al. 2013, Kalos, Nazimuddin et al. 2013, Kochenderfer, Dudley et al. 2013, Kochenderfer, Dudley et al. 2013, Lee, Shah et al. 2013, Park, Riviere et al. 2013, Maude, Frey et al. 2014).

Despite the success of CAR therapy in B-cell leukemia and lymphoma, the application of CAR therapy to T-cell malignancies has not yet been well established. Given that T-cell malignancies are associated with dramatically poorer outcomes compared to those of B-cell malignancies (Abramson, Feldman et al. 2014), CAR therapy in this respect has the potential to further address a great clinical need.

CD5 is expressed in more than 80% of T-cell acute lymphoblastic leukemia (T-ALL). One treatment option is to treat patients with anti-CD5 antibodies as T-cell leukemias or T-cell lymphomas expressing the CD5 surface molecule. However attempts have met limited success.

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

The present disclosure provides chimeric antigen receptors (CARS) targeting hematologic malignancies, compositions and methods of use thereof. In one aspect, the present invention refers to engineered cell comprising an engineered chimeric antigen receptor polynucleotide, the polynucleotide encodes for a chimeric antigen receptor polypeptide comprising: a signal peptide, an antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain; and wherein the antigen recognition domain is selected from the group consisting of CD2, CD3, CD4, CD5, and CD7 wherein the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain; with the proviso that: when the engineered cell comprises an endogenous cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to knock out or inactivate the gene that encodes for the cell surface antigen except when the antigen recognition domain is CD4. In another aspect, the present invention refers to *in-vitro* method of reducing the number of CD2, CD3, CD4, CD5, or CD7 positive T cell leukemia cells or CD4 positive T cell lymphoma cells, the method comprising the steps of: contacting CD2, CD3, CD4, CD5, or CD7 positive T cell leukemia cells or CD2, CD3, CD4,

CD5, or CD7 positive T cell lymphoma cells with an effective amount of an engineered cell comprising a polynucleotide that encodes for chimeric antigen receptor polypeptide comprising: a signal peptide, an antigen recognition domain selected from the group consisting of CD2, CD3, CD4, CD5, and CD7, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain; and optionally, assaying for CD2, CD3, CD4, CD5, or CD7 positive T leukemia cells or CD2, CD3, CD4, CD5, or CD7 positive lymphoma cells; wherein the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain; with the proviso that: when the engineered cell comprises a cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to delete the gene that encodes for the cell surface antigen except when the antigen recognition domain is CD4 In yet another aspect, the present invention refers to the use of an engineered cell comprising a polynucleotide that encodes for chimeric antigen receptor polypeptide comprising: a signal peptide, a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain in the manufacture of a medicament for treating a CD2, CD3, CD4, CD5, or CD7 associated cell proliferative disease in a patient in need thereof, wherein said medicament is to be administered to the patient; and optionally, assaying for CD2, CD3, CD4, CD5, or CD7 positive cells associated with the cell proliferative disease; wherein the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain, or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain; with the proviso that: when the engineered cell comprises a cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to delete the gene that encodes for the cell surface antigen, except when the antigen recognition domain is CD4; wherein the CD2, CD3, CD4, CD5, or CD7 associated cell proliferative disease is a cancer or a neoplastic disease, wherein the cancer is selected from the group consisting of acute lymphocytic cancer, acute myeloid leukemia, alveolar rhabdomyosarcoma, bladder cancer, bladder carcinoma, bone cancer, brain cancer, medulloblastoma, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, cancer of the oral cavity, cancer of the vulva, chronic lymphocytic leukemia, chronic myeloid cancer, colon cancer, esophageal cancer,

cervical cancer, fibrosarcoma, gastrointestinal carcinoid tumor, head and neck cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, hypopharynx cancer, kidney cancer, larynx cancer, leukemia, liquid tumors, liver cancer, lung cancer, non-small cell lung carcinoma, lymphoma, malignant mesothelioma, mastocytoma, melanoma, multiple myeloma, nasopharynx cancer, non-Hodgkin lymphoma, B-chronic lymphocytic leukemia, hairy cell leukemia, acute lymphoblastic leukemia (ALL), T-cell acute lymphocytic leukemia, Burkitt's lymphoma, extranodal NK/T cell lymphoma, NK cell leukemia/lymphoma, post-transplant lymphoproliferative disorders, ovarian cancer, pancreatic cancer, peritoneal cancer, omentum cancer, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer, skin cancer, small intestine cancer, soft tissue cancer, solid tumors, stomach cancer, testicular cancer, thyroid cancer, ureter cancer, thymic carcinoma, diffuse large cell lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), chronic lymphoid leukemia(CLL), T-cell lymphoma, T-cell neoplasms and peripheral T-cell lymphoma.

In one example, the disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide comprising: a signal peptide, a CD2 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain.

In another example, the disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide comprising: a signal peptide, a CD3 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain.

In another example, the disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide comprising: a signal peptide, a CD4 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain. In another example, the disclosure provides an engineered chimeric antigen receptor polypeptide, the polypeptide comprising: a signal peptide, a CD5 antigen recognition domain, a

CLAIMS

1. An engineered cell comprising an engineered chimeric antigen receptor polynucleotide, the polynucleotide encodes for a chimeric antigen receptor polypeptide comprising: a signal peptide, an antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain; and

wherein the antigen recognition domain is selected from the group consisting of CD2, CD3, CD4, CD5, and CD7

wherein

the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain;

with the proviso that:

when the engineered cell comprises an endogenous cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to knock out or inactivate the gene that encodes for the cell surface antigen

except when the antigen recognition domain is CD4.

2. The engineered chimeric antigen receptor polynucleotide according to claim 1, wherein said antigen recognition domain is CD3.

3. The engineered chimeric antigen receptor polynucleotide according to claim 1, wherein said antigen recognition domain is CD4.

4. The engineered chimeric antigen receptor polynucleotide according to claim 1, wherein said antigen recognition domain is CD5.

5. The engineered chimeric antigen receptor polynucleotide according to claim 1, wherein said antigen recognition domain is CD7.

6. An *in-vitro* method of reducing the number of CD2, CD3, CD4, CD5, or CD7 positive T cell leukemia cells or CD4 positive T cell lymphoma cells, the method comprising the steps of:

i. contacting CD2, CD3, CD4, CD5, or CD7 positive T cell leukemia cells or CD2, CD3, CD4, CD5, or CD7 positive T cell lymphoma cells with an

effective amount of an engineered cell comprising a polynucleotide that encodes for chimeric antigen receptor polypeptide comprising: a signal peptide, an antigen recognition domain selected from the group consisting of CD2, CD3, CD4, CD5, and CD7, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain; and

ii. optionally, assaying for CD2, CD3, CD4, CD5, or CD7 positive T leukemia cells or CD2, CD3, CD4, CD5, or CD7 positive lymphoma cells;

wherein

the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain;

with the proviso that:

when the engineered cell comprises a cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to delete the gene that encodes for the cell surface antigen except when the antigen recognition domain is CD4.

7. The method of reducing the number of CD2, CD3, CD4, CD5, or CD7 positive T cell leukemia cells or CD2, CD3, CD4, CD5, or CD7 positive T cell lymphoma cells according to claim 6, wherein said engineered cell is selected from the group consisting of CD4 T-cells, CD8 T-cells, Natural Killer cells, and NKT cells.

8. Use of an engineered cell comprising a polynucleotide that encodes for chimeric antigen receptor polypeptide comprising: a signal peptide, a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain, a hinge region, a transmembrane domain, at least one co-stimulatory domain, and a signaling domain in the manufacture of a medicament for treating a CD2, CD3, CD4, CD5, or CD7 associated cell proliferative disease in a patient in need thereof, wherein said medicament is to be administered to the patient; and optionally, assaying for CD2, CD3, CD4, CD5, or CD7 positive cells associated with the cell proliferative disease;

wherein

the engineered cell is a T cell comprising a CD2, CD3, CD4, CD5, or CD7 antigen recognition domain, or the engineered cell is an NK cell comprising CD2 or CD7 antigen recognition domain;

with the proviso that:

when the engineered cell comprises a cell surface antigen that is the target of the antigen recognition domain, the cell is genetically engineered to delete the gene that encodes for the cell surface antigen, except when the antigen recognition domain is CD4;

wherein the CD2, CD3, CD4, CD5, or CD7 associated cell proliferative disease is a cancer or a neoplastic disease, wherein the cancer is selected from the group consisting of acute lymphocytic cancer, acute myeloid leukemia, alveolar rhabdomyosarcoma, bladder cancer, bladder carcinoma, bone cancer, brain cancer, medulloblastoma, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, cancer of the oral cavity, cancer of the vulva, chronic lymphocytic leukemia, chronic myeloid cancer, colon cancer, esophageal cancer, cervical cancer, fibrosarcoma, gastrointestinal carcinoid tumor, head and neck cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, hypopharynx cancer, kidney cancer, larynx cancer, leukemia, liquid tumors, liver cancer, lung cancer, non-small cell lung carcinoma, lymphoma, malignant mesothelioma, mastocytoma, melanoma, multiple myeloma, nasopharynx cancer, non-Hodgkin lymphoma, B-chronic lymphocytic leukemia, hairy cell leukemia, acute lymphoblastic leukemia (ALL), T-cell acute lymphocytic leukemia, Burkitt's lymphoma, extranodal NK/T cell lymphoma, NK cell leukemia/lymphoma, post-transplant lymphoproliferative disorders, ovarian cancer, pancreatic cancer, peritoneal cancer, omentum cancer, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer, skin cancer, small intestine cancer, soft tissue cancer, solid tumors, stomach cancer, testicular cancer, thyroid cancer, ureter cancer, thymic carcinoma, diffuse large cell lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), chronic lymphoid leukemia(CLL), T-cell lymphoma, T-cell neoplasms and peripheral T-cell lymphoma.

9. The use according to claim 8, wherein cell proliferative disease is a CD4 associated cell proliferative disease selected from the group consisting of CD4 positive leukemia and CD4 positive lymphoma.

10. The use according to claim 9, wherein said cell proliferative disease is CD4 positive acute myeloid leukemia.

11. The use according to claim 9, wherein said cell acute myeloid leukemia is acute myeloid leukemia M4 or acute myeloid leukemia M5.

12. The use according to claim 9, wherein said engineered cell is selected from the group consisting of CD4 T-cells, CD8 T-cells, Natural Killer cells, or NKT cells.

13. The use according to claim 8, wherein cell proliferative disease is a CD5 associated cell proliferative disease; wherein the CD5 associated cell proliferative disease is selected from the group consisting of thymic carcinoma, non-Hodgkin's lymphoma, diffuse large cell lymphoma, small lymphocytic lymphoma (SLL), T-cell neoplasms, peripheral T-cell lymphoma, mantle cell lymphoma, T-cell acute lymphoblastic leukemia (T-ALL), and chronic lymphoid leukemia(CLL).

14. The use according to claim 13, wherein said engineered cell is selected from the group consisting of CD4 T-cell, CD8 T-cell, Natural Killer cell, or NKT cell.

15. The use according to claim 8, wherein the polynucleotide comprises SEQ ID NO. 4 or SEQ ID NO. 5.

16. The use according to claim 8, wherein the method further comprises that one or more of chemotherapy, radiation, immunosuppressive agents, and antiviral therapy are to be administered in conjunction with the engineered cell.

17. The use according to claim 13, wherein the polynucleotide comprises SEQ ID NO. 6 or SEQ ID NO. 7.

18. The use according to claim 13, wherein the method further that one or more of chemotherapy, radiation, immunosuppressive agents, and antiviral therapy are to be administered in conjunction with the engineered cell.