggc tctgtgagtg ctctgtggca gagctgtcct cccagacct 1801 ggaatctggg tgccgggctc ccaatggcac agggcccctg tgcagtggaa agggctcactg 1861 tcaatgtgga cgctgcagct gcagtggaca gagctctggg catctgtgcg agtgtgacga 1921 tgccagctgt gagcgacatg agggcatcct ctgcccagggc tttggtcgtc gccaatgtgg 1981 agtatgtcac tgtcatgcca accgcacggg cagagcatgc gaatgcagtg gggacatgga 2041 cagttgcatc agtcccaggg gagggtctctg cagtgggcat ggacgctgca aatgcaaccg 2101 ctgccagtgc ttggacggct actatggtgc tctatgcgac caatgccag gctgcaagac 2161 accatgagag agacaccggg actgtgcaga gtgtggggcc ttcaggactg gccactggc 2221 caccaactgc agtacagctt gtgccatac caatgtgacc ctggccttgg cccatctct 2281 ggatgatggc tgggtcaaaag agcggaccct ggacaaccag ctgttcttct tcttgggtgga 2341 ggatgagccc agaggcacgg tcgtgctcag agtgagacc caagaaaagg gagcagacca 2401 cacgcaggcc attgtgctgg gctgctgtag gggcatcgtg gcagtggggc tgggctggt 2461 cctggcttac cggctctcgg tggaaatcta tgaccgccgg gaatacagtc gctttgagaa 2521 ggagcagcaa caactcaact ggaagcagga cagtaatcct ctctacaaaa gtgccatcac 2581 gaccaccatc aatcctcgtt ttcaagaggc agacagtccc actctctgaa ggaggagggg 2641 acatttacc aaggctcttc tcttggagg acagtgggaa ctggagggtg agaggaaggg 2701 tgggtctgta agaccttggg aggggactaa ttcactggcg aggtgcccgc accaccctac 2761 ttcattttca gagtgacacc caagagggct gcttcccatg cctgcaacct tgcatccatc 2821 tgggctaccc cacccaagta tacaataaag tcttacctca gaccacaaaa aaaaaaaaa</p>
11	<p>NP_000876.3 Exemplary amino acid sequence for human α4 precursor</p>	<p>1 mawearrepg prraavretv mlllclgvpt grpynvdtes allyqgphnt lfgysvvlhs 61 hganrwlvg aptanwlana svinpgaiyr crigknpqgt ceqlqlgspn gepcgktcle 121 erdnqwlgtv lsrqpgengs ivtcghrwn 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 sivnlgidid dgfedvaiga pqeddlqgai yiyngradgi sstfsqrieg 421 lqiskslsmf gqsisgqida dnngyvdvav gafrrdsavl lrtrpvvivid aslshpesvn 481 rtkfcdveng wpsvcidltl cfsykgevp gyivlfynms ldvnrkaesp prfyfssngt 541 sdvitsiqv ssreanrth qafmrkdvrd iltpiqieaa yhlghvisk rsteefpplq 601 pilqqkkekd imkktinfar fcahencsad lqvsakigfl kphenktyla vgsmtlmln 661 vslnagdda yettlhvklp vglyfikile leekqincev tdnsgvvqld csigyiyvdh</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>721 lsridisfll dvsslsraee dlsitvhatc eneeemdnlk hsrvtvaapl kyevkltvhg 781 fvnptsfvyg sndenepetc mvekmnlftv vintgnsmav nvsveimvpn sfsqtdklf 841 nildvqtttg echfenyqrv caleqqksam qtlkgivrfl sktdkrllyc ikadphclnf 901 lcnfgkmesg keasvhiqle grpsilemde tsalkfeira tgfpepnprv ielnkdenva 961 hvllleglhhq rpkryftivi issslllgli vlllisyvmw kagffkrqyk silqeenrrd 1021 swsyinsksn dd</p>
12	<p>NP_000880.1 Exemplary amino acid sequence for human β7 precursor</p>	<p>1 mvalpmvlvl llvlrsgese ldakipstgd atewrnphls mlgscqpaps cqkcilshps 61 cawckqlnft asgeaearrc arreellarg cpleeleepg qqevlqdpq lsqgargega 121 tqlapqrvrv tlrpgeqqql qvrflraegy pvdlyylmdl sysmkddler vrqlghallv 181 rlqevthsvr igfgsfvdkv vlpfvstvps klrhpcptrl ercqspfsfh hvlsltgdaq 241 aferevgrqs vsgnldspg gfdailqaal cqeigwrvn srllvftsdd tfhtagdgkl 301 ggifmpsdgh chldsnlygs rstefdypsv gqvaqalsaa niqipfavts aalpvyyqels 361 klipksavge lsdssnvvq limdaynsls stvtlehssl ppgwhisyes qcegepekreg 421 kaedrgqcnh vringvtfw vslqathclp ephllrlral gfseelivel htldcncsd 481 tqppaphcsd ggghlqcgvc scapgrlgrl cecsvaelss pdlesgcrap ngtgplcsgk 541 ghcqcgrcsc sggssghlce oddascerhe gilcggfgrc qcgvchchan rtgracecsg 601 dmdscispeg glcshgrck cnrcqldgy ygalcdqcpq cktpcerhrd caecgaftrg 661 platncstac ahtnvtlala pildgdwcke rtdlnqlfff lveddargtv vlrvrpqekg 721 adhtqaiavg cvggivavg lglvlayrlsv eiyrreysr fekeqqqlnw kqdsnplyks 781 aitttinprf qeadsptl</p>
13	<p>NM_016602.2 Exemplary nucleic acid sequence encoding human CCR10</p>	<p>1 agagatgggg acggaggcca cagagcaggt ttcctggggc cactactctg gggatgaaga 61 ggacgcatac tcggctgagc cactgcccga gctttgctac aaggccgatg tccaggcctt 121 cagccgggccc tccaaccca gtgtctccct gaccgtggct gcgctgggtc tggccggcaa 181 tggcctggtc ctggccacc acctggcagc ccgacgcgca gcgctgctgc ccacctctgc 241 ccacctgctc cagctggccc tggccgacct cttgctggcc ctgactctgc ccttcgcggc 301 agcaggggct cttcagggtt ggagctctgg aagtgcacc tgccgcacca tctctggcct 361 ctactcgccc tccttccacg ccgcttccct cttctggccc tgtatcagcg ccgaccgcta 421 cgtggccatc gcgagagcgc tcccagccgg gccgcccgcc tccactcccg gccgagcaca 481 cttggtctcc gtcactgtgt ggctgctgct actgctcctg gcgctgctct cgctgctctt 541 cagccaggat gggcagcggg aaggccaacg acgctgtcgc ctcatcttcc ccgagggcct 601 cacgcagacg gtgaaggggg cgagcgcctt ggccgaggtg gccctgggct tcgctgctgc 661 gctgggctgc atggtagcct gctacgcgct tctggggccc acgctgctgg ccgcccgggg 721 gcccgagcgc cggcgtgccc tgcgctgctt ggtggctctg gtggcggcct tcgtggtgct 781 gcagctgccc tacagcctcg ccctgctgct ggatactgcc gatctactgg ctgcgagcga 841 gcggagctgc cctgccagca aacgcaagga tgtcgcactg ctggtgacca gcgcttggc 901 cctcgcccgc tgtggcctca atcccgttct ctacgccttc ctgggcctgc gcttcgcca 961 ggacctgccc aggctgctac ggggtgggag ctgccctca gggcctcaac cccgccgccc 1021 ctgccccccc cgccccccc tttcttctct ctcagctccc acggagacct acagtctctc 1081 ctgggacaac tagggctgag aatctagagg agggggcagg ctgagggctg tgggaaaggg 1141 gagtaggtgg gggaaactg agaaagaggc agggacctaa agggactacc tctgtgcctt 1201 gccacattaa attgataaca tggaaatgag atgcaaccca acaa</p>
14	<p>AF215981.1 Exemplary nucleic</p>	<p>1 agagatgggg acggaggcca cagagcaggt ttcctggggc cactactctg gggatgaaga 61 ggacgcatac tcggctgagc cactgcccga gctttgctac aaggccgatg tccaggcctt 121 cagccgggccc tccaaccca gtgtctccct gaccgtggct gcgctgggtc tggccggcaa</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	acid sequence encoding human CCR10	181 tggcctggtc ctggccacc acctggcagc ccgacgcgca gcgcgctcgc ccacctctgc 241 ccacctgctc cagctggccc tggccgacct cttgctggcc ctgactctgc ccttcgcggc 301 agcaggggct cttcagggct ggagtctggg aagtgccacc tgccgcacca tctctggcct 361 ctactcggcc tccttcacacg ccggcttctt cttctctggcc tgtatcagcg ccgaccgcta 421 cgtggccatc gcgcgagcgc tccagcccg gcccgggccc tccactcccg gccgcgcaca 481 cttggtctcc gtcacgtgtg ggctgctgtc actgtcctg gcgctgcctg cgctgctctt 541 cagccaggat gggcagcggg aaggccaacg acgctgtcgc ctcatcttcc ccgagggcct 601 cacgcagacg gtgaaggggg cgagcgccgt ggcgcagggt gccctgggct tcgcgctgcc 661 gctggcgctc atggtagcct gctacgcgct tctgggcccg acgctgctgg ccgccagggg 721 gcccgagcgc cggcgtgcgc tgcgcgtcgt ggtggtctct gtggcgccct tcgtggtgct 781 gcagctgccc tacagcctcg ccctgctgct ggatactgcc gatctactgg ctgcgcgcga 841 gcggagctgc cctgccagca aacgcaagga tgtcgcactg ctggtgacca gccgcttggc 901 cctcgcccgc tgtggcctca atcccgttct ctacgccttc ctgggcctgc gcttcgcca 961 ggacctgcgg aggctgtcac ggggtgggag ctgcacctca gggcctcaac cccgcccgcg 1021 ctgccccgcg cggccccgcg tttcttctct ctcagctccc acggagacct acagtctctc 1081 ctgggacaac tagggctgcg aatctagagg agggggcagg ctgagggctc tgggaaaggg 1141 gagtaggtgg gggaaactg 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 aysaep1pel cykadvgqafs rafqpsvslt vaalglagn 61 lvlathlaar raarsptsah llqlaladll laltlpfaaa galqgswslgs atcrtisgly 121 sasfhagflf lacisadryv aiara1pagp rpstpgrahl vsvivwllsl llalpal1fs 181 qdgqregqrr crlifpeglt qtvkgasava qvalgfalpl gvmvacyall grtllaargp 241 errralrvvv alvaafvvlq lpyslallld tadllaarer scpaskrkdv allvtsglal 301 arcglnpvly aflglrfrqd lrrllrggsc psgppprrgc prrprlsscs aptethslsw 361 dn
16	P46092.3 Exemplary amino acid sequence for human CCR10 precursor	1 mgteateqvs wghysgdeed aysaep1pel cykadvgqafs rafqpsvslt vaalglagn 61 lvlathlaar raarsptsah llqlaladll laltlpfaaa galqgswslgs atcrtisgly 121 sasfhagflf lacisadryv aiara1pagp rpstpgrahl vsvivwllsl llalpal1fs 181 qdgqregqrr crlifpeglt qtvkgasava qvalgfalpl gvmvacyall grtllaargp 241 errralrvvv alvaafvvlq lpyslallld tadllaarer scpaskrkdv allvtsglal 301 arcglnpvly aflglrfrqd lrrllrggsc psgppprrgc 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 taaggctccg ctgccttgat ggattataca cttgacctca gtgtgacaac agtgaccgac 181 tactactacc ctgatattct ctcaagcccc tgtgatgcgg aacttattca gacaaatggc 241 aagttgctcc ttgctgtctt ttattgcctc ctgtttgtag tcagtcttct gggaaacagc 301 ctggctcatc tggctcctgt ggtctgcaag aagctgagga gcatcacaga tgtatacctc 361 ttgaacctgg ccctgtctga cctgcttttt gtcttctcct tcccctttca gacctactat 421 ctgctggacc agtgggtggt tgggactgta atgtgcaaag tgggtgtctg cttttattac 481 attggcttct acagcagcat gtttttcatc accctcatga gtgtggacag gtacctggct 541 gttgtccatg ccgtgtatgc cctaaagggt aggaacgatca ggatgggac aacgctgtgc 601 ctggcagtat ggctaaccgc cattatggct accatcccat tgctagtgtt ttaccaagtg 661 gcctctgaag atggtgttct acagtgttat tcattttaca atcaacagac tttgaagtgg

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>721 aagatcttca ccaacttcaa aatgaacatt ttaggcttgt tgatccatt caccatcttt 781 atgttctgct acattaaaat cctgcaccag ctgaagaggt gtcaaaacca caacaagacc 841 aaggccatca ggttggtgct catttggtgc attgcatctt tacttttctg ggtccattc 901 aacgtggttc ttttcctcac ttccttgac agtatgcaca tcttgatgg atgtagcata 961 agccaacagc tgacttatgc cacccatgac acagaaatca tttcctttac tcaactgctgt 1021 gtgaaccctg ttatctatgc ttttgtggg gagaagtcca agaaacacct ctcagaaata 1081 tttcagaaaa gttgcagcca aatcttcaac tacctaggaa gacaaatgcc tagggagagc 1141 tgtgaaaagt catcatcctg ccagcagcac tcctcccggt cctccagcgt agactacatt 1201 ttgtgaggat caatgaagac taaatataaa aaacattttc ttgaatggca tgctagtgc 1261 agtgagcaaa ggtgtgggtg tgaaagggtt ccaaaaaaag ttcagcatga aggatgccat 1321 atatgttgtt gccaacactt ggaacacaat gactaaagac atagtgtgac atgctggca 1381 caacatcaag cctgtgattg tgtttattga tgatgttgaa caagtggtaa ctttaaagga 1441 ttctgtatgc caagtgaaaa aaaaagatgt ctgacctcct tacatat</p>
18	<p>BC107159.1 Exemplary nucleic acid sequence encoding human CCR8</p>	<p>1 ctttgtgaag aaggaattgg caaactgaa acctccagaa caaaggctgt cactaaggtc 61 ccgctgcctt gatggattat acactgacc tcagtgtgac aacagtgacc gactactact 121 acctgatat cttctcaagc ccctgtgatg cggaacttat tcagacaaat ggcaagttgc 181 tccttgctgt cttttattgc ctctgtttg tattcagtct tctgggaaac agcctggca 241 tcctggctct tgtggtctgc aagaagctga ggagcatcac agatgtatac ctcttgaacc 301 tggccctgct tgacctgctt tttgtcttct ccttcccctt tcagacctac tatctgctgg 361 accagtgggt gtttgggact gtaatgtgca aagtgtgtgc tggcttttat tacattggct 421 tctacagcag catgtttttc atcacctca tgagtgtgga caggtacctg gctgttgc 481 atgccctgta tgcctctaaag gtgaggacga tcaggatggg cacaacgctg tgcctggcag 541 tatggctaac cgccattatg gctaccatcc cattgctagt gttttacca gtggcctctg 601 aagatggtgt tctacagtgt tattcatttt acaatcaaca gactttgaag tggaaagatct 661 tcaccaactt caaatgaac attttaggct tgttgatccc attcaccatc tttatgttct 721 gctacattaa aatcctgcac cagctgaaga ggtgtcaaaa ccacaacaag accaaggcca 781 tcaggttggt gctcattgtg gtcattgcat ctttactttt ctgggtccca ttcaacgtgg 841 ttcttttct cacttcttg cacagtatgc acatcttga tggatgtgac ataagccaac 901 agctgactta tgccacctat gtcacagaaa tcatttctt 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 tttccaaaa aagttcagca tgaaggatgc cgtgtgtgtt 1261 gttgccaaca cttggaacac gatgactggg gacgtgggtg tgcatgcctg gcacaacatc 1321 aagcctgtga ttgtgtttat tgatgatggt gaacaagtgg tggctttgga ggattctgta 1381 tgccaagtga aaggggagat gtctgacctc cttcatatag</p>
19	<p>NP_005192.1 Exemplary amino acid sequence for human CCR8 precursor</p>	<p>1 mdytldlsvt tvtdyyypdi fsspcdaeli qtngklllav fycllfvfl lgnslvilvl 61 vvckklrsit dvyllnlals dllfvfsfpf qtyylldqwv fgtvmckvvs gfyiygfyss 121 mffitlmsvd rylavvhavy alkvrtirmg ttlclavwlt aimatipll fyqvasedgv 181 lqcysfynqq tlkwkiftfn kmnilgllip ftifmfcyik ilhqlkrcqn hnktkairlv 241 livviasllf wvpfnvvlfl tslhsmhild gcsisqqlty athvteiisf thccvnpviy 301 afvgekfkhh lseifqkscs qifnylgrqm presceksss cqghssrsss vdyil</p>
20	AAI07160.1	<p>1 mdytldlsvt tvtdyyypdi fsspcdaeli qtngklllav fycllfvfl lgnslvilvl</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	Exemplary amino acid sequence for human CCR8 precursor	61 vvckklrsit dvyllnlals dllfvfsfpf qtyylldqvw fgtvmckvvs gfyiygfyss 121 mffitlmsvd rylavvhavy alkvrtrimg ttlclavwlt aimatipllv fyqvasedgv 181 lqcysfynqq tlkwkiftnf kmnilgllip ftifmfcyik ilhqlkrcqn hnktkairlv 241 livviasllf wvpfnvvlfl tslhsmhild gcsisqqlty athvteiisf thccvnpviy 301 afvgekfkhh lseifqksccs qifnylgrqm presceksss cqqhssrsss vdyil
21	NM_005508.4 Exemplary nucleic acid sequence encoding human CCR4	1 gctcacagga agccacgcac ccttgaaagg caccgggtcc ttcttagcat cgtgcttctc 61 gagcaagcct ggcattgcct cacagacctt cctcagagcc gcttcagaa aagcaagctg 121 cttctggttg ggcccagacc tgccttgagg agcctgtaga gttaaaaaat gaaccccacg 181 gatatagcag acaccacctt cgatgaaagc atatacagca attactatct gtatgaaagt 241 atccccagc cttgcaccaa agaaggcatc aaggcatttg gggagctctt cctgccccca 301 ctgtattcct tggtttttgg atttggtctg cttggaatt ctgtggtggt tctggtcctg 361 tcaaatatac agcggctcag gtccatgact gatgtgtacc tgctcaacct tgccatctcg 421 gatctgctct tcgtgttttc cctccctttt tggggctact atgcagcaga ccagtgggtt 481 tttgggctag gtctgtgcaa gatgatttcc tggatgtact tgggtggcct ttacagtggc 541 atattctttg tcatgctcat gagcattgat agatacctgg caattgtgca cgcggtgttt 601 tccttgaggg caaggacctt gacttatggg gtcacacca gtttggttac atggctcagt 661 gctgtgttcg cctcccttcc tggctttctg ttcagcactt gttatactga gcgcaacct 721 acctactgca aaaccaagta ctctctcaac tccacgacgt ggaaggttct cagctccctg 781 gaaatcaaca ttctcgatt ggtgatcccc ttaggatca tgctgttttg ctactccatg 841 atcatcagga ccttgacgca ttgtaaaaat gagaagaaga acaaggcggg gaagatgatc 901 tttgcccgtg tggctcctct ccttgggttc tggacacctt acaacatagt gctcttcta 961 gagacctg tggagctaga agtccttcag gactgcacct ttgaaagata cttggactat 1021 gccatccagg ccacagaaac tctggctttt gttcactgct gccttaatcc catcatctac 1081 ttttttctgg gggagaaatt togcaagtac atcctacagc tcttcaaac ctgcaggggc 1141 ctttttctgc tctgccaata ctgtgggctc ctccaaattt actctgctga cacccccagc 1201 tcatcttaca cgcagtcacc catggatcat gatctccatg atgctctgta gaaaaatgaa 1261 atgggtgaaat gcagagtcga tgaactttcc acattcagag cttacttaaa attgtathtt 1321 agtaagagat tcctgagcca gtgtcaggag gaaggcttac acccacagtg gaaagacagc 1381 ttctcatcct gcaggcagct ttttctctcc cactagacaa gtccagcctg gcaagggttc 1441 acctgggctg aggcacacct cctcacacca ggcttgacct caggcatgag tcagtctgat 1501 gagaactctg agcagtgcct gaatgaagtt gtaggtaata ttgcaaggca aagactattc 1561 ccttctaacc tgaactgatg ggtttctcca gaggaattg cagagtactg gctgatggag 1621 taaatcgcta cttttgctg tggcaaatgg gccctct
22	P51679.1 Exemplary amino acid sequence for human CCR4 precursor	1 mnptdiadtt ldesiysnyy lyesipkpct kegikafgel flpplyslvf vfgllgnsvv 61 vlvlfkykrl rsmtdivylln laisdllfvf slpfgyyaa dqwvfglglc kmiswmylv 121 fysgiffvml msidrylaiv havfslrart ltygvitsla tswvavfasl pgflfstcyt 181 ernhtycktk yslnsttwkw lssleinilg lviplgimlf cysmiirtlg hcknekknka 241 vkmifavvvl flgfwtpyni vlflletlvel evlqdtfer yldyaiqate tlafvhccln 301 piiyfflgek frkyilqlfk tcrglfvlcq ycgllqiysa dtpsssytsq tmdhdlhdal
23	NM_001206609.1 Exemplary nucleic acid sequence encoding human	1 aatcatccga gaaccttggg ggggtggacag tgcccctttt acagatgaga aaactgaggc 61 ttgaagggga gaagcagctg cctctggcgg catggcttct ggctgcagga tgcccatgga 121 gtctgtggtg accctagacc tgtgtctcgg cttcctttgc tgaacttgaa caggaagatg 181 gcagtggggg ccagtgtctc agaaggagat aagatggctg gtgcatgcc tctgcaactc 241 ctctgttgc tgatctact gggccctggc aacagcttgc agctgtggga cacctgggca

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	CLA	<p>301 gatgaagccg agaaagcctt ggggtcccctg cttgcccggg accggagaca ggccaccgaa 361 tatgagtacc tagattatga tttcctgcca gaaacggagc ctccagaaat gctgaggaac 421 agcactgaca ccactcctct gactgggcctt ggaacccctg agtctaccac tgtggagcct 481 gctgcaaggc gttctactgg cctggatgca ggaggggagc tcacagagct gaccacggag 541 ctggccaaca tggggaacct gtccaaggat tcagcagcta tggagataca gaccactcaa 601 ccagcagcca cggaggcaca gaccactcaa ccagtgccca cggaggcaca gaccactcca 661 ctggcagcca cagaggcaca gacaactcga ctgacggcca cggaggcaca gaccactcca 721 ctggcagcca cagaggcaca gaccactcca ccagcagcca cggaggcaca gaccactcaa 781 cccacaggcc tggaggcaca gaccactgca ccagcagcca tggaggcaca gaccactgca 841 ccagcagcca tggaggcaca gaccactcca ccagcagcca tggaggcaca gaccactcaa 901 accacagcca tggaggcaca gaccactgca ccagaagcca cggaggcaca gaccactcaa 961 cccacagcca cggaggcaca gaccactcca ctggcagcca tggaggcctt gtccacagaa 1021 cccagtgcca cagaggcctt gtccatggaa cctactacca aaagaggctt gttcataccc 1081 ttttctgtgt cctctgttac tcacaagggc attcccatgg cagccagcaa tttgtccgtc 1141 aactaccagc tgggggcccc agaccacatc tctgtgaagc agtgctgctt ggccatccta 1201 atcttgccgc tgggtggccc tatctctctt gtgtgcaact tgggtgctggc ggtccgcctc 1261 tcccgaagg gccacatgta cccctgctgt aattactccc ccaccgagat ggtctgcatc 1321 tcatccctgt tgccctgatgg ggggtgagggg ccctctgcca cagccaatgg gggcctgtcc 1381 aaggccaaga gcccggcctt gacgccagag cccagggagg accgtgaggg ggtgacctc 1441 accctgcaca gcttctctcc ttagctcaact ctgccatctg ttttggcaag accccacctc 1501 cacgggctct cctgggccc ccttgagtgc ccagacccca ttccacagct ctgggcttcc 1561 tcggagacc cctggggatgg ggatcttcag ggaaggaact ctggccacc aaaccaggaca 1621 agagcagcct ggggccaagc agacgggcaa gtggagccac ctcttctct cctccgaggca 1681 tgaagcccag ccacatttca gccaggttcc aaggcaggag gccatttact tgagacagat 1741 tctctctctt ttctctctcc ccatctctct tgggtccctc taacatctcc catggctctc 1801 cccgctctct ctggctcaact gactctctct cccatgtacc caaggaagat ggagctcccc 1861 catcccacac gcaactgcaact gccatgtctt tttggttggc atggtcacca aacaggaagt 1921 ggacattcta agggaggagt actgaagagt gacggacttc tgaggctgtt tctgctgct 1981 cctctgactt ggggcagctt gggctctctt gggcacctct ctgggaaaac ccagggtgag 2041 gttcagcctg tgagggtctg gatgggttct gtgggcccga gggcagacct ttctttggga 2101 ctgtgtggac caaggagctt ccatctagtg acaagtgacc cccagctatc gcctcttggc 2161 ttcccctgtg gccactttcc aggggtggact ctgtcttgtt cactgcagta tcccactgca 2221 aggtccagtg caggcaataa atatgtgatg gacaaacgat agcggaatcc ttcaagggtt 2281 caaggctgtc tccttcaggc agccttcccg gaattctcca tccctcagtg caggatgggg 2341 gctggctctc agctgtctgc cctcagcccc tggcccccca ggaagcctct ttcattgggt 2401 gttaggttga cttagctttt gcctcttggc caacaggggg tctgtacat ccttgggtga 2461 ccagggaaaag ttcaggttat ggggggccc aaggagggtt gcccttccc caccagtgc 2521 cactttatct cacttctctc attaccagat tttggcccac agagtttggt ccccccaaaa 2581 cctcggacca atatcctctt aaacatcaat ctatcctctt gttaaagaaa aaaaaaaaa</p>
24	<p>NM_003006.4</p> <p>Exemplary nucleic acid sequence encoding human CLA</p>	<p>1 acacacagcc attgggggtt gctcggatcc gggactgccg caggggggtgc cacagcagtg 61 cctggcagcg tgggctggga ccttgtcact aaagcagaga agccacttct tctgggccc 121 cgaggcagct gtcccctgct ctgctgagca cgggtgtgca atgcctctgc aactcctct 181 gttgctgac ctactgggca ctggcaacag cttgcaactg tgggacacct gggcagatga 241 agccgagaaa gccttgggtc ccctgcttgc cggggaccgg agacaggcca ccgaatatga 301 gtacctagat tatgatttcc tgccagaaac ggagcctcca gaaatgctga ggaacagcac 361 tgacaccact cctctgactg ggcctggaac ccctgagtct accactgtgg agcctgctgc</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
		<p>421 aaggcgttct actggcctgg atgcaggagg ggcagtcaca gagctgacca cggagctggc 481 caacatgggg aacctgtcca cggattcagc agctatggag atacagacca ctcaaccagc 541 agccacggag gcacagacca ctcaaccagt gcccacggag gcacagacca ctccactggc 601 agccacagag gcacagacaa ctgcactgac ggccacggag gcacagacca ctccactggc 661 agccacagag gcacagacca ctccaccagc agccacggaa gcacagacca ctcaaccac 721 aggcctggag gcacagacca ctgcaccagc agccatggag gcacagacca ctgcaccagc 781 agccatggaa gcacagacca ctccaccagc agccatggag gcacagacca ctcaaccac 841 agccatggag gcacagacca ctgcaccaga agccacggag gcacagacca ctcaaccac 901 agccacggag gcacagacca ctccactggc agccatggag gccctgtcca cagaaccac 961 tgccacagag gccctgtcca tggaacctac taccaaaaga ggtctgttca taccttttc 1021 tgtgtctctct gttactcaca agggcattcc catggcagcc agcaatttgt ccgtcaacta 1081 ccagtgggg gccccagacc acatctctgt gaagcagtgct ctgtggcca tcctaactctt 1141 ggcgctggtg gccactatct tcttctgtgt cactgtggtg ctggcggctc gcctctccc 1201 caagggccac atgtacccc tgcgtaatta ctccccacc gagatggctc gcctctctc 1261 cctggtgctt gatgggggtg aggggcccctc tgccacagcc aatgggggctc tgtccaaggc 1321 caagagcccg ggcctgacgc cagagcccag ggaggaccct gaggggggatg acctcaccct 1381 gcacagcttc ctcccttagc tcaactctgc atctgttttg gcaagacccc acctccacgg 1441 gctctctctg gccaccctg agtgcccaga cccattcca cagctctggg cttctctcga 1501 gaccctggg gatggggatc ttcagggaag gaactctggc caccaaaaca ggacaagagc 1561 agcctggggc caagcagacg ggcaagtgga gccacctctt tcctccctcc gcggatgaag 1621 ccagccaca tttcagccga ggtccaaggc aggaggccat ttacttgaga cagattctct 1681 ccttttctct gtccccatc ttctctgggt cctctaaca tctcccatgg ctctccccg 1741 ttctctctgt cactggagtc tcctcccat gtaccaagg aagatggagc tccccatcc 1801 cacacgact gcaactgcat tgtcttttgg ttgccatggt caccaaacag gaagtggaca 1861 ttctaaggga ggagtactga agagtacgg acttctgagg ctgtttcctg ctgctcctct 1921 gacttggggc agcttgggtc ttcttgggca cctctctggg aaaaccagc gtgaggttca 1981 gcctgtgagg gctgggatgg gtttctgtgg cccaagggca gacctttctt tgggactgtg 2041 tggaccaagg agcttccatc tagtgacaag tgacccccag ctatgcctc ttgcttccc 2101 ctgtggccac tttccagggg ggactctgtc ttgttcaact cagtatcca actgcaggtc 2161 cagtgcaggc aataaatatg tgatggacaa acgatagcgg aatccttcaa ggtttcaagg 2221 ctgtctcctt caggcagcct tcccgaatt ctccatccct cagtgcagga tgggggctgg 2281 tcctcagctg tctgcctca gccctggcc cccaggaag cctctttcat gggctgtag 2341 gttgacttca gttttgctc ttggacaaca gggggtcttg tacatccttg ggtgaccagg 2401 aaaagttcag gctatggggg gccaaaggga gggctgcccc ttccccacca gtgaccactt 2461 tattccactt cctccattac ccagtttgg cccacagagt ttggtcccc ccaaacctcg 2521 gaccaatc cctctaaca tcaatctatc ctctgttaa agaaaaaaaa aaa</p>
25	NP_001193538.1 Exemplary amino acid sequence for human CLA precursor	<p>1 mavgasgleg dkmagamplq llllllillgp gnsllqlwdtw adeaekalgp llardrrqat 61 eyeyldydfi peteppemlr nstdtptltg pgtpesttve paarrstgld aggavteltt 121 elanmgnlst dsaameiqtt qpaateaqtt qpvppteaqtt plaateaqtt rltateaqtt 181 plaateaqtt ppaateaqtt qptgleaqtt apaameaqtt apaameaqtt ppaameaqtt 241 qtameaqtt apeateaqtt qptateaqtt plaamealst epsatealsm epttkrglfi 301 pfsvsvthk gipmaasnls vnypvgapdh isvkqcllai lilalvatif fvctvvlavr 361 lsrkghmypv rnysptemvc issllpdgge gpsatanggl skakspgltp epredregdd 421 ltlhsflp</p>
26	NP_002997.2	<p>1 mplqlllllli llgpgnslql wdtwadeaek algplllardr rqateyeyld ydfipetepp</p>

SEQ ID NO:	GenBank Accession Number and Description	Sequence
	Exemplary amino acid sequence for human CLA precursor	<pre> 61 emlrnstddt pltgpgtpes ttvepaarrs tglldaggavt elttelanmg nlstdsaame 121 iqttqpaate aqttqpvpte aqttplaate aqtrrltate aqttplaate aqttppaate 181 aqttqptgle aqttapaame aqttapaame aqttppaame aqttqtame aqttapeate 241 aqttqptate aqttplaame alstepsate alsmepttkr glfipfsvss vthkgipmaa 301 snlsvnyvpg apdhisvkqc llaililalv atiffvctvv lavrlsrkgh mypvrnyspt 361 emvcissllp dggegpsata ngglskaksp gltpepredr egddltlhsf lp </pre>

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 (CD3 ζ) or ITAM-containing portions thereof. In a specific embodiment, the intracellular domain is a CD3 ζ 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, synaptophysin, 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, KIAA0205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α 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 $\alpha v \beta 3$ (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-1 α , HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , or HIF-3 β . 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 is 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 entirety. 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. Chem.* 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 CD3 ζ 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 pyrrolidone. 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 CD3 ζ 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 = $\frac{1}{2}(\text{length} \times \text{width}^2)$.

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 CD3 ζ 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 CD3 ζ . The gastrointestinal homing receptors are introduced via lentiviral transduction of mouse CCR9 and $\alpha 4\beta 7$ 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 μ m 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, $\alpha 4\beta 7$, 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 CD3 ζ . The CAR T cells are further transduced with lentiviral vectors containing nucleic acid sequences encoding human CCR9 and $\alpha 4\beta 7$; 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 $\alpha 4\beta 7$ 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 CD3 ζ . The CAR T cells 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 μ m 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 CD3 ζ . The gastrointestinal homing receptors are introduced via lentiviral transduction of human CCR10 or CCR4, and CLA nucleic acid sequences. Treatment with 1,25(OH)₂VD₃ 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 $\alpha 4\beta 7$ 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 CD3 ζ 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 $1,25(\text{OH})_2\text{VD}_3$ 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 CD3 ζ 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

What is claimed is:

1. A T lymphocyte expressing a homing receptor not normally expressed by the T lymphocyte, and a chimeric antigen receptor (CAR).
2. The T lymphocyte of claim 1, wherein the homing receptor is a B cell zone homing receptor.
3. The T lymphocyte of claim 2, wherein the B cell zone homing receptor is CXCR5.
4. The T lymphocyte of claim 1, wherein the homing receptor is a gastrointestinal homing receptor.
5. The T lymphocyte of claim 4, wherein the gastrointestinal homing receptor is $\alpha 4\beta 7$.
6. The T lymphocyte of claim 4, wherein the gastrointestinal homing receptor is CCR9.
7. The T lymphocyte of claim 4, comprising a second gastrointestinal homing receptor.
8. The T lymphocyte of any one of claims 4-7, wherein the T lymphocyte is activated, expanded, or both activated and expanded in the presence of a Vitamin A metabolite, for a time and in an amount sufficient to cause increased expression of one or more gastrointestinal homing receptors.
9. The T lymphocyte of claim 8, wherein the Vitamin A metabolite is retinoic acid.
10. The T lymphocyte of claim 1, wherein the homing receptor is a skin homing receptor.
11. The T lymphocyte of claim 10, wherein the skin homing receptor is CLA.
12. The T lymphocyte of claim 10, wherein the skin homing receptor is CCR4.
13. The T lymphocyte of claim 10, wherein the skin homing receptor is CCR10.
14. The T lymphocyte of claim 10, comprising a second skin homing receptor.
15. The T lymphocyte of claim 14, comprising a third skin homing receptor.

16. The T lymphocyte of any one of claims 10-15, wherein the T lymphocyte is activated, expanded, or both activated and expanded in the presence of a Vitamin D metabolite for a time and in an amount sufficient to cause increased expression of one or more skin homing receptors.

17. The T lymphocyte of claim 16, wherein the Vitamin D metabolite is 1,26-dihydroxycholecalciferol (1,25(OH)₂D₃).

18. The T lymphocyte of any one of claims 10-17, wherein the T lymphocyte is activated, expanded, or both activated and expanded in the presence of IL-12 for a time and in an amount sufficient to cause increased expression of one or more skin homing receptors

19. The T lymphocyte of any one of claims 4-18, additionally comprising a B cell zone homing receptor.

20. The T lymphocyte of claim 19, wherein the B cell zone homing receptor is CXCR5.

21. A method of generating a population of T lymphocytes, wherein a plurality of said T lymphocytes home to the B cell zone of the lymph nodes, said method comprising engineering a population of T lymphocytes to express a B cell zone homing receptor.

22. The method of claim 21, wherein the receptor is CXCR5.

23. A method of generating a population of T lymphocytes, wherein a plurality of said T lymphocytes home to the gastrointestinal tract, said method comprising engineering a population of T lymphocytes to express a gastrointestinal homing receptor.

24. The method of claim 23, wherein the gastrointestinal homing receptor is $\alpha 4\beta 7$.

25. The method of claim 23, wherein the gastrointestinal homing receptor is CCR9.

26. The method of claim 23, wherein the population of T lymphocytes is engineered to express a second gastrointestinal homing receptor.

27. The method of any one of claims 23-26, the method further comprising a step wherein the population of T lymphocytes is activated, expanded, or both activated and expanded in the presence of a Vitamin A metabolite for a time and in an amount sufficient to cause increased expression of one or more gastrointestinal homing receptors.

28. The method of claim 27, wherein the Vitamin A metabolite is retinoic acid.
29. A method of generating a population of T lymphocytes, wherein a plurality of said T lymphocytes home to skin tissue or cells, said method comprising engineering a population of T lymphocytes to express a receptor which homes to skin tissue or cells.
30. The method of claim 29, wherein the skin homing receptor CLA.
31. The method of claim 29, wherein the skin homing receptor is CCR4.
32. The method of claim 29, wherein the skin homing receptor is CCR10.
33. The method of claim 29, wherein the population of T lymphocytes is engineered to express a second skin homing receptor.
34. The method of claim 33, wherein the population of T lymphocytes is engineered to express a third skin homing receptor.
35. The method of any one of claims 29-34, wherein the method further comprises a step wherein the population of T lymphocytes is activated, expanded, or both activated and expanded in the presence of a Vitamin D metabolite for a time and in an amount sufficient to cause increased expression of one or more skin homing receptors.
36. The method of claim 35, wherein the Vitamin D metabolite is 1,26-dihydroxycholecalciferol (1,25(OH)₂D₃).
37. The method of any one of claims 29-36, wherein the method further comprises a step wherein the population of T lymphocytes is activated, expanded, or both activated and expanded in the presence of IL-12 for a time and in an amount sufficient to cause increased expression of one or more skin homing receptors.
38. The method of any one of claims 23-37, wherein the method comprises a step of engineering the population of T lymphocytes to express a B cell zone homing receptor.
39. The method of claim 38, wherein the B cell zone homing receptor is CXCR5.
40. The method of any of claims 21-39, wherein the method further comprises a step of administering a lentiviral vector encoding a chimeric antigen receptor (CAR).

41. A method of treating a cancer or tumor in an individual comprising administering to an individual in need thereof a T lymphocyte comprising (i) a B cell zone homing receptor; and (ii) a CAR.

42. The method of claim 41, wherein the B cell zone homing receptor is CXCR5.

43. A method of treating a gastrointestinal cancer or tumor in an individual comprising administering to an individual in need thereof a T lymphocyte comprising (i) a gastrointestinal homing receptor; and (ii) a CAR.

44. The method of claim 43, wherein the gastrointestinal homing receptor is $\alpha 4\beta 7$.

45. The method of claim 43, wherein the gastrointestinal homing receptor is CCR9.

46. The method of claim 43, wherein the T lymphocyte comprises a second gastrointestinal homing receptor.

47. The method of any one of claims 43 to 46, wherein the extracellular domain of the CAR binds an antigen associated with a gastrointestinal tumor or cancer.

48. A method of treating a skin cancer or a skin tumor in an individual comprising administering to an individual in need thereof a T lymphocyte comprising (i) a skin homing receptor; and (ii) a CAR.

49. The method of claim 48, wherein the skin homing receptor is CLA.

50. The method of claim 48, wherein the skin homing receptor is CCR4.

51. The method of claim 48, wherein the skin homing receptor is CCR10.

52. The method of claim 48, wherein the T lymphocyte comprises a second skin homing receptor.

53. The method of claim 52, wherein the T lymphocyte comprises a third skin homing receptor.

54. The method of any one of claims 48 to 53, wherein the extracellular domain of the CAR binds an antigen associated with a skin tumor or cancer.

55. The method of any one of claims 41-46 or 48-53, 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, synaptophysin, 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, KIAA0205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α 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 α v β 3 (CD61), galactin, and Ral-B.

56. The method of any one of claims 43-54, wherein the T lymphocyte further comprises a B cell zone homing receptor.

57. The method of claim 56, wherein the B cell zone homing receptor is CXCR5.

58. A T lymphocyte comprising (i) a B cell zone homing receptor; and (ii) a CAR for use in a method of treating a cancer or tumor in an individual comprising administering said T lymphocyte to an individual in need thereof.

59. The T lymphocyte for use according to claim 58, wherein the B cell zone homing receptor is CXCR5.

60. A T lymphocyte comprising (i) a gastrointestinal homing receptor; and (ii) a CAR for use in a method of treating a gastrointestinal cancer or tumor in an individual comprising administering said T lymphocyte to an individual in need thereof.

61. The T lymphocyte for use according to claim 60, wherein the gastrointestinal homing receptor is $\alpha 4\beta 7$.

62. The T lymphocyte for use according to claim 60, wherein the gastrointestinal homing receptor is CCR9.

63. The T lymphocyte for use according to claim 60, wherein said T lymphocyte comprises a second gastrointestinal homing receptor.

64. The T lymphocyte for use according to any one of claims 60 to 63, wherein the extracellular domain of the CAR binds an antigen associated with a gastrointestinal tumor or cancer.

65. A T lymphocyte comprising (i) a skin homing receptor; and (ii) a CAR for use in a method of treating a skin cancer or a skin tumor in an individual comprising administering said T lymphocyte to an individual in need thereof.

66. The T lymphocyte for use according to claim 65, wherein the skin homing receptor is CLA.

67. The T lymphocyte for use according to claim 65, wherein the skin homing receptor is CCR4.

68. The T lymphocyte for use according to claim 65, wherein the skin homing receptor is CCR10.

69. The T lymphocyte for use according to claim 65, wherein said T lymphocyte comprises a second skin homing receptor.

70. The T lymphocyte for use according to claim 69, wherein said T lymphocyte comprises a third skin homing receptor.

71. The T lymphocyte for use according to any one of claims 65 to 70, wherein the extracellular domain of the CAR binds an antigen associated with a skin tumor or cancer.

72. The T lymphocyte for use according to any one of claims 58-63 or 65-70, 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, synaptophysin, 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, KIAA0205, Mart2, Mum-1, 2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α 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 $\alpha\text{v}\beta\text{3}$ (CD61), galactin, and Ral-B.

73. The T lymphocyte for use according to any one of claims 60-71, wherein said T lymphocyte further comprises a B cell zone homing receptor.

74. The T lymphocyte for use according to claim 73, wherein the B cell zone homing receptor is CXCR5.