

[0004] Engineered immune cells have been shown to possess desired qualities in therapeutic treatments, particularly in oncology. Two main types of engineered immune cells are those that contain chimeric antigen receptors (termed “CARs” or “CAR-Ts”) and T-cell receptors (“TCRs”). These engineered cells are engineered to endow them with antigen specificity while retaining or enhancing their ability to recognize and kill a target cell. Chimeric antigen receptors may comprise, for example, (i) an antigen-specific component (“antigen binding molecule”), (ii) one or more costimulatory domains, and (iii) one or more activating domains. Each domain may be heterogeneous, that is, comprised of sequences derived from different protein chains. Chimeric antigen receptor-expressing immune cells (such as T cells) may be used in various therapies, including cancer therapies. It will be appreciated that costimulating polypeptides as defined herein may be used to enhance the activation of CAR-expressing cells against target antigens, and therefore increase the potency of adoptive immunotherapy.

[0005] T cells can be engineered to possess specificity to one or more desired targets. For example, T cells can be transduced with DNA or other genetic material encoding an antigen binding molecule, such as one or more single chain variable fragment (“scFv”) of an antibody, in conjunction with one or more signaling molecules, and/or one or more activating domains, such as CD3 zeta.

[0006] In addition to the CAR-T cells’ ability to recognize and destroy the targeted cells, successful T cell therapy benefits from the CAR-T cells’ ability to persist and maintain the ability to proliferate in response to antigen.

[0007] A need exists to identify novel and improved therapies for treating DLL3 related diseases and disorders.

SUMMARY

[0008] The disclosure relates to engineered immune cells (such as CARs or TCRs), antigen binding molecules (including but not limited to, antibodies, scFvs, heavy and/or light chains, and CDRs of these antigen binding molecules) with specificity to DLL3.

[0009] Chimeric antigen receptors of the disclosure typically comprise: (i) a DLL3 specific antigen binding molecule, (ii) one or more costimulatory domain, and (iii) one or more activating domain. It will be appreciated that each domain may be heterogeneous, thus comprised of sequences derived from different protein chains.

[0009a] In one aspect, the present disclosure refers to a chimeric antigen receptor comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises: a) a variable heavy chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:42 or SEQ ID NO:52 or SEQ ID NO:62; or b) a variable heavy chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:43 or SEQ ID NO:53 or SEQ ID NO:63; or c) a variable heavy chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:44 or SEQ ID NO:54 or SEQ ID NO:64; or d) a variable light chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:47 or SEQ ID NO:57 or SEQ ID NO:67; or e) a variable light chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:48 or SEQ ID NO:58 or SEQ ID NO:68; or f) a variable light chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID:49 or SEQ ID NO:59 or SEQ ID NO:69; or g) a variable heavy chain CDR1 comprising an amino acid sequence of a variable heavy chain CDR1 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or h) a variable heavy chain CDR2 comprising an amino acid sequence of a variable heavy chain CDR2 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or i) a variable heavy chain CDR3 comprising an amino acid sequence of a variable heavy chain CDR3 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or j) a variable light chain CDR1 comprising an amino acid sequence of a variable light chain CDR1 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or k) a variable light chain CDR2 comprising an amino acid sequence of a variable light chain CDR2 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or l) a variable light chain CDR3 comprising an amino acid sequence of a variable light chain CDR3 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or m) a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 1H2.1, clone 8D2, or clone 6B2; or n) a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 1H2.1, clone 8D2, or clone 6B2.

[0009b] In another aspect, the present disclosure refers to a polynucleotide encoding the chimeric antigen receptor as described herein. In another aspect, the present disclosure refers to a vector comprising the polynucleotide as described herein. In yet another aspect, the present disclosure refers to an immune cell comprising the vector as described herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising an

immune cell as described herein. In another aspect, the present disclosure refers to a chimeric antigen receptor comprising: (a) a VH region of clone 1H2.1 and a VL region of clone 1H2.1; (b) a VH region of clone 8D2 and a VL region of clone 8D2; or (c) a VH region of clone 6B2 and a VL region of clone 6B2; wherein the VH and VL region is linked by at least one linker.

[0009c] In a further aspect, the present disclosure refers to an immune cell comprising the chimeric antigen receptor as described herein. In a further aspect, the present disclosure refers to a pharmaceutical composition comprising the cell as described herein. In a further aspect, the present disclosure refers to an isolated polynucleotide comprising a sequence encoding the chimeric antigen receptor as described herein. In a further aspect, the present disclosure refers to a vector comprising the polynucleotide as described herein. In a further aspect, the present disclosure refers to an immune cell comprising the vector as described herein.

[0009d] In a further aspect, the present disclosure refers to an isolated polypeptide comprising the amino acid sequence of construct 1H2.1 CD28T, construct 1H2.1 4-1BB, construct 8D2 CD28T, construct 8D2 4-1BB, construct 6B2 CD28T, or construct 6B2 4-1BB. In a further aspect, the present disclosure refers to a vector encoding the polypeptide as described herein. In a further aspect, the present disclosure refers to an immune cell comprising the polypeptide as described herein. In a further aspect, the present disclosure refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises a variable heavy chain CDR3 comprising the amino acid sequence of a variable heavy chain CDR3 of clone 1H2.1, clone 8D2, or clone 6B2.

[0009e] In a further aspect, the present disclosure refers to a vector comprising the polynucleotide as described herein. In a further aspect, the present disclosure refers to an immune cell comprising the vector as described herein. In a further aspect, the present disclosure refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), said CAR or TCR comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises: a. a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 1H2.1, clone 8D2, or clone 6B2; and/or b. a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 1H2.1, clone 8D2, or clone 6B2. In a still further aspect, the present disclosure refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding

molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:42), CDR2 (SEQ ID NO:43), and CDR3 (SEQ ID NO:44) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:47), CDR2 (SEQ ID NO:48), and CDR3 (SEQ ID NO:49). In a still further aspect, the present disclosure refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:52), CDR2 (SEQ ID NO:53), and CDR3 (SEQ ID NO:54) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:57), CDR2 (SEQ ID NO:58), and CDR3 (SEQ ID NO:59). In a still further aspect, the present disclosure refers to an isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:62), CDR2 (SEQ ID NO:63), and CDR3 (SEQ ID NO:64) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:67), CDR2 (SEQ ID NO:68), and CDR3 (SEQ ID NO:69). In a still further aspect, the present disclosure refers to the use of the polynucleotide as described herein, the polypeptide as described herein, the chimeric antigen receptor as described herein, the cell as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0010] In some examples, the disclosure relates to a chimeric antigen receptor comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises at least one of: (a) a variable heavy chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NO:42 or SEQ ID NO:52 or SEQ ID NO:62 by not more than 3, 2, 1, or 0 amino acid residues; (b) a variable heavy chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NO:43 or SEQ ID NO:53 or SEQ ID NO:63 by not more than 3, 2, 1, or 0 amino acid residues; (c) a variable heavy chain CDR3 comprising an amino acid sequence differing from that of SEQ ID NO:44 or SEQ ID NO:54 or SEQ ID NO:64 by not more than 3, 2, 1, or 0 amino acid residues; (d) a variable light chain CDR1 comprising an amino acid sequence differing from that of SEQ ID NO:47 or SEQ ID NO:57 or SEQ ID NO:67 by not more than 3, 2, 1, or 0 amino acid residues; (e) a variable light chain CDR2 comprising an amino acid sequence differing from that of SEQ ID NO:48 or

SEQ ID NO:58 or SEQ ID NO:68 by not more than 3, 2, 1, or 0 amino acid residues; (f) a variable light chain CDR3 comprising an amino acid sequence differing from that of SEQ ID:49 or SEQ ID NO:59 or SEQ ID NO:69 by not more than 3, 2, 1, or 0 amino acid residues.

[0011] In other examples, the chimeric antigen receptor further comprises at least one costimulatory domain. In further examples, the chimeric antigen receptor further comprises at least one activating domain.

[0012] In certain examples the costimulatory domain is a signaling region of CD28, CD28T, CD8, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, Programmed Death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class 1 molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFTR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

[0013] In some examples, the costimulatory domain is derived from 4-1BB. In other examples, the costimulatory domain is derived from CD28 or CD28T. In other examples, the costimulatory domain is derived from CD8. In other examples, the costimulatory domain is derived from OX40. See also Hombach *et al.*, *Oncoimmunology*. 2012 Jul. 1; 1(4): 458–466. In still other examples, the costimulatory domain comprises ICOS as described in Guedan *et al.*, August 14, 2014; *Blood*: 124 (7) and Shen *et al.*, *Journal of Hematology & Oncology* (2013) 6:33. In

still other examples, the costimulatory domain comprises CD27 as described in Song *et al.*, Oncoimmunology. 2012 Jul. 1;1(4): 547–549.

[0014] In certain examples, the CD28 costimulatory domain comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:8. In additional examples, the CD8 costimulatory domain comprises SEQ ID NO:14. In additional examples, the 4-1BB costimulatory domain comprises SEQ ID NO:16. In further examples, the activating domain comprises CD3, CD3 zeta, or CD3 zeta having the sequence set forth in SEQ ID NO:10.

[0015] In other examples, the disclosure relates to a chimeric antigen receptor wherein the costimulatory domain comprises SEQ ID NO:2 and the activating domain comprises SEQ ID NO:10.

[0016] The disclosure further relates to polynucleotides encoding the chimeric antigen receptors, and vectors comprising the polynucleotides. The vector can be, for example, a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof. The disclosure further relates to immune cells comprising the vectors. In some examples, the lentiviral vector is a pGAR vector.

[0017] Exemplary immune cells include, but are not limited to T cells, tumor infiltrating lymphocytes (TILs), NK cells, TCR-expressing cells, dendritic cells, or NK-T cells. The T cells can be autologous, allogeneic, or heterologous. In other examples, the disclosure relates to pharmaceutical compositions comprising the immune cells of described herein.

[0018] In certain examples, the disclosure relates to antigen binding molecules (and chimeric antigen receptors comprising these molecules) comprising at least one of:

- (a) a VH region differing from the amino acid sequence of the VH region of 1H2.1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 1H2.1 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;
- (b) a VH region differing from the amino acid sequence of the VH region of 8D2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 8D2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

(c) a VH region differing from the amino acid sequence of the VH region of 6B2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues and a VL region differing from the amino acid sequence of the VL region of 6B2 by no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues;

and wherein the VH and VL region or regions are linked by at least one linker.

[0019] In other examples, the disclosure relates to antigen binding molecules (and chimeric antigen receptors comprising these molecules) wherein the linker comprises at least one of the scFv G4S linker and the scFv Whitlow linker.

[0020] In other examples, the disclosure relates to vectors encoding the polypeptides of the disclosure and to immune cells comprising these polypeptides. Preferred immune cells include T cells, tumor infiltrating lymphocytes (TILs), NK cells, TCR-expressing cells, dendritic cells, or NK-T cells. The T cells may be autologous, allogeneic, or heterologous.

[0021] In other examples, the disclosure relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises a variable heavy (V_H) chain CDR3 comprising an amino acid sequence of SEQ ID NO:44 or SEQ ID NO:54 or SEQ ID NO:64. The polynucleotides may further comprise an activating domain. In preferred examples, the activating domain is CD3, more preferably CD3 zeta, more preferably the amino acid sequence set forth in SEQ ID NO:9.

[0022] In other examples, the disclosure includes a costimulatory domain, such as CD28, CD28T, OX40, CD8, 4-1BB/CD137, CD2, CD3 (alpha, beta, delta, epsilon, gamma, zeta), CD4, CD5, CD7, CD9, CD16, CD22, CD27, CD30, CD 33, CD37, CD40, CD 45, CD64, CD80, CD86, CD134, CD137, CD154, PD-1, ICOS, lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), CD247, CD276 (B7-H3), LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF, TNFr, integrin, signaling lymphocytic activation molecule, BTLA, Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFTR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRP1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D,

ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD83 ligand, or fragments or combinations thereof. Preferred costimulatory domains are recited hereinbelow.

[0023] In further examples, the disclosure relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), wherein said CAR or TCR comprises an antigen binding molecule that specifically binds to DLL3, and wherein the antigen binding molecule comprises a variable light (V_L) chain CDR3 comprising an amino acid sequence selected from SEQ ID NO:47, SEQ ID NO:57 and SEQ ID NO:67. The polynucleotide can further comprise an activating domain. The polynucleotide can further comprise a costimulatory domain.

[0024] In other examples, the disclosure relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:42), CDR2 (SEQ ID NO:43), and CDR3 (SEQ ID NO:44) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:47), CDR2 (SEQ ID NO:48), and CDR3 (SEQ ID NO:49).

[0025] In other examples, the disclosure relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:52), CDR2 (SEQ ID NO:53), and CDR3 (SEQ ID NO:54) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:57), CDR2 (SEQ ID NO:58), and CDR3 (SEQ ID NO:59).

[0026] In other examples, the disclosure relates to isolated polynucleotides encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:62), CDR2 (SEQ ID NO:63), and

CDR3 (SEQ ID NO:64) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:67), CDR2 (SEQ ID NO:68), and CDR3 (SEQ ID NO:69).

[0027] The disclosure further relates to antigen binding molecules to DLL3 comprising at least one variable heavy chain CDR3 or variable light chain CDR3 sequence as set forth herein. The disclosure further relates to antigen binding molecules to DLL3 comprising at least one variable heavy chain CDR1, CDR2, and CDR3 sequences as described herein. The disclosure further relates to antigen binding molecules to DLL3 comprising at least one variable light chain CDR1, CDR2, and CDR3 sequences as described herein. The disclosure further relates to antigen binding molecules to DLL3 comprising both variable heavy chain CDR1, CDR2, CDR3, and variable light chain CDR1, CDR2, and CDR3 sequences as described herein.

[0028] Additional heavy and light chain variable domains and CDR polynucleotide and amino acid sequences suitable for use in DLL3-binding molecules according to the present disclosure are found in U.S. Provisional Application Number 62/199,944, filed on July 31, 2015.

[0029] The disclosure further relates to methods of treating a disease or disorder in a subject in need thereof comprising administering to the subject the antigen binding molecules, the CARs, TCRs, polynucleotides, vectors, cells, or compositions according to the disclosure. Suitable diseases for treatment include, but are not limited to, adrenal, liver, kidney, bladder, breast, gastric, ovarian, cervical, uterine, esophageal, colorectal, prostate (e.g., prostate adenocarcinoma), pancreatic, lung (both small cell and non-small cell), thyroid, carcinomas, sarcomas, glioblastomas, head and neck tumors, large cell neuroendocrine carcinoma (LCNEC), medullary thyroid cancer, glioblastoma, neuroendocrine prostate cancer, (NEPC), high-grade gastroenteropancreatic cancer (GEP) and malignant melanoma.

BRIEF DESCRIPTION OF THE FIGURES

[0030] FIG. 1, depicts expression of DLL3 CARs in T cells from a healthy donor.

[0031] FIG. 2, depicts cytolytic activity of lentivirus-transduced CAR T cells from healthy donor.

[0032] FIG. 3, depicts cytokine production by CAR T cells from a healthy donor.

[0033] FIG. 4, depicts flow cytometric analysis of T cell proliferation in response to DLL3-expressing target cells.

[0034] FIG. 5, depicts in vivo anti-tumor activity of DLL3 CAR T cells in mouse xenogeneic model of human SCLC.

[0035] FIG. 6, depicts survival analysis of mouse SCLC xenogeneic model following DLL3 CAR T cell treatment.

[0036] FIG. 7, depicts the pGAR vector map.

DETAILED DESCRIPTION OF THE INVENTION

[0037] It will be appreciated that chimeric antigen receptors (CARs or CAR-Ts) and T cell receptors (TCRs) are genetically engineered receptors. These engineered receptors can be readily inserted into and expressed by immune cells, including T cells in accordance with techniques

What is Claimed

1. A chimeric antigen receptor comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises:
 - a) a variable heavy chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:42 or SEQ ID NO:52 or SEQ ID NO:62; or
 - b) a variable heavy chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:43 or SEQ ID NO:53 or SEQ ID NO:63; or
 - c) a variable heavy chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:44 or SEQ ID NO:54 or SEQ ID NO:64; or
 - d) a variable light chain CDR1 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:47 or SEQ ID NO:57 or SEQ ID NO:67; or
 - e) a variable light chain CDR2 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID NO:48 or SEQ ID NO:58 or SEQ ID NO:68; or
 - f) a variable light chain CDR3 comprising an amino acid sequence differing by not more than 3, 2, 1, or 0 amino acid residues from that of SEQ ID:49 or SEQ ID NO:59 or SEQ ID NO:69; or
 - g) a variable heavy chain CDR1 comprising an amino acid sequence of a variable heavy chain CDR1 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - h) a variable heavy chain CDR2 comprising an amino acid sequence of a variable heavy chain CDR2 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - i) a variable heavy chain CDR3 comprising an amino acid sequence of a variable heavy chain CDR3 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - j) a variable light chain CDR1 comprising an amino acid sequence of a variable light chain CDR1 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - k) a variable light chain CDR2 comprising an amino acid sequence of a variable light chain CDR2 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - l) a variable light chain CDR3 comprising an amino acid sequence of a variable light chain CDR3 sequence of clone 1H2.1, clone 8D2, or clone 6B2; or

- m) a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 1H2.1, clone 8D2, or clone 6B2; or
 - n) a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 1H2.1, clone 8D2, or clone 6B2.
- 2. The chimeric antigen receptor according to claim 1 further comprising at least one costimulatory domain.
- 3. The chimeric antigen receptor according to claim 1 further comprising at least one activating domain.
- 4. The chimeric antigen receptor according to claim 2 wherein the costimulatory domain is a signaling region of CD28, CD8, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.
- 5. The chimeric antigen receptor according to claim 4 wherein the costimulatory domain comprises CD28.

6. The chimeric antigen receptor according to claim 5 wherein the CD28 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, or SEQ ID NO:8.
7. The chimeric antigen receptor according to claim 4 wherein the costimulatory domain comprises CD8.
8. The chimeric antigen receptor according to claim 7 wherein the CD8 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:14.
9. The chimeric antigen receptor according to claim 4 wherein the costimulatory domain comprises 4-1BB.
10. The chimeric antigen receptor according to claim 9 wherein the CD8 costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:16.
11. The chimeric antigen receptor according to claim 3 wherein the activating domain comprises CD3.
12. The chimeric antigen receptor according to claim 7 wherein the CD3 comprises CD3 zeta.
13. The chimeric antigen receptor according to claim 8 wherein the CD3 zeta comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.
14. The chimeric antigen receptor according to claim 1 wherein the costimulatory domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:2 and the activating domain comprises a sequence that differs at no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 amino acid residues from the sequence of SEQ ID NO:10.
15. A polynucleotide encoding the chimeric antigen receptor of claim 1.
16. A vector comprising the polynucleotide of claim 15.

17. The vector according to claim 16 which is a retroviral vector, a DNA vector, a plasmid, a RNA vector, an adenoviral vector, an adenovirus associated vector, a lentiviral vector, or any combination thereof.
18. An immune cell comprising the vector of claim 16.
19. The immune cell according to claim 18, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
20. The immune cell according to claim 19, wherein the cell is an autologous T cell.
21. The immune cell according to claim 19, wherein the cell is an allogeneic T cell.
22. The immune cell of claim 18, wherein the vector is introduced into a cell that is isolated from a patient's body or that is grown from a sample taken from a patient's body.
23. The immune cell of claim 18, wherein the vector is introduced into a cell that is isolated from a donor's body or that is grown from a sample taken from a patient's body.
24. A pharmaceutical composition comprising an immune cell of claim 18.
25. A chimeric antigen receptor comprising:
 - (a) a VH region of clone 1H2.1 and a VL region of clone 1H2.1;
 - (b) a VH region of clone 8D2 and a VL region of clone 8D2; or
 - (c) a VH region of clone 6B2 and a VL region of clone 6B2;wherein the VH and VL region is linked by at least one linker.
26. The chimeric antigen receptor according to claim 25, wherein the linker comprises the scFv G4S linker or the scFv Whitlow linker.
27. The chimeric antigen receptor according to claim 25, further comprising a costimulatory domain.
28. The chimeric antigen receptor according to claim 25, further comprising an activating domain.
29. The chimeric antigen receptor according to claim 27 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), CD3 gamma, CD3 delta, CD3

epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

30. An immune cell comprising the chimeric antigen receptor of claim 25.
31. The immune cell according to claim 30, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
32. The T cell of claim 31 that is an autologous T cell.
33. The T cell of claim 32 that is an allogeneic T cell.
34. A pharmaceutical composition comprising the cell of claim 30.
35. An isolated polynucleotide comprising a sequence encoding the chimeric antigen receptor of claim 25.
36. A vector comprising the polynucleotide according to claim 35.
37. An immune cell comprising the vector of claim 36.
38. The immune cell according to claim 37, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
39. The T cell of claim 38 that is an autologous T cell.

40. The T cell of claim 38 that is an allogeneic T cell.
41. An isolated polypeptide comprising the amino acid sequence of construct 1H2.1 CD28T, construct 1H2.1 4-1BB, construct 8D2 CD28T, construct 8D2 4-1BB, construct 6B2 CD28T, or construct 6B2 4-1BB.
42. A vector encoding the polypeptide of claim 41.
43. An immune cell comprising the polypeptide of claim 41.
44. The immune cell according to claim 43, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
45. The T cell of claim 44 that is an autologous T cell.
46. The T cell of claim 44 that is an allogeneic T cell.
47. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises a variable heavy chain CDR3 comprising the amino acid sequence of a variable heavy chain CDR3 of clone 1H2.1, clone 8D2, or clone 6B2.
48. The polynucleotide according to claim 47 further comprising an activating domain.
49. The polynucleotide according to claim 48 wherein the activating domain is CD3.
50. The polynucleotide according to claim 49 wherein the CD3 is CD3 zeta.
51. The polynucleotide according to claim 50 wherein the CD3 zeta comprises the amino acid sequence set forth in SEQ ID NO:9.
52. The polynucleotide according to claim 47 further comprising a costimulatory domain.
53. The polynucleotide according to claim 52 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll

ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.

54. The polynucleotide according to claim 53 wherein the CD28 costimulatory domain encodes the amino acid sequence set forth in SEQ ID NO 2.
55. A vector comprising the polynucleotide of claim 47.
56. An immune cell comprising the vector of claim 55.
57. The immune cell of claim 56, wherein the immune cell is a T cell, tumor infiltrating lymphocyte (TIL), NK cell, TCR-expressing cell, dendritic cell, or NK-T cell.
58. The T cell of claim 57 that is an autologous T cell.
59. The T cell of claim 57 that is an allogeneic T cell.
60. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR), said CAR or TCR comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule comprises:
 - a. a variable heavy chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable heavy chain sequence of clone 1H2.1, clone 8D2, or clone 6B2; and/or
 - b. a variable light chain sequence differing by not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0 residues from the variable light chain sequence of clone 1H2.1, clone 8D2, or clone 6B2.
61. The polynucleotide according to claim 60 further comprising an activating domain.
62. The polynucleotide according to claim 61 wherein the activating domain is CD3.

63. The polynucleotide according to claim 62 wherein the CD3 is CD3 zeta.
64. The polynucleotide according to claim 63 wherein the CD3 zeta comprises the amino acid sequence set forth in SEQ ID NO:9.
65. The polynucleotide according to claim 60 further comprising a costimulatory domain.
66. The polynucleotide according to claim 65 wherein the costimulatory domain is a signaling region of CD28, OX-40, 4-1BB/CD137, CD2, CD7, CD27, CD30, CD40, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1 (CD11a/CD18), CD3 gamma, CD3 delta, CD3 epsilon, CD247, CD276 (B7-H3), LIGHT, (TNFSF14), NKG2C, Ig alpha (CD79a), DAP-10, Fc gamma receptor, MHC class I molecule, TNF receptor proteins, an Immunoglobulin protein, cytokine receptor, integrins, Signaling Lymphocytic Activation Molecules (SLAM proteins), activating NK cell receptors, BTLA, a Toll ligand receptor, ICAM-1, B7-H3, CDS, ICAM-1, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alpha, CD8beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRT AM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, a ligand that specifically binds with CD83, or any combination thereof.
67. The polynucleotide according to claim 66 wherein the CD28 costimulatory domain comprises the nucleotide sequence set forth in SEQ ID NO:3.
68. The polynucleotide according to claim 67 wherein the CD28 costimulatory domain comprises the nucleotide sequence set forth in SEQ ID NO:1.
69. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:42), CDR2 (SEQ ID NO:43), and CDR3 (SEQ ID NO:44) and the antigen binding

molecule light chain comprises CDR1 (SEQ ID NO:47), CDR2 (SEQ ID NO:48), and CDR3 (SEQ ID NO:49).

70. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:52), CDR2 (SEQ ID NO:53), and CDR3 (SEQ ID NO:54) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:57), CDR2 (SEQ ID NO:58), and CDR3 (SEQ ID NO:59).
71. An isolated polynucleotide encoding a chimeric antigen receptor (CAR) or T cell receptor (TCR) comprising an antigen binding molecule that specifically binds to DLL3, wherein the antigen binding molecule heavy chain comprises CDR1 (SEQ ID NO:62), CDR2 (SEQ ID NO:63), and CDR3 (SEQ ID NO:64) and the antigen binding molecule light chain comprises CDR1 (SEQ ID NO:67), CDR2 (SEQ ID NO:68), and CDR3 (SEQ ID NO:69).
72. Use of the polynucleotide according to claim 15, 47, 60, 69, 70 or 71, the polypeptide according to claim 41, the chimeric antigen receptor according to claim 1 or 25, the cell according to claim 18, 30, 37, 43, or 56, or the pharmaceutical composition according to claim 24 or 34 in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.
73. The use according to any of claims 72, 73, 74, 75, or 76 wherein the disease or disorder is cancer.
74. The use according to claim 73 wherein the cancer is adrenal, liver, kidney, bladder, breast, gastric, ovarian, cervical, uterine, esophageal, colorectal, prostate (e.g., prostate adenocarcinoma), pancreatic, lung (both small cell and non- small cell), thyroid, carcinomas, sarcomas, glioblastomas, head and neck tumors, large cell neuroendocrine carcinoma (LCNEC), medullary thyroid cancer, glioblastoma, neuroendocrine prostate cancer, (NEPC), high-grade gastroenteropancreatic cancer (GEP) and malignant melanoma.
75. The use according to claim 73, wherein the cancer is small cell lung cancer.
76. The lentiviral vector according to claim 17, wherein the lentiviral vector is a pGAR vector.