

Therefore, there remains a need for improved chimeric antigen receptor-based therapies that allow for more effective, safe, and efficient targeting of T-cell associated malignancies.

SUMMARY

In one aspect, the present disclosure provides an engineered cell including a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain comprises one of FcER1A, FcER1, Ig E, CD19, BCMA, or CD45.

In another aspect, the present disclosure provides an engineered polypeptide including a chimeric antigen receptor polypeptide including a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain includes one of FcER1A, CD19, BCMA, or CD45; and at least one enhancer; wherein a high efficiency cleavage site is disposed between the chimeric antigen receptor polypeptide and enhancer. In yet another aspect, the present disclosure provides an engineered polypeptide that encodes for the polypeptide as described herein.

In another aspect, the present disclosure provides an engineered cell including a first chimeric antigen receptor polypeptide including a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and a second chimeric antigen receptor polypeptide including a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain; wherein the first antigen recognition domain and second antigen recognition domain are different; and the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, CLL-1, BAFFR, BCMA, and CS-1.

In another aspect, the present disclosure provides an engineered polypeptide including a first chimeric antigen receptor polypeptide including a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and a second chimeric antigen receptor polypeptide including a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain;

wherein the first antigen recognition domain and the second antigen recognition domain are different; and the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, BAFFR, CLL-1, BCMA, and CS-1. In yet another aspect, the present disclosure provides an engineered polypeptide that encodes for the polypeptide as described herein.

In another aspect, the present disclosure provides the use of an engineered cell as described herein in the manufacture of a medicament for treating asthma; wherein the chimeric antigen receptor comprises FcER1A or FcER1. In yet another aspect, the present disclosure provides an *in vitro* method of lysing target cells having FcER1A FcER1 or Ig E cell surface antigen comprising contacting said cells with the engineered cells as described herein.

In another aspect, the present disclosure provides the use of an engineered cell as described herein in the manufacture of a medicament for treating an autoimmune disease; wherein said autoimmune disease comprises systemic lupus erythematosus (SLE), multiple sclerosis (MS), Inflammatory bowel disease (IBD), Rheumatoid arthritis, Sjögren syndrome, dermatomyosities, autoimmune hemolytic anemia, Neuromyelitis optica (NMO), NMO Spectrum Disorder (NMOSD), idiopathic thrombocytopenic purpura (ITP), antineutrophil cytoplasmic autoantibodies (ANCA)s associated with systemic autoimmune small vessel vasculitis syndromes or microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), or eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).

In an example, the present disclosure provides a method of treating an autoimmune disease, said method including administering an engineered cell described above to a patient in need thereof; wherein said autoimmune disease comprises systemic lupus erythematosus (SLE), multiple sclerosis (MS), Inflammatory bowel disease (IBD), Rheumatoid arthritis, Sjögren syndrome, dermatomyosities, autoimmune hemolytic anemia, Neuromyelitis optica (NMO), NMO Spectrum Disorder (NMOSD), idiopathic thrombocytopenic purpura (ITP), antineutrophil cytoplasmic autoantibodies (ANCA)s associated with systemic autoimmune small vessel vasculitis syndromes or microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), or eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).

In yet another aspect, the present disclosure provides an *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell as described herein; wherein said target cells have one or more of the following cell surface antigens: FcER1A, FcERi, Ig E, CD19, BCMA, or CD45.

5 In yet another aspect, the present disclosure provides an *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell as described herein; wherein said target cells have one or more of the following cell surface antigens: CD4, CD19, CD33, CD123, BAFFR, CLL-1, BCMA, and CS-1.

10 In yet another aspect, the present disclosure provides the use of an effective amount of cells as described herein in the manufacture of a medicament for treating asthma in a patient. In yet another aspect, the present disclosure provides the use of an effective amount of cells as described herein in the manufacture of a medicament for preventing or mediating organ rejection in a patient. In another example, the present disclosure provides a method of treating asthma. The method includes administering an engineered cell described above.

15 In another example, the present disclosure provides a method of treating organ rejection. The method includes administering an engineered cell described above.

In yet another example, the present disclosure provides an engineered cell comprising: a first chimeric antigen receptor polypeptide comprising a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and optionally, one or more of: a second chimeric antigen receptor polypeptide comprising a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain; wherein the first antigen recognition domain and second antigen recognition domain are different; and the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, CLL-1, BAFFR, BCMA, and CS-1; or one or more enhancer selected from the group consisting of IL-15/IL-15 sushi, IL-15/IL-15 sushi anchor, 4-1BBL, and IL-15.

25 In one example, the present disclosure provides an engineered cell having a first chimeric antigen receptor polypeptide including a first antigen recognition domain, a first signal peptide, a first hinge region, a first transmembrane domain, a first co-stimulatory domain, and a first signaling domain; and a second chimeric antigen receptor polypeptide including a second

antigen recognition domain, a second signal peptide, a second hinge region, a second transmembrane domain, a second co-stimulatory domain, and a second signaling domain; wherein the first antigen recognition domain is different than the second antigen recognition domain.

5 In yet another aspect, the present disclosure provides an engineered cell comprising: a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain comprises one of GD2 and GD3.

10 In yet another aspect, the present disclosure provides an engineered polypeptide comprising a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain comprises one of GD2 and GD3; and optionally, at least one enhancer; wherein a high efficiency cleavage site is disposed between the chimeric antigen receptor polypeptide and enhancer.

15 In yet another aspect, the present disclosure provides an engineered polynucleotide that encodes for the engineered polypeptide as described herein.

20 In yet another aspect, the present disclosure provides an engineered cell comprising: a first chimeric antigen receptor polypeptide comprising a first signal peptide, GD2 antigen recognition domain, a first hinge region, a first transmembrane domain, a first signalling domain, and a first co-stimulatory domain; and a second chimeric antigen receptor polypeptide comprising a second signal peptide, GD3 antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain.

25 In yet another aspect, the present disclosure provides an engineered polypeptide comprising: a first chimeric antigen receptor polypeptide comprising a first signal peptide, GD2 antigen recognition domain, a first hinge region, a first transmembrane domain, a first signalling domain, and a first co-stimulatory domain; and a second chimeric antigen receptor polypeptide comprising a second signal peptide, GD3 antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain.

In yet another aspect, the present disclosure provides an engineered polynucleotide that encodes for the engineered polypeptide as described herein. In yet another aspect, the present disclosure provides the use of an engineered cell that co-expresses one or more enhancers with a GD2 or GD3 engineered CAR polypeptide in the manufacture of a medicament for increasing persistence of CAR engineered cells in a patient.

In yet another aspect, the present disclosure provides an *in vitro* method of lysing target cells having GD2 or GD3 cell surface antigen, said method comprising contacting target cells with the engineered cells as described herein. In yet another aspect, the present disclosure provides an *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell as described herein; wherein said target cells have one or more of the following cell surface antigens: GD2 and GD3. In yet another aspect, the present disclosure provides the use of an engineered cell as described herein in the manufacture of a medicament for treating a cell proliferative disease.

In another example, the present disclosure provides an engineered polypeptide including a chimeric antigen receptor and an enhancer.

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In another example, the present disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide including: a signal peptide, a CD45 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain. In another embodiment, the present disclosure provides a polynucleotide encoding for the aforementioned polypeptide.

In another example, the present disclosure provides an engineered cell having the engineered polypeptide or polynucleotide described above.

In another example, the present disclosure provides a method of reducing the number of target cells including the steps of (i.) contacting said target cells with an effective amount of an engineered cell having at least one chimeric antigen receptor polypeptide, for engineered cells having multiple chimeric antigen receptor polypeptides, each chimeric antigen receptor polypeptide is independent; and (ii.) optionally, assaying for the reduction in the number of said

cells. The target cells include at least one cell surface antigen selected from the group consisting of interleukin 6 receptor, ROR1, PSMA, PSCA, MAGE A3, Glycolipid, glypican 3, F77, GD-2, WT1, CEA, HER-2/neu, IL13R α 2, Met, mesothelin, EGFR, EGFRvIII, MUC16, NKG2D ligands, thyroglobulin, MAGE-3, MAGE-4, MAGE-5, MAGE- 6, alpha-fetoprotein, CA 19-9, CA 72-4, NY-ESO, FAP, ErbB, c-Met, MART-1, MUC1, MUC2, MUC3, MUC4, MUC5, CD30, EGFRvIII, CD33, CD123, CLL-1, immunoglobulin kappa and lambda, CD38, CD52, CD19, CD20, CD22, CD38, CD45, BCMA, CS1, BAFF receptor, TACI, CD3, CD4, CD8, CD5, CD7, CD2, CD45, CD70 and CD138.

In another example, the present disclosure provides methods for treating B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, multiple myeloma, acute myeloid leukemia, chronic myeloid leukemia, chronic myeloproliferative neoplasms, myelodysplastic syndromes, granulocytic sarcoma, histiocytic sarcoma, B-cell acute lymphoblastic leukemia (B-ALL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), chronic myelomonocytic leukemia, and cell proliferative diseases by administering any of the engineered cells described above to a patient in need thereof.

In some examples, the disclosed disclosure comprises methods and compositions of controlling the proliferation of T cells, for instance, CAR T cells or therapeutic T cells using CAMPATH. The methods further relate to compositions and methods for ablating CAR T cells using CAMPATH after tumor depletion or in emergency cases, for example, unexpected side effects caused by CAR Therapy. In further examples, CD52 is incorporated into CD5 CAR engineered cell or any CAR engineered cell and can be used as a "safety switch" for CAR therapy.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1. A schematic representation of cCAR construct (hereinafter, "multiple CAR or compound CAR"). Multiple or compound CAR targets multiple antigens (e.g. cell type 1 or cell type 2 or the same cell type). Multiple or cCAR T cell immunotherapies comprises individual component CAR comprising a different or same antigen recognition domain, a hinge region, a transmembrane domain, various co-stimulatory domain(s) and an intracellular signaling domain.

Figure 2A. A schematic representation of cCAR-T construct. The construct comprises a

SFFV promoter driving the expression of-multiple modular units of CARs linked by a P2A peptide. Upon cleavage of the linker, the cCARs split and engage upon targets expressing CD33 and/or CD123. As a novel cCAR construct, the activation domains of the construct may include, but is not limited to, 4-1BB on the CD33 CAR segment and a CD28 region on the CD123 CAR.

5 **Figure 2B.** A Western blot depicting the expression of transduced CD33CD123 cCAR-T cells. The figure depicts expression of two different CAR proteins, i.e., CD33 CAR and CD123 CARs. The cCAR-T cells expressing both CD33 and CD123 CARs upon cleavage of the linker generate two distinct and consistently intense protein bands. Green Fluorescent Protein (GFP) is included as negative control.

10 **Figure 2C.** Flow cytometry representing the efficiency of transduction. Upper panel shows the lentiviral titer for CD33CD123 cCARs (also referred to as CD33CD123-2G-CAR) tested on 293FT HEK (human embryonic kidney) cells to gauge maximum transduction efficiency before usage on UCB (umbilical cord blood) and PB (peripheral blood) T-cells. Lower panel shows CD33CD123 cCAR (also referred to as CD33CD123-2G-CAR) T-cells

CLAIMS

1. A engineered cell comprising:

a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain,
5 a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain;
wherein said antigen recognition domain comprises one of FcER1A, FcER1, Ig E, CD19,
BCMA, or CD45.
2. The engineered cell according to claim 1, wherein the co-stimulatory domain is CD28 or
4-1 BB; and the signaling domain is CD3 zeta.
- 10 3. The engineered cell according to claim 1, further comprising one or more enhancer
selected from the group consisting of IL-15/IL-15 sushi, IL-15/1L-15 sushi anchor, 4-1BBL, and
IL-15.
4. An engineered polypeptide comprising a chimeric antigen receptor polypeptide
comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane
15 domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition
domain comprises one of FcER1A, CD19, BCMA, or CD45; and at least one enhancer; wherein
a high efficiency cleavage site is disposed between the chimeric antigen receptor polypeptide and
enhancer.
5. The engineered polypeptide according to claim 4, wherein the engineered polypeptide
20 comprises two enhancers; and two high efficiency cleavage sites.
6. The engineered polypeptide according to claim 4, wherein the high efficiency cleavage
site is selected from the group consisting of P2A, T2A, E2A, and F2A.

7. An engineered polynucleotide that encodes for the polypeptide of claim 4.

8. A engineered cell comprising:

a first chimeric antigen receptor polypeptide comprising a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and

a second chimeric antigen receptor polypeptide comprising a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain;

wherein

the first antigen recognition domain and second antigen recognition domain are different; and

the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, CLL-1, BAFFR, BCMA, and CS-1.

9. The engineered cell according to claim 8, wherein the first antigen recognition domain and second antigen recognition domain are selected from the group comprising: CD19 and CD123, CD19 and BAFFR, BCMA and CD19, BCMA and CS1, CD123 and CD33, CD33 and CLL-1, CD4 and CD123, CD19 and CS-1, and CD4 and CLL-1.

10. An engineered polypeptide comprising:

a first chimeric antigen receptor polypeptide comprising a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and

a second chimeric antigen receptor polypeptide comprising a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain;

wherein

5 the first antigen recognition domain and the second antigen recognition domain are different; and

the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, BAFFR, CLL-1, BCMA, and CS-1.

10 11. The engineered polypeptide according to claim 10, wherein the first antigen recognition domain and second antigen recognition domain are selected from the group comprising: CD19 and CD123, BCMA and CD19, CD19 and BAFFR, BCMA and CS1, CD123 and CD33, CD33 and CLL-1, CD4 and CD123, CD19 and CS-1, and CD4 and CLL-1.

12. The engineered polypeptide according to claim 10, wherein the first co-stimulatory
15 domain and the second co-stimulatory domain are different.

13. The engineered polypeptide according to claim 10, wherein a high efficiency cleavage site is disposed between the first antigen recognition domain and second antigen recognition domain.

14. An engineered polynucleotide that encodes for the polypeptide of claim 9.

20 15. Use of an engineered cell according to claim 1 in the manufacture of a medicament for treating asthma; wherein the chimeric antigen receptor comprises FcER1A or FcER1.

16. An *in vitro* method of lysing target cells having FcER1A FcER1 or Ig E cell surface antigen comprising contacting said cells with the engineered cells according to claim 1.

17. The use according to claim 15, wherein the target cell comprises plasma cells, mast cells, or basophil cells.

5 18. Use of an engineered cell according to claim 1 in the manufacture of a medicament for treating an autoimmune disease; wherein said autoimmune disease comprises systemic lupus erythematosus (SLE), multiple sclerosis (MS), Inflammatory bowel disease (IBD), Rheumatoid arthritis, Sjögren syndrome, dermatomyosities, autoimmune hemolytic anemia, Neuromyelitis optica (NMO), NMO Spectrum Disorder (NMOSD), idiopathic thrombocytopenic purpura (ITP),
10 antineutrophil cytoplasmic autoantibodies (ANCA) associated with systemic autoimmune small vessel vasculitis syndromes or microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), or eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).

19. Use of an engineered cell according to claim 7 in the manufacture of a medicament for
15 treating an autoimmune disease; wherein said autoimmune disease comprises systemic lupus erythematosus (SLE), multiple sclerosis (MS), Inflammatory bowel disease (IBD), Rheumatoid arthritis, Sjögren syndrome, dermatomyosities, autoimmune hemolytic anemia, Neuromyelitis optica (NMO), NMO Spectrum Disorder (NMOSD), idiopathic thrombocytopenic purpura (ITP),
antineutrophil cytoplasmic autoantibodies (ANCA) associated with systemic autoimmune small
20 vessel vasculitis syndromes or microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), or eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome).

20. An *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell according to claim 3; wherein said target cells have one or more of the following cell surface antigens: FcER1A, FcERi, Ig E, CD19, BCMA, or CD45.

21. An *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell according to claim 9; wherein said target cells have one or more of the following cell surface antigens: CD4, CD19, CD33, CD123, BAFFR, CLL-1, BCMA, and CS-1.

22. Use of an effective amount of cells according to claim 1 in the manufacture of a medicament for treating asthma in a patient.

23. Use of an effective amount of cells according to claim 7 in the manufacture of a medicament for preventing or mediating organ rejection in a patient.

24. A engineered cell comprising:

a first chimeric antigen receptor polypeptide comprising a first signal peptide, first antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and

optionally, one or more of:

a second chimeric antigen receptor polypeptide comprising a second signal peptide, second antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain;

wherein

the first antigen recognition domain and second antigen recognition domain are different; and

the first antigen recognition domain and second antigen rejection domain are selected from the group consisting of CD4, CD19, CD33, CD123, CLL-1, BAFFR, BCMA, and CS-1; or

one or more enhancer selected from the group consisting of IL-15/IL-15 sushi, IL-15/1L-15 sushi anchor, 4-1BBL, and IL-15.

25. An engineered cell comprising:

a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain comprises one of GD2 and GD3.

26. The engineered cell according to claim 25, wherein the co-stimulatory domain is CD28 or 4-1 BB; and the signaling domain is CD3 zeta.

27. The engineered cell according to claims 25, further comprising one or more enhancers selected from the group consisting of IL-15/IL-15 sushi, IL-15/1L-15 sushi anchor, 4-1BBL, and IL-15.

28. An engineered polypeptide comprising a chimeric antigen receptor polypeptide comprising a signal peptide, antigen recognition domain, a hinge region, a transmembrane domain, a signaling domain, and a co-stimulatory domain; wherein said antigen recognition domain comprises one of GD2 and GD3; and optionally, at least one enhancer; wherein a high efficiency cleavage site is disposed between the chimeric antigen receptor polypeptide and enhancer.

29. The engineered polypeptide according to claim 28, wherein the engineered polypeptide comprises two enhancers; and two high efficiency cleavage sites.

30. The engineered polypeptide according to claim 29, wherein the high efficiency cleavage site is selected from the group consisting of P2A, T2A, E2A, and F2A.

31. An engineered polynucleotide that encodes for the engineered polypeptide of claim 25.

32. An engineered cell comprising:

5 a first chimeric antigen receptor polypeptide comprising a first signal peptide, GD2 antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and

a second chimeric antigen receptor polypeptide comprising a second signal peptide, GD3 antigen recognition domain, a second hinge region, a second transmembrane domain, a second
10 signaling domain, and a second co-stimulatory domain.

33. An engineered polypeptide comprising:

a first chimeric antigen receptor polypeptide comprising a first signal peptide, GD2 antigen recognition domain, a first hinge region, a first transmembrane domain, a first signaling domain, and a first co-stimulatory domain; and

15 a second chimeric antigen receptor polypeptide comprising a second signal peptide, GD3 antigen recognition domain, a second hinge region, a second transmembrane domain, a second signaling domain, and a second co-stimulatory domain.

34. The engineered polypeptide according to claim 33, wherein the first co-stimulatory domain and the second co-stimulatory domain are different.

20 35. The engineered polypeptide according to claim 33, wherein a high efficiency cleavage site is disposed between the first antigen recognition domain and second antigen recognition domain.

36. An engineered polynucleotide that encodes for the engineered polypeptide of claim 33.
37. Use of an engineered cell that co-expresses one or more enhancers with a GD2 or GD3 engineered CAR polypeptide in the manufacture of a medicament for increasing persistence of CAR engineered cells in a patient.
- 5 38. An *in vitro* method of lysing target cells having GD2 or GD3 cell surface antigen, said method comprising contacting target cells with the engineered cells according to claim 26.
39. An *in vitro* method of depleting target cells, said method comprising contacting said cells with an engineered cell according to claim 25; wherein said target cells have one or more of the following cell surface antigens: GD2 and GD3.
- 10 40. Use of an engineered cell according to claim 25 in the manufacture of a medicament for treating a cell proliferative disease.
41. The use according to claim 40, wherein the cell proliferative disease is selected from the group consisting of medulloblastoma/primitive neuroectodermal tumor of the center nervous system (CNS), malignant glioma, neuroblastoma, retinoblastoma, ependymoma, sarcoma,
- 15 melanoma, breast cancer, ovarian cancer, glioblastoma, Ewing's sarcoma, and small cell lung carcinoma.